External stimulation of the trigeminal nerve for the prevention and acute treatment of episodic and chronic migraine

Systematic Review

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Health Technology Assessment

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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Content

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List of abbreviations

AED .....adverse device effects
C .....comparator
CG .....control group
CM.....chronic migraine
EM.....episodic migraine
e-TNS .....external trigeminal nerve stimulator
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
Hrs.....hours
ICD .....implantable cardioverter defibrillator
ICHD .....International Classification of Headache Disorders
IG.....intervention group
HIS .....International Headache Society
IQR.....inter-quartile range
Min.....minutes
mITT .....modified intention to treat
MOH .....medication overuse headache
Mos.....months
MRI .....magnetic resonance imaging
NA .....not available
NSAIDs.....Nonsteroidal Anti-inflammatory Drugs
Pts.....patients
QoL.....quality of life
RCT.....randomized controlled trial
RoB.....risk of bias
s-TNS .....supraorbital transcutaneous neurostimulation
SADE .....serious adverse device event
SD.....standard deviation
Yrs .....years
VAS.....visual analogue scale
WCD .....wearable cardioverter defibrillator

Summary

Introduction

Health Problem

According to the International Headache Society (IHS), migraine is a primary headache disorder described by periodic attacks of headache, typically accompanied by loss of appetite, nausea, vomiting, sensitivity to light, to noise or to odor, and movement hypersensitivity [1]. Migraine has two major types, migraine with aura and migraine without aura. Both may share the above symptoms, while migraine with aura also includes transient focal neurological symptoms that may precede or accompany a headache [2]. The difference between episodic migraine (EM) and chronic migraine (CM) essentially lies in frequency of headache days [1]. While in EM, headaches occurs less than 15 times per month, in CM, headaches must occur more than 15 times per month in the last three consecutive months.

migraine: primary headache disorder, migraine with aura and migraine without aura, episodic (EM) and chronic migraine (CM)

According to Global Burden of Disease 2015, migraine was ranked to be the third-highest cause of disability worldwide in both males and females under the age of 50 years [2]. EM affects more than 10% of the population and has higher prevalence in women (18%) than in men (6%) [1]. CM affects 1-5% of the general population [1]. As migraine is essentially a cerebral disorder, the major cause of EM and CM is genetics [3]. The progression from EM to CM develops at a rate of about 2.5% per year, yet migraine patients show a great intra-individual variability and so also move back from CM to EM [4].

migraine: third-highest cause of disability under 50 years of age in 2015, EM has higher prevalence in women, a cerebral disorder, main cause is genetics

Description of Technology

The external trigeminal nerve stimulator (e-TNS) (Cefaly®) is an intervention that stimulates the upper nerve branch (supraorbital nerve) of the trigeminal nerve with the aim of reducing the frequency and length of migraine attacks [5]. The supraorbital nerve ends at the vertex of the scalp, thus providing sensory innervation to the forehead, upper eyelid, and anterior scalp. The self-adhesive e-TNS electrode is placed at the forehead targeting the supraorbital nerve [6]. The battery-operated electrical pulse generator connects magnetically to the electrode from where it conducts electrical micro-pulses [5]. The e-TNS is either used for the *prevention* of a migraine attack through daily 20 minute sessions, or it is used for *acute treatment* as a 60 or 120 minutes long intervention during the migraine attack. The pulse width of 250 µs and maximum intensity of 16 mA is the same for both modes, but the *preventive* mode has the pulse frequency of 60 Hz, while the *acute treatment* mode has 100 Hz [5].

e-TNS: stimulates the supraorbital nerve with micro-impulses both for prevention as well as acute treatment of EM and CM

In 2014, the e-TNS device was approved by the FDA as a Class II medical device for the indication of "prophylactic treatment of episodic migraine in patients over the age of 18" [7], and in 2017, FDA granted also the *acute* migraine *treatment* approval [8]. According to information provided by the manufacturer, the e-TNS (Cefaly®) device also bears a CE mark in Europe from January 2008 for the broad indication of headaches.

e-TNS approved by FDA for both prevention as well as acute treatment, holds a CE-mark in Europe for the indication of headaches

The claimed benefit of e-TNS is the reduction of the frequency and length of migraine attacks. E-TNS claims to be less invasive, have a better effectiveness-safety ratio, less side effects, no serious side effects, and fewer contraindications. Furthermore, it claims to reduce the acute anti-migraine drug intake, thus preventing medication overuse headache.

claimed benefit: reduction of migraine attacks and drug intake, less invasive, no serious side effects

Methods

aim: is e-TNS vs. standard therapy or placebo more effective and safer

The aim of this systematic review was to investigate whether e-TNS, as a *preventive* or *acute therapy*, is more effective and safer than standard drug therapy or placebo with respect to improvement in migraine episodes, quality of life (QoL), satisfaction, and side effects. The EUnetHTA Core Model for Rapid Assessment of Relative Effectiveness was the main source for selecting relevant assessment elements.

systematic literature search in four databases, 422 hits

The systematic literature search was conducted in the following four databases (Medline via Ovid, Embase, The Cochrane Library, CRD (DARE, NHS-EED, HTA)). The search was not limited to a year of publication, but it was limited to prospective studies and articles published in English or German. After deduplication, overall 433 citations were included.

search in clinical trial registries for ongoing trials, 70 hits, 7 relevant

Furthermore, the following clinical trial registries were assessed for registered ongoing clinical trials or observational studies (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) yielding 70 results, of which seven were relevant.

19 publications from the manufacturer, 4 confidential, hand-search yielded 7 hits

The only manufacturer of e-TNS (Cefaly®) submitted 19 publications of which four were unpublished at the time of writing of the report and hence were confidential and not included. No new citations were identified. By hand-search, additional seven publications were found, resulting in overall 440 hits.

Results

Available evidence

2 RCTs for effectiveness: 1 for prevention (90 days follow up) and 1 for acute treatment (24 hours follow-up), comparator: placebo, sponsored by STX Med – Cefaly® Technology

For the assessment of clinical effectiveness, two studies met the inclusion criteria. One randomized controlled trial (RCT) for the *preventive* use of e-TNS [9] and one RCT for the *acute treatment* use of e-TNS [10]. Both compared the e-TNS (Cefaly®) to a sham (Cefaly®) device. The latter was not in the form of a peer-reviewed publication, but in the form of a study protocol and study results published at clinicaltrials.gov [10]. The studies were sponsored by the manufacturer STX Med – Cefaly® Technology or by the Walloon Region (where the manufacturer provided the e-TNS devices), respectively. In the *preventive* study, the length of follow-up was 90 days and it included 67 patients (34 received e-TNS) [9]. While in the *acute treatment* study, the follow-up was 24 hours and it included 106 patients (52 received e-TNS) [10].

7 studies for safety, 2 RCTs and 5 prospective case series, 3 for prevention with 60 and 120 days of follow-up, 2 for acute treatment with 24 hours follow-up

For the assessment of safety, seven studies met the inclusion criteria. Two RCTs (described above [9, 10]), and five prospective case series (three for *prevention* with the total of 84 patients [11-13] and two for *acute treatment* with the total of 95 patients [14, 15]). One of the case series studies was not in the form of a peer-reviewed publication, but in the form of a study protocol and study results published at clinicaltrials.gov [15]. Three were sponsored by STX Med – Cefaly® Technology [13-15] and in the remaining two, the source of funding was unclear, but it was stated that the devices were provided by the manufacturer [11, 12]. In the *preventive* case series studies, the length of follow-up ranged from 60 to 120 days [11-13], while in the *acute treatment* case series studies, the follow-up was 24 hours [14, 15].

Clinical effectiveness

Concerning *prevention*, the results from the RCT (34 e-TNS patients) suggest that e-TNS is more effective than sham treatment in EM patients when measured by 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), acute antimigraine drug intake (4.24 less instances of acute drug intake per month), improvement in responder rate of migraine days (26.2% more response to verum treatment) and satisfaction (31.2% difference in satisfaction with the control group) [9].

prevention: e-TNS more effective than placebo in reduction of migraine attacks, migraine days, headache days, responder rate, and satisfaction

Concerning *acute treatment*, the RCT showed that e-TNS caused more improvement in pain reduction than sham on a VAS scale (out of 11 points) at 1/2/24 hours post-*acute treatment* (1.68/1.02/1.08 more improvement points, respectively) [10]. Concerning the minimal clinically important difference (MCID), however, it remains unclear if the improvement measured is of clinical importance because the results oscillate around the lower end of the clinically meaningful benefit threshold [16]. There was also an increase of one intervention group (IG) patient in acute antimigraine drug intake at two hours post-*acute treatment* compared to control (CG), but a decrease of three verum patients compared to control at 24 hours [10].

acute treatment: e-TNS more effective than placebo in improving pain reduction at 1/2/24 hours post-acute treatment, MCID questionable, unclear in reduction of antimigraine drug intake

Safety

Concerning safety, in both *prevention* and *acute treatment* studies, no serious adverse device effects occurred.

no serious adverse device effects occurred in any of the studies

In terms of adverse device effects in the *prevention* studies, two studies reported that there were none [9, 12], while intolerance to paraesthesia (burning sensation) was reported in 34.3% of patients in [13]. Furthermore, headache after stimulation as well as neck tension were reported in one study [11], where headache occurred in 8.7% of patients, while there was neck tension in 4.3%.

adverse device effects in prevention studies: intolerance to paraesthesia, headache after stimulation, neck tension

In terms of adverse device effects in the *acute treatment* studies, one study reported that there were none [14, 15], while intolerance to paraesthesia was documented in two *acute treatment* studies in 5.8% (IG n=52) vs. 1.9% (CG n=54) [10] and 11.9% of patients [15]. Nausea after stimulation was reported in two studies in 1.9% (IG n=52) vs. 0% (CG n=54) [10] and 3.5% of patients [15].

Furthermore, arousal changes (insomnia, sleepiness/fatigue, drowsiness), dizziness, vomiting, pain in the jaw, discomfort in teeth, pain in eyes, and cold feet occurred in one study all in 1.7% of patients [15]. In the same study, 18.3% of patients reported skin allergy/irritation.

skin allergy/irritation adverse device effects in acute treatment studies: intolerance to paraesthesia, nausea after stimulation, arousal changes (insomnia, sleepiness/fatigue, drowsiness), dizziness, vomiting, pain in the jaw, discomfort in teeth, pain in eyes, cold feet,

Upcoming evidence

Currently, there is only one ongoing RCT for the *acute treatment* use of e-TNS that aims to recruit 600 patients with an estimated primary completion date of October 2018 (NCT03465904).

1 ongoing RCT for the acute treatment (end in October 2018)

Reimbursement

The e-TNS is currently not reimbursed in the Austrian setting as part of the Austrians social health insurance coverage. As stated by the manufacturer, Cefaly® is reimbursed in the Netherlands, Switzerland, and in the USA for Veterans by Tricare.

e-TNS is not reimbursed in Austria

Discussion

quality of evidence for effectiveness (RCTs): low to very low, quality of evidence for safety (case series and RCTs): high, moderate, low, very low

Concerning the effectiveness (RCTs) of *prevention* and *acute treatment* with e-TNS, the quality of evidence was low to very low. The main reasons were the small sample size, uncertainty about sufficient reporting of adverse device effects, and the wrong comparator. Concerning safety, the quality of evidence ranged from high, moderate, to low and very low (as two case-series were judged to have a high risk of confounding as co-interventions were either not clearly described [13], or it was clearly stated that *preventive* as well as *acute treatments* for CM were not changed during the study [11]).

no standardized evaluation of satisfaction and quality of life, 24 hours follow-up for acute therapy too short

In terms of outcomes, standardized evaluation of satisfaction and quality of life was lacking, and the follow-up of 24 hours that was applied to all three *acute treatment* studies is considered short. Also, consistency of the effect of e-TNS is undermined because in medication studies, several attacks must be treated in one person to prove that the acute therapy works and that was not the case.

prevention studies represent real clinical context – e-TNS used at home, not the case for acute treatment, problem with compliance

In terms of generalizability of the data, the *prevention* studies represent the real clinical context, as the patients used the e-TNS in their homes, but the *acute treatment* studies were conducted in the hospital setting, yet the e-TNS should be used in the home setting for *acute treatment* as well. Compliance is considered to be one of the key issues as in the *preventive* RCT [9], it was 61.7% (IG) vs. 54.4% (CG) and it was not reported in the *acute treatment* RCT [10]. In the survey with 2,313 patients, 46.6% of patients were unsatisfied who, in terms of compliance, used the device for the recommended period of time only in 48.6% of cases [17].

advantages: improvement in patient autonomy, reduction in medication intake, non-invasive, economic savings; disadvantages: unclear mechanism of action, unclear long-term safety profile, small effects on VAS

While e-TNS has the potential to improve patients' autonomy and reduce the total medication intake, its non-invasive nature needs to be put in the context of the paucity of knowledge about its mechanism of action and thus its long term safety profile. It is not clear to what extent the electrical field applied in such close proximity to the brain for an extended period of time influences the brain. Furthermore, the potential cost-effectiveness of e-TNS associated with its potential improvement in economic productivity of migraine patients [18] needs to be contrasted with the small effects measured by the VAS.

conclusions about effectiveness and positive safety profile are considered inflated, target population are also drug responsive patients and hence an RCT with best practice comparators necessary

Furthermore, given the small size of the highly selective sample of patients included in the evidence base (as compared to the large burden of disease that migraine creates), the conclusions about effectiveness and the positive safety profile are considered to be inflated. The target population of e-TNS are not only patients refractory to medication, but mainly drug responsive patients, which makes e-TNS aim to replace the use of medication. That is why larger controlled trials with best practice interventions (for *prevention* as well as *acute treatment* use of e-TNS) as comparators are necessary for potentially considering e-TNS to be part of the standard practice.

Recommendation

e-TNS currently not recommended in the catalogue of benefits

The inclusion in the catalogue of benefits is currently not recommended.

Zusammenfassung

Einleitung

Gesundheitsproblem

Migräne = primäre Kopfschmerzstörung, Migräne mit Aura vs. Migräne ohne Aura, episodische Migräne (EM) vs. chronische Migräne (CM)

Laut der International Headache Society (IHS) ist Migräne eine primäre Kopfschmerzstörung, die durch periodische Attacken von Kopfschmerzen beschrieben wird und typischerweise von Appetitlosigkeit, Übelkeit, Erbrechen, Lichtempfindlichkeit und Lärm oder Geruch und Bewegungsüberempfindlichkeit begleitet wird [1]. Es können zwei Haupttypen unterschieden werden: Migräne mit Aura und Migräne ohne Aura. Beide Typen können die oben genannten Symptome umfassen, während mit Migräne mit Aura auch vorübergehende fokale neurologische Symptome einhergehen können, die Kopfschmerzen vorausgehen oder begleiten können [2]. Der Unterschied zwischen episodischer Migräne (EM) und chronischer Migräne (CM) liegt im Wesentlichen an der Häufigkeit der Kopfschmerztage [1]. Während bei einer EM Kopfschmerzen an weniger als 15 Tage pro Monat auftreten, liegt bei einer CM eine Häufigkeit von mehr als 15 Mal Kopfschmerzen pro Monat in den letzten drei aufeinander folgenden Monaten auf.

Migräne = dritthäufigste Invaliditätsurlache weltweit, EM häufiger bei Frauen, Hauptursache in der Genetik

Nach dem Global Burden of Disease 2015 wurde Migräne sowohl bei Männern als auch bei Frauen unter 50 Jahren als weltweit dritthäufigste Ursache von Invalidität eingestuft [2]. EM betrifft mehr als 10 % der Bevölkerung und hat eine höhere Prävalenz bei Frauen (18 %) als bei Männern (6 %) [1]. CM betrifft 1-5% der Allgemeinbevölkerung [1]. Da Migräne im Wesentlichen eine zerebrale Störung ist, wird angenommen, dass die Hauptursache von EM und CM in der Genetik liegt [3]. Die Progression von EM zu CM entwickelt sich mit einer Rate von etwa 2,5 % pro Jahr, MigränepatientInnen zeigen jedoch eine große intraindividuelle Variabilität und somit auch eine Rückentwicklung von CM zu EM [4].

Beschreibung der Technologie

e-TNS – Nervenstimulation des N. supraorbitalis durch elektrische Mikroimpulse als Präventionstherapie oder Akuttherapie

Bei der Anwendung des externe Trigeminus-Nervenstimulator (e-TNS) (Cefaly®) wird der obere Nervenast (N. supraorbitalis) des Trigeminusnervs stimuliert, um die Häufigkeit und Dauer von Migräneattacken zu reduzieren [5]. Der N. supraorbitalis endet an der Spitze der Kopfhaut, wodurch die Stirn, das obere Augenlid und die vordere Kopfhaut sensorisch innerviert werden. Die selbstklebende e-TNS-Elektrode wird stirnseitig auf den N. supraorbitalis gelegt [6]. Der batteriebetriebene elektrische Impulsgenerator verbindet sich magnetisch mit der Elektrode und leitet von dort elektrische Mikroimpulse ab [5]. Das e-TNS wird entweder zur Vorbeugung einer Migräneattacke durch tägliche 20-minütige Sitzungen oder als akute Behandlungsmethode für jeweils 60 oder 120 Minuten lange Interventionen während einer Migräneattacke verwendet. Die Pulsbreite von 250 µs und die maximale Intensität von 16 mA sind für beide Modi gleich, wohingegen sich die Pulsfrequenz zwischen präventiver und akuter Behandlung unterscheidet: während der präventiven Behandlung arbeitet das Gerät mit einer Pulsfrequenz von 100 Hz und im akuten Behandlungsmodus mit 60 Hz [5].

e-TNS von FDA als Präventionstherapie und Akuttherapie zugelassen, CE-Kennzeichnung für Europa

Im Jahr 2014 wurde das e-TNS-Gerät von der FDA als Medizinprodukt der Klasse II für die Indikation „prophylaktische Behandlung von episodischer Migräne bei PatientInnen über 18 Jahren“ zugelassen [7]. Im Jahr 2017 bewilligte die FDA auch die akute Migränebehandlung mit dem e-TNS-Gerät [8]. Nach Angaben des Herstellers trägt das e-TNS (Cefaly®)-Gerät seit Jänner 2008 auch in Europa die CE-Kennzeichnung für die breite Indikation Kopfschmerzen.

geringere Häufigkeit und Dauer von Migräneattacken, weniger invasive Therapie, reduzierte Einnahme von Anti-Migräne-Medikamenten

Der erwartete Vorteil von e-TNS ist die Verringerung der Häufigkeit und Dauer von Migräneattacken. Zusätzlich scheint das Gerät weniger invasiv zu sein, da es ein besseres Verhältnis von Effektivität und Sicherheit, weniger Nebenwirkungen, keine ernsthaften Nebenwirkungen und weniger Kontraindikationen vorweisen soll. Darüber hinaus wird behauptet, dass die akute Einnahme von Anti-Migräne-Medikamenten durch die Anwendung von e-TNS reduziert wird, wodurch Kopfschmerzen durch Medikamentenübergebrauch verhindert werden könnten.

Methoden

Ziel: e-TNS vs. Standardtherapie oder Placebo in Bezug auf Wirksamkeit und Sicherheit

Ziel dieser systematischen Übersichtsarbeit war es, zu untersuchen, ob e-TNS als präventive oder akute Therapie wirksamer und sicherer ist als eine medikamentöse Standardtherapie oder eine Placebo-Therapie hinsichtlich der Verbesserung von Migränepisoden, der Lebensqualität, der Zufriedenheit und der Nebenwirkungen. Das EUnetHTA-Core-Modell für schnelle Assessments zur relativen Wirksamkeit war die wichtigste Quelle für die Auswahl relevanter Bewertungselemente.

systematische Literatursuche in 4 Datenbanken, 433 Treffer

Die systematische Literatursuche wurde in den folgenden vier Datenbanken durchgeführt (Medline via Ovid, Embase, The Cochrane Library, CRD (DARE, NHS-EED, HTA)). Die Suche beschränkte sich nicht auf ein Publikationsjahr, jedoch auf prospektive Studien und Artikel in englischer oder deutscher Sprache. Nach der Deduplizierung wurden insgesamt 433 Zitate gezählt.

Suche nach laufenden klinischen Studien in klinischen Studienregistern

Darüber hinaus wurden die folgenden klinischen Studienregister (ClinicalTrials.gov, WHO-ICTRP, EU-klinische Studien) für die Suche nach registrierte laufende klinische Studien oder Beobachtungsstudien herangezogen. Die Suche ergab 70 Ergebnisse, von denen sieben relevant waren.

19 Veröffentlichungen von Hersteller erhalten, Handsuche weitere 7 Treffer

Der einzige Hersteller von e-TNS (Cefaly®) reichte 19 Veröffentlichungen ein, von denen vier zum Zeitpunkt der Verfassung des Berichts noch nicht veröffentlicht waren und daher vertraulich behandelt wurden. Keine neuen Zitate wurden identifiziert. Bei der Handsuche wurden weitere sieben Publikationen gefunden, was insgesamt 440 Treffer ergab.

Ergebnisse

Verfügbare Evidenz

2 RCTs für Wirksamkeit: 1 für Prävention, 90 Tage Follow-up und 1 für Akuttherapie, 24h Follow-up, Komparator: Placebo, von STX Med – Cefaly® Technology gesponsert

Zur Beurteilung der klinischen Wirksamkeit erfüllten zwei Studien die Einschlusskriterien. Eine randomisierte kontrollierte Studie (RCT) für die präventive Verwendung von e-TNS [9] und ein RCT für die Akutbehandlung mit e-TNS [10]. Beide verglichen das e-TNS (Cefaly®) mit einem Placebo-Gerät. Das RCT zur Akuttherapie [10] erfolgte nicht in Form einer begutachteten Publikation, sondern in Form eines Studienprotokolls und der Studienergebnisse, die bei clinicaltrials.gov veröffentlicht wurden. Die Studien wurden vom Hersteller STX Med – Cefaly® Technology oder von der Wallonischen Region (wo der Hersteller die e-TNS-Geräte anbietet) gesponsert. In

der präventiven Studie [9] betrug die Nachbeobachtungszeit 90 Tage und umfasste 67 PatientInnenen (34 erhielten e-TNS). Während die Nachbeobachtungszeit der akuten Behandlungsstudie [10] 24 Stunden betrug und 106 PatientInnen (52 erhielten e-TNS) umfasste.

Zur Beurteilung der Sicherheit erfüllten sieben Studien die Einschlusskriterien. Diese umfassten die zwei oben beschriebenen RCTs [9, 10], und fünf prospektive Fallserien (drei zur Prävention mit insgesamt 84 Patienten [11-13] und zwei zur Akutbehandlung mit insgesamt 95 Patienten [14, 15]). Eine der Fallserienstudien [15] wurde nicht in Form einer Peer-Review-Veröffentlichung, sondern in Form eines Studienprotokolls und der Studienergebnisse bei clinicaltrials.gov veröffentlicht. Drei der Fallserienstudien [13-15] wurden von STX Med – Cefaly® Technology gesponsert. Bei den Übrigen [11, 12] war die Finanzierung unklar, es wurde jedoch angegeben, dass die Geräte vom Hersteller bereitgestellt wurden. In den präventiven Fallserienstudien [11-13] lag die Nachbeobachtungsdauer zwischen 60 und 120 Tagen, während in den Akutbehandlungsstudien [14, 15] die Nachbeobachtungszeit bei 24 Stunden lag.

7 Studien für Sicherheit: 2 RCTs und 5 prospektive Fallserien – 3 Prävention mit 60 und 120 Tagen Follow-up und 2 Akuttherapie mit 24h Follow-up

Klinische Wirksamkeit

Bezüglich der Präventionsbehandlung mit e-TNS zeigten die Ergebnisse der RCT (34 e-TNS-PatientInnen), dass die Behandlung mit e-TNS bei EM-PatientInnen wirksamer ist als die Placebo-Behandlung, gemessen durch die Reduktion der Migräneanfälle (0,67 weniger Migräneattacken pro Monat), Migränetage (1,74 weniger Migränetage pro Monat), Kopfschmerztage (2,28 weniger Kopfschmerztage pro Monat), akute Anti-Migräne-Medikamenteneinnahme (4,24 weniger Fälle von akuter Medikamenteneinnahme pro Monat) und Steigerung der Responderrate (26,2 % mehr Reaktion auf e-TNS-Behandlung) und der Zufriedenheit (31,2 % Unterschied in der Zufriedenheit mit der Kontrollgruppe) [9].

Prävention: e-TNS bei EM-Pat. wirksamer als Placebo

In Bezug auf die Akutbehandlung mit e-TNS zeigte das RCT, dass e-TNS eine Verbesserung der Schmerzreduktion auf einer VAS-Skala (von 11 Punkten) nach 1/2/24 Stunden nach der Akutbehandlung im Vergleich zur Placebo-Behandlung bewirkte (Reduktion um 1,68/1,02/1,08 VAS-Punkte) [10]. Bezüglich des minimalen, klinisch wichtigen Unterschieds (MCID) bleibt jedoch unklar, ob die gemessene Verbesserung auf der VAS-Skala von klinischer Bedeutung ist, da die Ergebnisse um das untere Ende der klinisch relevanten Nutzenschwellenwerte schwanken [16]. Es gab auch eine Zunahme von einem Patienten in der Interventionsgruppe bezüglich der akuten Anti-Migräne-Medikamenteneinnahme zwei Stunden nach der akuten e-TNS-Behandlung im Vergleich zur Kontrolle, aber eine Abnahme von drei PatientInnen im Vergleich zur Kontrolle nach 24 Stunden [10].

Akuttherapie: e-TNS vs. Placebo → Verbesserung der Schmerzempfindung → MCID jedoch unklar + weniger Pat mit Medikamenteneinnahme 24h nach e-TNS Therapie

Sicherheit

Was die Sicherheit betrifft, so traten sowohl in den Studien zur Vorbeugung als auch in der Akutbehandlung keine schwerwiegenden Nebenwirkungen auf.

keine schwerwiegenden Nebenwirkungen in keiner Studie

In zwei Präventionsstudien kam es auch zu keinen sonstigen Nebenwirkungen [9, 12], wohingegen bei 34,3 % der PatientInnen in [13] eine Intoleranz gegenüber Parästhesien berichtet wurde. Darüber hinaus wurden in einer Studie Kopfschmerzen nach der Stimulation (8.7 % der PatientInnen), sowie Nackenverspannungen (4.3 %) berichtet [11].

Prävention – sonstige Nebenwirkungen: Intoleranz gegenüber Parästhesien, Kopfschmerzen, etc.

Akuttherapien – sonstige Nebenwirkungen: Intoleranz gegenüber Parästhesien, Übelkeit, etc.

Im Hinblick auf Nebenwirkungen in den Akutbehandlungsstudien berichtete eine Studie, dass es zu keinen Nebenwirkungen kam [14, 15], während eine Intoleranz gegenüber Parästhesien in zwei Akutbehandlungsstudien bei 5,8% (IG n = 52) vs. 1,9 % (CG n = 54) [10] und 11,9 % der PatientInnen auftrat [15]. Übelkeit nach der Stimulation wurde in zwei Studien in 1,9 % (IG n = 52) gegenüber 0 % (CG n = 54) [10] und 3,5 % der PatientInnen berichtet [10].

weite Nebenwirkungen: Sensibilitätsveränderungen, Schwindel, Erbrechen, etc.

Darüber hinaus traten in 1,7 % der Fälle Sensibilitätsveränderungen (Schlaflosigkeit, Schläfrigkeit/Müdigkeit, Benommenheit), Schwindel, Erbrechen, Kieferschmerzen, Zahnbeschwerden, Augenschmerzen und kalte Füße auf [10]. In derselben Studie berichteten 18,3 % der PatientInnen über eine Hautallergie/-reizung.

Laufende Studien

1 laufendes RCT zur e-TNS Akutbehandlung (Okt. 2018)

Zurzeit gibt es lediglich ein laufendes RCT für die Akutbehandlung von e-TNS, das 600 PatientInnen umfasst, die mit einem geschätzten primären Abschlussdatum im Oktober 2018 rekrutieren werden sollen (NCT03465904).

Kostenerstattung

e-TNS in Österreich nicht erstattet

Die Kosten für das e-TNS Gerät werden derzeit im Rahmen der österreichischen gesetzlichen Krankenversicherung in Österreich nicht erstattet. Wie vom Hersteller angegeben, wird Cefaly® in den Niederlanden, der Schweiz und in den USA für Veterans by Tricare erstattet.

Diskussion

Qualität der Evidenz zur Wirksamkeit (RCT) niedrig – sehr niedrig, Qualität der Evidenz zur Sicherheit hoch, moderat, niedrig und sehr niedrig

In Bezug auf die Wirksamkeit (RCTs) von e-TNS war die Qualität der Evidenz (Prävention und Akutbehandlung) niedrig bis sehr niedrig. Die Hauptgründe dafür waren der kleine Stichprobenumfang, die Unsicherheit bezüglich ausreichender Berichterstattung von Nebenwirkungen und die Wahl des falschen Komparators. Bezüglich der Sicherheit von e-TNS, reichte die Qualität der Evidenz von hoch, moderat, zu niedrig und sehr niedrig. Zwei Fallserien weisen ein hohes Risiko von Störvariablen auf, da Kointerventionen entweder nicht eindeutig beschrieben wurden [13], oder klar festgehalten wurde, dass sowohl präventive als auch akute CM-Behandlungen während der Studie nicht verändert wurden [11].

keine standardisierte Bewertung für Zufriedenheit und Lebensqualität, 24h Follow-up für Akuttherapiestudien zu kurz

In Bezug auf die gewählten Endpunkte fehlte eine standardisierte Bewertung für Zufriedenheit und Lebensqualität. Das Follow-up Intervall von 24 Stunden, das in allen drei Akutbehandlungsstudien angewendet wurde, wird als zu kurz erachtet. Außerdem wurde die Bestätigung der Wirkung von e-TNS geschwächt, da in Medikationsstudien mehrere Migräneattacken bei einer Person behandelt werden müssen, um zu beweisen, dass die Akuttherapie funktioniert und dies aber nicht der Fall war.

Präventionsstudien repräsentieren tatsächlichen klinischen Kontext – e-TNS Anwendung zuhause → für Akuttherapiestudien ebenfalls notwendig, Problematik der Anwendung: Compliance

Bezüglich der Generalisierbarkeit der Daten stellen die Präventionsstudien den tatsächlichen klinischen Kontext dar, da die PatientInnen das e-TNS in ihrem Zuhause anwenden konnten. Die Akutbehandlungsstudien wurden jedoch im Krankenhaus durchgeführt. Auch für die Akutbehandlungsstudien sollte das e-TNS in häuslicher Umgebung angewendet werden. Compliance wird als eines der Hauptprobleme angesehen, wie im präventiven RCT [9] veranschaulicht: 61,7 % (IG) vs. 54,4 % (CG). Im Akutbehandlungs-RCT wurden keine Compliance-Raten berichtet [10]. Eine Befragung mit 2.313 PatientInnen ergab, dass 46,6 % der PatientInnen unzufrieden mit dem e-TNS-

Gerät waren. Die PatientInnen nutzten das Gerät (in Bezug auf Compliance) lediglich in 48,6 % der Fälle für den empfohlenen Zeitraum [17].

e-TNS hat zwar den Vorteil, die Autonomie der PatientInnen zu verbessern und die Gesamteinnahme von Medikamenten zu reduzieren. Jedoch muss die nicht-invasive Natur in den Kontext des Mangels an Wissen über den Wirkungsmechanismus und somit über das langfristige Sicherheitsprofil gestellt werden. Es ist nicht klar, in welchem Ausmaß das elektrische Feld, das in solch einer Nähe zum Gehirn für eine längere Zeit angewendet wird, das Gehirn beeinflusst. Darüber hinaus muss die potentielle Kosteneffektivität von e-TNS, die mit einer potenziellen Verbesserung der wirtschaftlichen Produktivität von MigränepatientInnen in Zusammenhang steht [18], mit den kleinen Auswirkungen verglichen werden, die von der VAS ableitbar sind.

Vorteile: Autonomie der Pat., Reduktion der Medikamenteneinnahme, jedoch mangelnde Evidenz zum Wirkungsmechanismus und zum langfristigen Sicherheitsprofil

Insgesamt werden die Schlussfolgerungen über die Wirksamkeit und das positive Sicherheitsprofil des e-TNS-Geräts als überhöht angesehen. Begründet wird dies aufgrund der kleinen Größe der hochselektiven PatientInnenstichprobe (verglichen mit der großen Krankheitslast, die Migräne verursacht). Die Zielpopulation von e-TNS sind nicht nur PatientInnen, die refraktär auf Medikamente reagieren, sondern ebenso auf Arzneimittel ansprechende PatientInnen, um zu untersuchen, in welchem Ausmaß e-TNS eine Verringerung der Medikamenteneinnahme mit sich bringt. Aus diesem Grund sind größere kontrollierte Studien mit Best-Practice-Interventionen (zur Prävention und zur Akutbehandlung von e-TNS) als Komparatoren erforderlich, um e-TNS möglicherweise als Teil der Standardpraxis zu betrachten.

Schlussfolgerungen überschätzt, aufgrund zu kleiner Stichprobengröße im Vergleich zur Krankheitslast von Migräne, größere RCTs mit Best-Practice-Interventionen als Vergleichstherapie erforderlich

Empfehlung

Die Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen.

e-TNS derzeit nicht für Aufnahme in den Leistungskatalog empfohlen

1 Scope

1.1 PICO question

PIKO-Frage

Is the e-TNS, as a preventive or acute therapy, in comparison to placebo or the standard therapy (triptan, NSAIDs/paracetamol, or combination of triptan together with NSAIDs/paracetamol for acute treatment or topiramate and propranolol for prevention) in patients with episodic or chronic migraine more effective or equally effective concerning improvement in migraine episodes, quality of life (QoL), and satisfaction; and safer regarding the side effects?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Prophylactic or acute therapy in adult patients with episodic and chronic migraine. MeSH-term: Headache Disorders, Migraine Disorders ICD-10 code: G43.909	
Intervention	External trigeminal nerve stimulation (e-TNS) Supraorbital transcutaneous nerve stimulation (s-TNS) – original name changed after GMDN code to e-TNS Product name: Cefaly® MeSH-term: Trigeminal Nerve, Electrical Stimulation	
Control	*Acute treatment*: • NSAIDs/Paracetamol • Triptan • Triptan + NSAIDs/Paracetamol • Placebo MeSH-term: Anti-Inflammatory Agents, Non-Steroidal	*Prevention*: • Topiramate • Propranolol • Placebo MeSH-term: Propranolol, Topiramate
Outcomes		
Efficacy	Crucial outcomes for the *preventive* use of e-TNS: • Reduction in monthly migraine days • Reduction in monthly acute antimigraine drug intake • Satisfaction Crucial outcomes for the *acute treatment* use of e-TNS: • Change in pain score units on VAS scale compared to baseline at 1/2/24 hours • Patients on acute antimigraine medication at 2/24 hours • Satisfaction Further outcomes for the *preventive* use of e-TNS: • Reduction in monthly migraine attacks • Reduction in monthly headache days • Responder rate • QoL • Compliance	

Efficacy *(continuation)*	Further outcomes for the *acute treatment* use of e-TNS: ❖ Headache pain free patients at 2/24 hours post-*acute treatment* ❖ Improvement in nausea, vomiting, sensitivity to light and sound at 2 hours ❖ QoL ❖ Compliance
Safety	Crucial Serious adverse device effects (SADEs) for both *preventive* and *acute treatment* use of e-TNS: ❖ SADEs Further Adverse device effects (ADEs) for both *preventive* and *acute treatment* use of e-TNS: ❖ Pain/intolerance to paraesthesia (burning sensation) ❖ Arousal changes (insomnia, sleepiness/fatigue) ❖ Headaches after stimulation ❖ Skin allergy ❖ Neck tension ❖ Nausea after stimulation ❖ Dizziness ❖ Vomiting ❖ Pain in the jaw ❖ Discomfort in teeth ❖ Pain in eyes ❖ Cold feet
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is e-TNS and the comparator(s)?
A0020	For which indications has e-TNS received marketing authorisation or CE marking?
B0002	What is the claimed benefit of e-TNS in relation to the comparators?
B0003	What is the phase of development and implementation of e-TNS and the comparator(s)?
B0004	Who administers e-TNS and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use e-TNS and the comparator(s)?
B0009	What supplies are needed to use e-TNS and the comparator(s)?
A0021	What is the reimbursement status of e-TNS?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is e-TNS used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for episodic/chronic migraine?
A0004	What is the natural course of episodic/chronic migraine?
A0005	What is the burden of disease for the patients with episodic/chronic migraine?
A0006	What are the consequences of episodic/chronic migraine for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the episodic/chronic migraine currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is e-TNS utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of e-TNS on mortality?
D0003	What is the effect of e-TNS on the mortality due to causes other than the target disease?
D0005	How does e-TNS affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does e-TNS affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of e-TNS on patients' body functions?
D0016	How does the use of e-TNS affect activities of daily living?
D0012	What is the effect of e-TNS on generic health-related quality of life?
D0013	What is the effect of e-TNS on disease-specific quality of life?
D0017	Was the use of e-TNS worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is e-TNS in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying e-TNS?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of e-TNS?
C0007	Are e-TNS and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of e-TNS and the comparator(s)?

2.2 Sources

Description of the technology

Quellen

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturer

Health problem and Current Use

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Handsearch of clinical guideline (AHRQ, Up-to-date, EBM guidelines)
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturer

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted in the following four databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

Einschränkungen nach Studiendesign und Sprache
433 Hits

The systematic search was not limited to a year of publication. The search was limited to prospective studies and articles published in English or German. After deduplication, overall 433 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden klinischen Studien

Furthermore, the following clinical trial registries were assessed for registered ongoing clinical trials or observational studies: ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials. The search yielded 70 results, of which 7 were relevant to the research question under assessment. For detailed search strategies, see the appendix.

keine zusätzlichen Publikationen durch Hersteller

The only manufacturer of e-TNS (Cefaly®) submitted 19 publications of which 4 were unpublished at the time of writing of the report and hence were confidential and not included. No new citations were identified.

nach Handsuche
440 Treffer

By hand-search, additional 7 publications were found, resulting in overall 440 hits.

2.4 Flow chart of study selection

Literaturauswahl

Overall 441 hits were identified. The references were screened by three independent researchers and all disagreements were solved through discussion. The selection process is displayed in Figure 2-1.

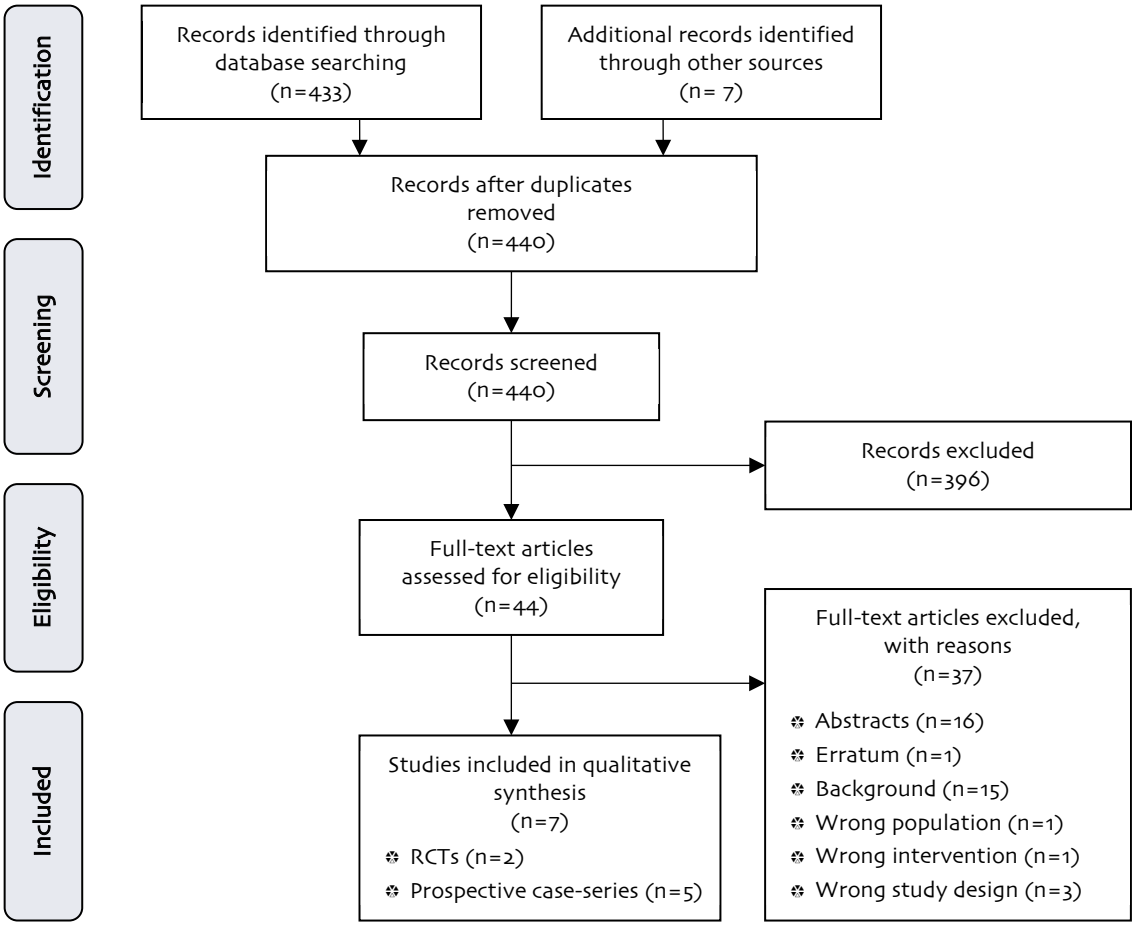

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion und Evaluierung des RoB und der Evidenzstärke durch 3 unabhängige WissenschafterInnen

The data retrieved from the selected studies were systematically extracted into a data-extraction-table (see Appendix Tables A-1 to A-4). No further data pro-cessing (e.g. indirect comparison) was applied. Three independent researchers (MS, SW, HJ) systematically assessed the quality of evidence (see Tables 7-1 and 7-2) and the risk of bias (RoB) using the checklists presented in the Appendix Tables A-5 and A-6).

2.6 Synthesis

Datensynthese auf Outcome-Level mittels GRADE

Based on the data-extraction-table (see Appendix Tables A-1 to A-4), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [36]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Tables 7-1 and 7-2).

3 Description and technical characteristics of the technology

Features of the technology and comparators

B0001 – What is e-TNS and the comparator(s)?

The external trigeminal nerve stimulator (e-TNS) (Cefaly®) is an intervention that stimulates the upper nerve branch (supraorbital nerve) of the trigeminal nerve (the fifth cranial nerve) with the aim of reducing the frequency and length of migraine attacks [5]. The supraorbital nerve ends at the vertex of the scalp, thus providing sensory innervation to the forehead, upper eyelid, and anterior scalp. The self-adhesive e-TNS electrode is placed at the forehead targeting the supraorbital nerve [6]. The battery-operated electrical pulse generator connects magnetically to the electrode from where it conducts electrical micro-pulses to the upper branch of the trigeminal nerve (see Figure 3-1) [5]. The e-TNS is either used for the *prevention* of a migraine attack through daily 20-minute-sessions, or it is used for *acute treatment* as a 60 or 120 minutes long intervention during the migraine attack. The pulse width of 250 µs and maximum intensity of 16 mA is the same for both modes, but the *preventive* mode has the pulse frequency of 60 Hz, while the *acute treatment* mode has 100 Hz [5].

e-TNS soll durch elektrische Impulse den supraorbitalen Nerv stimulieren – Reduktion der Häufigkeit und Dauer einer Migräneattacke

e-TNS für Prävention und akute Therapie

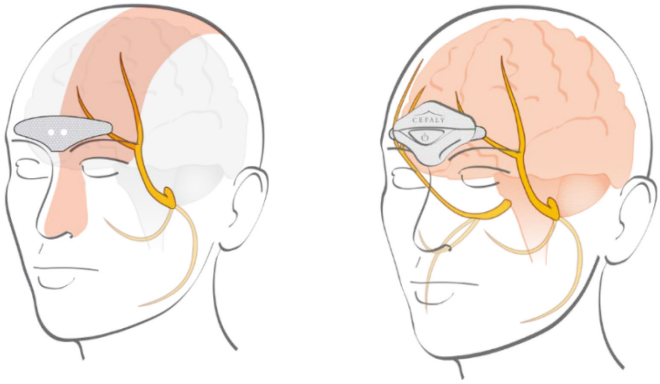

Figure 3-1: e-TNS (Cefaly®) electrode and electrical pulse generator.

There is a lack of clarity about the pathophysiology of migraine and hence also about the exact mechanism of action of e-TNS. One assumption is that migraine attacks are triggered by the physiological communication between first cervical spinal nerve roots and the spinal trigeminal tract [19]. The application of e-TNS to the supraorbital nerve is then supposed to use this nerve pathway to spread the impulse from the frontalis muscle to peripheral muscles, which may make it recorded in other muscles far from the application area [19]. In this way, the e-TNS could act therapeutically on the inhibitory circuit in the spinal cord causing a neuromuscular facilitation and a reduction in contractions of frontalis muscles [19]. Alternatively, another assumption is that e-TNS exerts its beneficial effects via slow neuromodulation of central pain-controlling areas [20]. It is assumed that it reduces the hypometabolism of the orbitofrontal cortex as well as the rostral parts of the anterior cingulate cortex as the metabolic activity in these areas is decreased in mi-

unklare Pathophysiologie von Migräne und unklarer Wirkmechanismus von e-TNS:
1 Annahme: e-TNS für neuromuskuläre Erleichterung und eine Verringerung der Kontraktionen
2. Annahme: e-TNS für langsame Neuromodulation zentraler Schmerzkontrollbereiche

graine [20]. Furthermore, e-TNS may interfere with the threshold and the extent of trigeminal system activation, thus resolving or preventing migraine attacks [21].

akute Therapie: rezeptfreie und rezeptpflichtige Alternativen für episodische und chronische Migräne

Alternative treatments concern both *prevention* as well as *acute treatment* of episodic (EM) as well as chronic migraine (CM). In terms of treatment, most EM patients with few migraine attacks can be managed with acute therapy such as over the counter nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol. Those can be taken alongside prescription medication in the class of triptans or vasoactive medication (dihydroergotamine) [1]. Both NSAID's/ paracetamol as well as triptans/dihydroergotamine are used as monotherapies, while combination use is only recommended if necessary [1].

unterschiedliche präventive Therapien für episodische und chronische Migräne

The main group of candidates for preventive treatment are those patients who have contraindications or severe adverse events associated with acute medications, or those with infrequent, but very severe and lengthy attacks [1]. Preventive treatment options for EM include non-drug interventions such as acupuncture, relaxation, cognitive behavioural therapy, or stress management [22].

In Austria, first line preventive treatment options include Metoprolol, Propranolol, Flunarizin, Topiramate, and Valproat, while second-line substances are Amitriptylin, Sartane, Venlafaxin [23]. Preventive treatment options for CM are the injection of Onabotulinumtoxin A [1].

alternative Neuromodulations-interventionen für episodische und chronische Migräne

There are also other alternative neuromodulation interventions for both EM and CM that are not part of standard clinical practice such as non-invasive single pulse transcranial magnetic stimulation, transcranial direct current stimulation, or non-invasive vagus nerve stimulation [24]. Invasive neuromodulation techniques include occipital nerve stimulation [24].

alternative Neuromodulations-behandlungen: nicht-invasive transkranielle Magnetstimulation (TMS): fluktuierendes Magnetfeld induziert Ionenstrom zu darunterliegendem Kortex

Non-invasive single pulse transcranial magnetic stimulation (TMS) is an intervention that has been in use over 30 years for the treatment of depression, epilepsy, movement disorders of neurorehabilitation [24]. It is applied externally to the scalp through the use of a coil that creates a fluctuating magnetic field, inducing an ionic current to the underlying cortex. The current then aims to change the firing pattern and excitability of cortical neurons [24]. While single pulse claims to depolarize neurons, repetitive pulse stimuli claim to modify the plasticity of the cerebral cortex even in remote areas inducing functional activation or deactivation in the brain [22]. A recent systematic review of TMS suggests that its evidence base consists of five RCTs with the total of 313 patients concluding the TMS' effectiveness [25].

transkranielle Gleichstromstimulation (DCS): reversible Veränderungen der Erregbarkeit von Neuronen

Transcranial direct current stimulation (DCS) is a neuromodulation technique that, similarly to TMS, can cause reversible changes of the excitability of neurons by acting on their membrane potential when applied to the cortex [24]. The evidence base for DCS is small as a sham RCT showed no significant effect of DCS and its only data come from a proof of concept case series study with ten patients in whom the frequency of migraine attacks was claimed to be reduced [24].

nicht-invasive Vagus-Nervenstimulation (VNS): unklarer Wirkmechanismus

Non-invasive vagus nerve stimulation (VNS) is an intervention with an unclear mechanism of action and a small evidence base [22, 24]. The main hypothesis is the afferent anatomical connection between the vagus nerve and the trigeminal nucleus caudalis as well as the nociceptive inputs from the dura mater terminating in the nucleus tracturs solitarius could justify an ascending antinociceptive effect of the vagus nerve on the trigeminal nuclear complex (thus influencing migraine attacks) [24].

Invasive occipital nerve stimulation (ONS) aims to inhibit nociceptive activity in small c-fiber and A-delta fibers through the stimulation of the occipital nerve [22]. The occipital nerve originates at the base of the neck where the ONS device is connected with leads to a power source. Centrally, ONS reduces activation of brain regions involved in pain processing and thus may improve migraine symptoms. The evidence base for ONS includes four multicentre RCTs where some conclude that it does while others that it does not improve migraine symptoms in statistically significant ways [22].

invasive Okzipitalnervenstimulation (ONS): Hemmung der nozizeptiven Aktivität in kleinen c-Faser und A-Delta-Fasern durch Stimulation des Occipitalisnervs

A0020 – For which indications has e-TNS received marketing authorisation or CE marking?

In 2014, the e-TNS device was approved by the FDA as a Class II medical device for the indication of "prophylactic treatment of episodic migraine in patients over the age of 18". Furthermore, the FDA stated in 2012 that "the Cefaly® device should not be used by an individual with chronic migraine, refractory migraine, medication overuse headache, or chronic tension-type headaches" [7], but in 2017 granted also the *acute* migraine *treatment* approval [8]. According to information provided by the manufacturer, the e-TNS (Cefaly®) device also bears a CE mark in Europe from January 2008 for the broad indication of headaches.

2014 FDA Zulassung für Prävention, 2017 FDA Zulassung für akute Therapie 2008 CE Kennzeichnung für Kopfschmerzen

B0002 – What is the claimed benefit of e-TNS in relation to the comparators?

The claimed benefit of e-TNS is the reduction of the frequency and length of migraine attacks. When compared to pharmacological therapy for both EM and CM patients, e-TNS claims to be less invasive, have a better effectiveness-safety ratio, less side effects, no serious side effects, and fewer contraindications. Thus, allegedly, it provides an *acute treatment* option for EM patients who refuse medication. Furthermore, e-TNS claims to reduce the acute antimigraine drug intake, thus preventing medication overuse headache (MOH), providing an *acute treatment* option to drug refractory patients, and thus possibly postponing/preventing deterioration of EM to CM.

angenommener Nutzen: Reduktion der Häufigkeit und Dauer von Migräneattacken, keine schwerwiegenden Nebenwirkungen, Prävention von medikamenteninduzierten Kopfschmerzen

B0003 – What is the phase of development and implementation of e-TNS?

It is a novel technology that is in its emerging phase with its pilot study published in 2009, hence it is not part of standard clinical practice [26]. The current device is the second generation that is identical to the first one in terms of function, but that changed the latching mechanism of the pulse generator onto the electrode to be magnetic.

neue Technologie: Pilotstudie aus 2009, nun 2 Generation

By 2018, there have been a total of seven prospective clinical studies published on the *prevention* and *acute treatment* both EM as well as CM.

2018: 7 prospektive klinische Studien zu Prävention und akuter Therapie publiziert

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers e-TNS and the comparator(s) and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use e-TNS and the comparator(s)?

Gerät von PatientInnen selbst anwendbar

offizieller Vertreiber ist belgischer Hersteller

The e-TNS is administered in the home setting by patients, which requires no special premises to be used for the administration of e-TNS. In terms of its distribution, the official distributor is the Belgian manufacturer CEFALY®-Technology. In Germany, it is BOSANA Medizintechnik GmbH [37] and in Austria, the company Linde.

B0009 – What supplies are needed to use e-TNS and the comparator(s)?

für Anwendung selbstklebende Elektroden und e-TNS Gerät notwendig

The supplies needed for the use of e-TNS are a set of self-adhesive electrodes and the e-TNS device.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of e-TNS?

erstattet in NL, CH, 1 Versicherung in USA, nicht in Österreich

The e-TNS is currently not reimbursed in the Austrian setting as part of the Austrian social health insurance coverage. As stated by the manufacturer, Cefaly® is reimbursed in the Netherlands, Switzerland, and in the USA for Veterans by Tricare.

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is e-TNS used?

A0002 – What is the disease or health condition in the scope of this assessment?

The e-TNS is used for both *prevention* and *acute treatment* of EM as well as CM patients. According to the International Headache Society (IHS), migraine is a primary headache disorder described by periodic attacks of headache, typically accompanied by collateral symptoms, such as loss of appetite, nausea, vomiting, sensitivity to light (photophobia), to noise (phenophobia) or to odor, and movement hypersensitivity [1]. Migraine has two major types, migraine with aura and migraine without aura. Both may share the above symptoms, while migraine with aura also includes transient focal neurological symptoms that may precede or accompany a headache [2].

Migränesymptome mit/ohne Aura: Appetitlosigkeit, Übelkeit, Erbrechen, hypersensibel auf Licht, Lärm und Geruch, Bewegungsüberempfindlichkeit

The difference between EM and CM lies in frequency of headache days [1]. While EM is defined as migraine with or without aura that occurs less than 15 times per month, CM is defined by headaches that occur more than 15 times per month in the last three consecutive months of which eight or more days meet criteria for migraine with or without aura and/or respond to migraine-specific treatment. Furthermore, these symptoms must occur in a patient with a lifetime history of at least five prior migraine attacks not attributed to another causative disorder and no medication overuse [2].

episodische Migräne (EM): <15 Tage/Monat

chronische Migräne (CM): >15 Tage/Monat in den letzten 3 Monaten

A0003 – What are the known risk factors for episodic/chronic migraine?

A0004 What is the natural course of episodic/chronic migraine?

As migraine is essentially a cerebral disorder, the major cause of EM and CM is genetics [3]. The progression from EM to CM, however, develops at a rate of about 2.5% per year. Important to note, however, is that a substantial number of patients also converts back from CM to EM and hence, the relationship between the two is not only one way [4]. Migraine patients show a great intra-individual variability in the frequency of migraine attacks [4].

Migräne = Hirnstörung Genetik als Hauptursache; Progression von EM zu CM, Rückentwicklung von CM zu EM auch möglich

Furthermore, migraine tends to peek in midlife and can be caused by further modifiable and non-modifiable factors [1]. Modifiable factors include obesity, snoring, low educational level, and low socioeconomic status, stressful life events, asthma, allergic rhinitis, head and neck injury, and comorbid depression [1]. Non-modifiable factors include older age, female gender, Caucasian ethnicity, genetics, and the presence of cutaneous allodynia [1].

veränderbare Faktoren: z. B. Übergewicht, Schnarchen, Stress, Kopf-Hals-Verletzung; nicht-veränderbare Faktoren: z. B. Alter, weibliches Geschlecht

Migraine is a chronic disease that can occur over an individual's lifetime. Migraine attacks usually last between four to 72 hours and can be triggered by a variety of factors such as stress, menstruation, birth control pills, physical exertion and fatigue, lack of sleep, hunger, head trauma, and certain foods or drinks that contain chemicals such as nitrites, glutamate, aspartate, tyramine. It can be further triggered by specific medications and chemicals that include nitroglycerin, estrogens, hydralazine, perfumes, smoke, and organic solvents with a strong odor [27].

Migräneattacken zwischen 4-72 h; Auslöser: Stress, Menstruation, körperliche Anstrengung, Nahrungsmittel und Medikamente

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with episodic/chronic migraine?

EM: 10% der Bevölkerung – Prävalenz höher für Frauen als Männer (18 % vs. 6 %)

CM: 1-5 % der Bevölkerung – höhere Invalidität, geringere HRQoL, höhere Depressionsrate als EM

According to Global Burden of Disease 2015, migraine was ranked to be the third-highest cause of disability worldwide in both males and females under the age of 50 years [2]. EM affects more than 10% of the population and has higher prevalence in women (18%) than in men (6%) [1]. CM affects 1-5% of the general population and compared to EM, CM patients tend to experience more headache related disability, decreased headache-related quality of life (HRQoL), greater healthcare utilization, and higher levels of anxiety and depression [22]. The main burden of disease lies in periodic attacks of headache that are typically associated with accompanying symptoms listed above.

A0006 – What are the consequences of episodic/chronic migraine for the society?

75-90 % der wirtschaftlichen Belastung durch Fehlzeiten am Arbeitsplatz, da höchste Inzidenzrate zwischen 35. und 45. Lebensjahr

The consequences of EM and CM for the society lie not only in the costs related to mainly pharmacological treatment, but also in the costs from a societal perspective (economic costs) that are present when migraine attacks impede on a person's life, particularly on work activity. That is especially true because on the high prevalence on migraine in general and the fact that the highest incidence of migraine attacks occurs between the 35th and 45th year of life in particular. The main part of this economic burden is borne by employers who have to cover for the reduced workplace productivity that makes 75-90% of the total economic cost of migraine [18].

Current clinical management of the disease or health condition

A0024 – How is episodic/chronic migraine currently diagnosed according to published guidelines and in practice?

Diagnose von Migräne nach den ICHD-3 Kriterien

For the diagnosis of migraine, the International Classification of Headache Disorders 3rd edition (ICHD-3) criteria are used as the common tool [2]. The ICHD-3 criteria distinguish between EM that can be with or without aura, and CM.

Diagnosekriterien für Migräne ohne Aura:
A: ≥5 Attacken mit Kriterien B-D
B: Kopfwehattacken von 4-72 hrs
C: 2/4 Kriterien
D: 1/2 Symptomen

The diagnostic criteria for migraine without aura are:

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache with at least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache at least one of the following symptoms occur:
  - nausea and/or vomiting
  - photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

The diagnostic criteria for migraine with aura are:

- A. At least five attacks fulfilling criteria B and C
- B. One or more of the following fully reversible aura symptoms:
  - visual
  - sensory
  - speech and/or language
  - motor
  - brainstem
  - retinal
- C. At least three of the following six characteristics:
  - at least one aura symptom spreads gradually over ≥5 minutes
  - two or more aura symptoms occur in succession
  - each individual aura symptom lasts 5-60 minutes
  - at least one aura symptom is unilateral
  - at least one aura symptom is positive
  - the aura is accompanied, or followed within 60 minutes, by headache
- D. Not better accounted for by another ICHD-3 diagnosis.

Diagnosekriterien für Migräne mit Aura:
A: ≥5 Attacken mit Kriterien B und C
B: 1 oder mehrere Aura-Symptome
C: zumindest 3 der Aura Charakteristika

The diagnostic criteria for CM are:

- A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C
- B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura.
- C. On ≥8 days/month for >3 months, fulfilling any of the following criteria:
  - criteria C and D for migraine without aura
  - criteria B and C for migraine with aura
  - believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- D. Not better accounted for by another ICHD-3 diagnosis.

Diagnosekriterien für CM:
A: ≥15 Kopfwehtage/ Monat für 3 Monate
B: ≥5 Attacken nach Kriterien B-D für ohne Aura und/oder Kriterien B und C für mit Aura
C: ≥ 8 Tage/ Monat für >3 Monte, die eines der Kriterien erfüllen

Diagnosis is further made by collecting a typical medical history, family history, and neurological examination. Specific diagnostic examinations do not exist.

zusätzliche Kriterien: Anamnese, Familien-Anamnese, neurologische Untersuchung

A0025 – How is episodic/chronic migraine currently managed according to published guidelines and in practice?

The current management option of EM and CM include both, drug and non-drug interventions.

The guideline of the German Society for Neurology and the German Society for Migraine and Headache suggests to use analgesics as the first line acute treatment for mild migraine attacks (ASS, Ibuprofen, Metamizol, Diclofenac-Kalium, Paracetamol) [23]. For medium and severe migraine attacks, they further recommend the use of triptan (5-HT1B/1D-Agonists) therapy (almotriptan, eletriptan, frovatriptan, sodium rizatriptan, rizatriptan, sumatriptan and zolmitriptan) [23]. In emergency acute treatment of an attack, Metoclopramid with Lysin-Acetylsalicylat or Sumatriptan are recommended [23].

akute Erstlinientherapie für milde Migräne-attacken: Analgetika, für mittel – schwere Attacken: Triptan, Notfalltherapie: Metoclopramid mit Lysin-Acetylsalicylat oder Sumatriptan;

Bei lineffiziente Monotherapie: Triptan mit NSAID

In cases when monotherapy is insufficient, combining a triptan with an NSAID is superior to monotherapy [23, 28]. Such combination therapy is recommended by NICE as the first line acute treatment of migraine attacks [29]. Furthermore, antiemetics such as Domperidon and Metoclopramid are recommende for the treatment of nausea and vomiting [1, 23]. The efficacy of non-drug therapies has been poorly studied and so, pharmacological therapy outlined above remains to be the standard acute migraine treatment.

Erstlinientherapie für Prävention: Beta-Blocker, Kalzium-Agonist, Antikonvulsiva, Amitriptylin, Onabotulinumtoxina

In case of frequent migraine attacks or migraine attacks with pronounced symptoms, a migraine prophylaxis should be started [23]. Migraine prophylactic drugs of first choice with strong evidence base are the beta-blockers (metoprolol and propranolol) [29], the calcium antagonist flunarizine, the anticonvulsants topiramate and valproic acid, amitryptilin, and onabotulinumtofin A (for chronic migraine) [23].

zusätzlich Lebensstilveränderungen und nicht-medikamentöse Therapien, nicht invasive Neuromodulations-behandlungen für Prävention

Drug therapy should be supplemented with lifestyle interventions (regular aerobic outdoor sports,) and non-drug behavioural therapies (relaxation procedures, cognitive behavioural therapy) [23]. Patients with high-frequency migraine attacks and significant impairment of QoL should use psychological pain therapy (pain management, stress management, stress relief) [23]. As additional or alternative options to drug therapy recommended for prophylaxis are non-invasive neuromodulation techniques, occipital nerve blocks, and invasive neuromodulation (in refractory migraine cases) [23].

Target population

A0007 – What is the target population in this assessment?

Zielpopulation: Pats älter als 18 Jahre mit EM oder CM

The target population of this assessment are adult patient of more than 18 years of age with episodic as well as chronic migraine.

A0023 – How many people belong to the target population?

Prävalenz EM (10 %) und CM (1-5 %); geschätzter Verkauf von +/- 150 Geräten/Jahr/ 1 Million der Population

As outlined in A0005, EM affects more than 10% of the population and has higher prevalence in women (18%) than in men (6%) [1], while CM affects 1-5% [22]. The manufacturer Cefaly® forecasts to sell +/- 150 device units per year and per million of population with the maximum plateau of 500 units per year and per million. Applying this to the Austrian context, in the population of 8.7 million, approximately 1.300 devices are expected to be sold.

A0011 – How much is e-TNS utilised?

keine Antwort verfügbar

As the e-TNS is only used in the private sector, the answer to this question is not available. E-TNS is marketed and publicly available in online shops for approximately 300,- Euro (https://www.humacentris.de/produkt-kategorie/migraenetherapie/).

5 Clinical effectiveness

5.1 Outcomes

wesentliche Endpunkte für Prävention

The following outcomes were defined as *crucial* to derive a recommendation concerning the *preventive* use of e-TNS:

- Reduction in monthly migraine days
- Reduction in monthly acute antimigraine drug intake
- Satisfaction

wesentliche Endpunkte für akute Therapie

The following outcomes were defined as *crucial* to derive a recommendation concerning the acute *treatment* use of e-TNS:

- Change in pain score units on VAS scale compared to baseline at 1/2/24 hours
- Patients on acute antimigraine medication at 2/24 hours
- Satisfaction

zusätzlich berücksichtigte Endpunkte

Further outcomes concerning the *preventive* use of e-TNS considered were:

- Reduction in monthly migraine attacks
- Reduction in monthly headache days
- Responder rate
- QoL
- Compliance

Further outcomes concerning the *acute treatment* use of e-TNS considered were:

- Headache pain free patients at 2/24 hours post treatment
- Improvement in nausea, vomiting, sensitivity to light and sound at 2 hours
- QoL
- Compliance

Reduktion Migränetage/ Monat: mehrere Migränetage während einer Attacke möglich,

inkludiert auch Symptome zusätzlich zu Kopfschmerzen und ICHD-3 Kriterien

The outcome of **Reduction in monthly migraine days** was chosen as crucial to derive a recommendation concerning the *preventive* use of e-TNS because it is understood to capture best the impact of the diagnosis of migraine on the patient. Compared to **Reduction in monthly migraine attacks**, the patient can experience more migraine days as a result of a single migraine attack and compared to **Reduction in monthly headache days,** headache is understood as only one migraine symptom among a variety of others. Also, the ICHD-3 diagnostic criteria distinguish between episodic and chronic migraine precisely on the basis of the number of migraine days per month [2].

Responderrate Anzahl der Patienten mit einer 50 % oder mehr Reduktion der Häufigkeit von Migränetagen

Responder rate refers to the number of patients with a 50% or greater reduction in frequency of migraine days at the end of the study vs. the baseline. The authors agreed to include responder rate with regard to migraine days as an outcome, as the number of migraine days had been chosen as a crucial outcome.

Reduktion der Medikamenteneinnahme

Reduction of monthly acute antimigraine drug intake measures one of the preventive goals of e-TNS, which is the reduction of the use of pharmacological interventions that may cause medication overuse headache.

% der PatientInnen – Zufriedenheit mit Gerät (Skala)

Satisfaction was measured in both *preventive* as well as *acute treatment* use of e-TNS. It was defined as the percentage of patients who were satisfied with the treatment (on the scale of very-moderately-not at all) [9] and/or expressed the desire to continue with the treatment [11, 13].

VAS-Skala: Maß für Schmerzintensität nach 1/2/24 Std. Behandlung mit e-TNS; minimaler klinisch wichtiger Unterschied (MCID) = zwischen 0.8 -4 Punkte

Change in pain score units on VAS scale compared to baseline at 1/2/24 hours concerns the *acute treatment* with e-TNS. The outcome measures patients' experience of pain intensity during the migraine attack and after 1/2/24 hours post e-TNS *acute treatment* using an eleven-point visual analogue scale (VAS) (from 0 no pain to 10 maximum pain) [14]. Concerning the minimum clinically important difference (MCID) on the VAS, a systematic review concludes that the threshold lies between 0.8 and 4 points (cm of improvement measured on the VAS scale) [16]. Further studies suggest that the threshold of MCID in emergency department patients was 1.2 points [30].

% der Pat. ohne Kopfschmerz 2/24 h nach e-TNS Behandlung

Headache pain free patients at 2/24 hours concerns the *acute* e-TNS *treatment* and it refers to the percentage of patients having a reduction from baseline headache during a migraine attack to no headache at 2/24 hours [15].

Anzahl der Pat. mit Medikamenteneinnahme 2/24 h nach e-TNS Anwendung

Patients on acute antimigraine medication at 2/24 hours concerns the *acute treatment* with e-TNS. It measures the need of patients to take acute antimigraine medication at 2/24 hours post e-TNS *acute treatment* [14].

Compliance-Prüfung durch in e-TNS Gerät eingebautes elektronisches System

Concerning *prevention*, **compliance** was assessed by a built-in electronic system in the e-TNS device that recorded the use of e-TNS stimulators by each patient [12]. Concerning *acute treatment*, compliance was defined as withdrawal, loss to follow-up, or violation of protocol [15].

% der PatientInnen mit Verbesserung der am Meisten störenden Migränesymptome

Improvement in nausea, vomiting, sensitivity to light and sound at 2 hours concerns the *acute* e-TNS *treatment* and it refers to the improvement in most bothersome migraine symptoms. It captures the percentage of patients with an improvement in nausea, vomiting, sensitivity to light and sound at 2 hours after the beginning of the e-TNS session [15].

5.2 Included studies

2 RCTs: 1 RCT für Prävention, 1 RCT für akute Therapie; Vergleich von e-TNS zu Placebo: Endpunktveränderungen = relative Veränderungen

For the assessment of clinical effectiveness, two studies met the inclusion criteria. One randomized controlled trial (RCT) for the *preventive* use of e-TNS [9] and one RCT for the *acute treatment* use of e-TNS [10]. Both compared the e-TNS (Cefaly®) to a sham (Cefaly®) device. The latter was not in the form of a peer-reviewed publication, but in the form of a study protocol and study results published at clinicaltrials.gov [10].

Study characteristics

1 RCT: Belgien, gesponsert von der Wallonischen Region, FU 90 Tage
1 RCT: USA, gesponsert von STX Med-Cefaly® FU24 h

Both RCTs were conducted in multiple centres, were double-blind, and were conducted in Belgium [9] and the US [10]. The studies were sponsored by the manufacturer STX Med – Cefaly® Technology or by the Walloon Region (where the manufacturer provided the e-TNS devices). In the *preventive* study, the length of follow-up was 90 days [9], while in the *acute treatment* study, the follow-up was 24 hours [10].

In the *preventive* RCT [9], the e-TNS device had a pulse frequency of 60 Hz, pulse width of 250 µs, and maximum intensity 16 mA. The comparator had the pulse frequency of 1 Hz, pulse width 30 µs, and maximum intensity 1 mA. Both were used for 20 minutes long sessions per day [9]. In the *acute treatment* RCT [10], the e-TNS device had a pulse frequency of 100 Hz, a pulse width of 250 µs, and a maximum intensity of 16 mA. The comparator had pulse frequency of 3 Hz and a pulse width of 250 µs. Both were used as 60 minutes long interventions [10]. See Table 5-1.

Unterschiede in Pulsfrequenz, Pulsbreite und maximale Intensität des e-TNS Geräts

Table 5-1: Technical characteristic of the e-TNS (Cefaly®) devices

	Preventive e-TNS device [9, 11-13]	*Preventive* e-TNS sham device [9]	*Acute treatment* e-TNS device [10, 14, 15]	*Acute treatment* e-TNS sham device [10]
Pulse frequency	60 Hz	1 Hz	100 Hz	3 Hz
Pulse width	250 µs	30 µs	250 µs	250 µs
Maximum intensity	16 mA	1 mA	16 mA	NA
Length of treatment	20 min/day	20 min/day	60 – 120 min	60 min

Patient characteristics

Schoenen et al. included 67 patients, of which 34 were in the intervention group (IG) and 33 in the control group (CG) and 91% were women [9]. Of the 67 patients, eight (11.9%) were lost to follow-up. Chou et al. included 106 patients, of which 52 were in the IG and 54 in the CG and 86.8% were women [10]. Of the 106 patients, five (9.6%) of IG patients and two (3.7%) of the CG patients were lost to follow-up. The mean age of patients was similar in both studies and ranged between 34.59 and 40.09.

2 RCTs:
67 Pts. (91 % Frauen) +
106 Pts. (86,8 %),
durchschnittl. Alter:
35 – 40 Jahre

In terms of the differences between inclusion and exclusion criteria between the two RCTs [9, 10], Schoenen et al. included only EM patients [9], while Chou et al. included both EM and CM patients [10]. Chou et al. required the migraine attack to last at least for 3 hours, have pain intensity stabilized for 1 hour, and have the headache located in the frontal-retro-peri-orbital area [10]. Schoenen et al. further excluded patients who had preventive antimigraine treatment three months prior, in whom more than three antimigraine medications failed, who had medication overuse headache, frequent/chronic tension type headache, or severe neurologic or psychiatric disorders [9]. Chou et al. excluded patients who were pregnant, who had Botox or supra-orbital nerve blocks in the past four months, who had other primary/secondary headache (except medication overuse), temporal/occipital headache, or complicated migraine (hemiphlegic, basilar-type, ophthalmoplegic, migranous infarction). Furthermore, they excluded patients who used opioid medication, migraine abortive medications in past three hours, or who had allodynia (oversensitivity to pain), metal or electric implants in head, cardiac pacemaker, implantable cardioverter defibrillator (ICD), or wearable cardioverter defibrillator (WCD) or who previously used a Cefaly® device.

Unterschiede bei Ein- und Ausschlusskriterien:

EM/CM PatientInnen, Migränekriterien, präventive Medikamenteneinnahme, medikamenteninduzierte Kopfschmerzen, Kopfschmerztypen anders als Migräne, neurologische oder psychiatrische Störungen, Schwangerschaft, elektronische Implantate, etc.

Study characteristics and results of included studies are displayed in Table A-1 to A-4 and in the evidence profile in Tables 7-1 and 7-2.

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of e-TNS on mortality?

D0003 – What is the effect of e-TNS on the mortality due to causes other than episodic/chronic migraine?

keine Evidenz zur gesamten oder krankheitsspezifischen Mortalität

No evidence was found to answer the research questions. None of the included studies reported cases of overall or disease-specific mortality, neither in the *acute treatment* nor the sham group.

Morbidity

D0005 – How does e-TNS affect symptoms and findings (severity, frequency) of episodic/chronic migraine?

Prevention

präventive Anwendung von e-TNS:

In terms of the *preventive* effect of e-TNS, the symptoms of migraine attacks, headache days, and migraine days (and responder rate of >50% reduction in migraine days) were measured.

signifikant weniger Migräneattacken/Monat in IG

In EM, patients in the IG had a mean reduction in monthly migraine attacks of 0.82 days, while patients in the CG of 0.15 days. The difference (net gain in the IG) was 0.67 days (p=0.044) [9].

signifikant weniger Kopfschmerztage in IG

With respect to headache days, patients in the IG had a mean reduction of 2.51 days, while patients in the CG of 0.23 days. The difference (net gain in the IG) was 2.28 day (p = 0.041) [9].

weniger Migränetage in der IG, nicht statistisch signifikant bei 5 %

With respect to migraine days, patients in the IG had a mean reduction of 2.06 days, while patients in the CG of 0.32 days. The difference (net gain in the IG) was 1,74 days (p = 0.054) [9].

höhere Responderrate in der IG

The responder rate, the number of patients with a 50% or greater reduction in frequency of migraine days at the end of the study vs. the baseline, was 40% (12 patients) in the IG as opposed to 13.8% (4 patients) in the CG [9]. For further details, see Table A-1.

Acute treatment

akute Anwendung von e-TNS:

In terms of the *acute treatment* effect of e-TNS during the migraine attack, the intensity of pain was measured on a VAS scale (0 (no pain) to 10 (maximum pain)), at 1/2/24 hours post-*acute treatment*.

signifikante Verbesserung der Schmerzintensität in IG (+1,68 Punkte) nach 1h

In both EM and CM, patients in the IG had a mean reduction of 3.46 points (SD=2.32) at one hour post intervention, while patients in the CG of 1.78 points (SD=1.89). The difference (net gain in the IG) was 1.68 points (p= 0.0001) [10].

signifikante Verbesserung der Schmerzintensität in IG (+1,02 Punkte) nach 2h

At two hours post intervention, patients in the IG had a mean reduction of 2.87 points (SD=2.24), while patients in the CG of 1.85 points (SD=1.96). The difference (net gain in the IG) was 1.02 points (p=0.028) [10].

At 24 hours post intervention, patients in the IG had a mean reduction of 3.46 points (SD=2.65), while patients in the CG of 2.38 points (SD=2.27). The difference (net gain in the IG) was 1.08 points (p=0.062) [10]. For further details, see Table A-1.

nicht signifikante Verbesserung der Schmerzintensität in IG (+1,08 Punkte) nach 2h

D0006 – How does e-TNS affect progression (or recurrence) of episodic/chronic migraine?

Because the use of antimigraine medication is associated with side effects, namely with MOH, because patients can be refractory to antimigraine medication, and because episodic migraine can naturally progress into chronic migraine [1], which can lead to additional antimigraine drug intake, the outcome of acute antimigraine drug intake is reported here.

Übernutzung resultiert mlgw in Kopfschmerzen + Entwicklung von EM zu CM – zusätzliche Medikamente

Prevention

Präventivbehandlung:

In terms of the *preventive* use of e-TNS in EM, patients in the IG had a mean reduction in monthly acute antimigraine drug intake of 4.2 instances (decrease from 11.45 (SD=8.35) at baseline to 7.25 (SD=7.31) at 90 days follow-up with p = 0.0057). Patients in the CG had an increase of 0.04 instances (increase from 9.24 (SD=4.75) to 9.28 (SD=5.69) with p=0.822). The difference (net gain in the IG) was 4.24 instances (p=0.0072) [9].

signifikant weniger Anti-Migräne-Medikamenten-einnahme/Monat in IG

Acute treatment

Akutbehandlung:

In terms of the *acute treatment* use of e-TNS in EM and CM, there were three patients (5.8%) in the IG on acute antimigraine medication at two hours post intervention, while in the CG, there were two (3.7%). The difference (net loss in the IG) was 1 patient (p=0.666) [10].

mehr Pat. mit akuter Anti-Migräne-Medikamenteneinnahme nach 2h, nicht statistisch signifikant

At 24 hours post intervention, there were 18 patients in the IG (34.6%) on acute antimigraine medication, while in the CG, there were 21 patients (38.9%). The difference (net gain in the IG) was 3 patients (3.3%) (p=1) [10].

weniger Pat. mit akuter Anit-Migräne-Medikamenteneinnahme nach 24h, nicht statistisch signifikant

Function

D0011 – What is the effect of e-TNS on patients' body functions?

The effect of e-TNS on patients' body functions is associated with arousal changes and skin issues. The use of e-TNS is correlated to the experience of sleepiness, fatigue, or insomnia [17, 31]. It is further associated with paraesthesia (tingling, tickling, pricking, numbness or burning of a person's skin) and local skin allergy [17].

Effekte auf Körper: Schläfrigkeit, Müdigkeit, Schlaflosigkeit, Hautprobleme (z. B. Hautallergien)

D0016 – How does the use of e-TNS affect activities of daily living?

The *preventive* use of e-TNS requires the patient to spend 20 minutes per day performing the stimulation. The *acute treatment* use is only applied during the attack as a 60-120 minutes long intervention.

Prävention: 20 min/Tag, akute Therapie: 60-120 min/Attacke

Health-related quality of life

D0012 – What is the effect of e-TNS on generic health-related quality of life?

D0013 – What is the effect of e-TNS on disease-specific quality of life?

keine Evidenz zur Beantwortung der Frage

No evidence was found to answer the research questions. None of the included studies reported QoL, neither in the *preventive/acute treatment* nor the sham groups.

Patient satisfaction

D0017 – Was the use of e-TNS worthwhile?

e-TNS für Prävention: 70.6 % der Pts. mit hoher bis moderater Zufriedenheit

Patient satisfaction was only reported in the *preventive* study in Schoenen et al. where 70.6% (IG) as opposed to 39.4% (CG) of patients reported moderate to high satisfaction (31.2% difference) [9].

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- SADEs

schwerwiegende Nebenwirkungen = wesentlicher Endpunkt

Further outcomes considered were:

- Pain/intolerance to paraesthesia (burning sensation)
- Arousal changes (insomnia, sleepiness/fatigue)
- Headaches after stimulation
- Skin allergy
- Neck tension
- Nausea after stimulation
- Dizziness
- Vomiting
- Pain in the jaw
- Discomfort in teeth
- Pain in eyes
- Cold feet

weitere Sicherheitsendpunkte: Schmerz, Schlaflosigkeit/ Müdigkeit, Kopfschmerz, Hautallergie, Nackenverspannung, Übelkeit, Schwindel, etc.

The serious adverse events associated with the *preventive* as well as *acute treatment* use of e-TNS are considered crucial.

schwerwiegende Nebenwirkungen entscheidend für Empfehlungen

6.2 Included Studies

For the assessment of safety, seven studies met the inclusion criteria. Two RCTs are described in the section on clinical effectiveness above [9, 10]. Further five prospective case series that met the inclusion criteria for assessing safety will be described below. One of the five case series publications was not in the form of a peer-reviewed publication, but in the form of a study protocol and study results published at clinicaltrials.gov [15].

2 RCTs,
5 prospektive Fallserien
1/5 nicht publiziert

Study characteristics

Two case series were conducted in more than one centre [11, 13] and the remaining three were single centre studies [12, 14, 15]. Three were sponsored by STX Med – Cefaly® Technology and were conducted in the US and Greece. In the remaining two case series studies from Italy, the source of funding was unclear, but it was stated that the devices were provided by the manufacturer [11, 12].

2 multizentrisch,
3 in einem Zentrum,
3 gesponsert von STX Med-Cefaly®,
2 unklare Finanzierung

In the *preventive* case series studies, the length of follow-up ranged from 60 to 120 days [11-13], while in the *acute treatment* case series studies, the follow-up was 24 hours post treatment [14, 15].

FU Prävention: 60-120 Tage,
FU akute Therapie: 24h

The devices used for the *preventive* as well as *acute treatment* use of e-TNS are the same as outlined in Table 5-1. One study did not indicate the device type [13].

Gerätecharakteristika vgl. oben

Patient characteristics

Prävention: 3 Studien = 151 PatientInnen, Alter 33-45 Jahre

akute Therapie: 2 Studien = 199 PatientInnen, Alter 39-47 Jahre

The three *preventive* case series studies included 24, 23, and 37 patients, respectively [11-13]. Hence, together with the *preventive* RCT [9], the total number of patients receiving e-TNS for the *prevention* of migraine attacks was 118. Together with the CG, out of the 151 patients, 75-91% were women and a total of 24 patients was lost to follow-up. The mean age varied between 32.9 to 45 years. The two *acute treatment* case series studies included 35 and 60 patients, respectively [14, 15]. Hence, together with the *acute treatment* RCT [10], the total number of patients receiving e-TNS for the *acute treatment* of migraine attacks was 147. Together with the CG, out of the 201 patients, 80-89.6% were women and a total of 24 patients were lost to follow-up. The mean age varied between 39.4 to 46.9 years.

Ein-Ausschlusskriterien für Prävention: EM, CM, medikamenteninduzierte Kopfschmerzen, Kopfschmerztyp, Schwangerschaft, neurologische, systemische oder psychiatrische Krankheit

In terms of the differences between inclusion criteria in the *preventive* use of e-TNS, the main difference is that Russo et al. and Schoenen et al. only include EM patients [9, 12], while DiFiore et al. include only CM patients for more than one year [11], and Vikelis et al. both EM and CM patients [13]. DiFiore et al. further include patients both with and without MOH [11], but Schoenen et al. exclude them [9], and Vikelis et al. include patients refractory/intolerant to Topiramate [13]. Exclusion criteria are either not explicit, or they differ. Russo et al. exclude patients with other types of headache, patients on daily medication intake, migraine drug-naïve patients, and patients without structural brain abnormalities [12]. DiFiore et al. exclude pregnant patients and patients with major neurological, systemic, or psychiatric illnesses [11].

Ein-Ausschlusskriterien für akute Therapie: EM, CM, Krankheitsbeginn/-dauer, Schmerzintensität, Kopfschmerztyp, Migränetypen,

In terms of the differences between inclusion criteria in the *acute treatment* use of e-TNS, the main difference is that Chou et al. include both EM and CM patients [10, 14], while Mann only includes EM patients [15]. Mann furthermore only includes those patients, who had their migraine onset before 50 years of age and who have had 2-8 moderate to severe attacks per month in the prior two months [15]. Chou et al. further include patients whose attack has lasted for more than three hours, their pain intensity was stabilized for an hour, or those patients who have had a frontal-retro-peri-orbital headache [10, 14].

Botox-Therapie, Medikamenteneinnahme, Implantate, Schwangerschaft

Both Chou et al. and Mann exclude patients with Botox in the head and supra-orbital nerve blocks in past four months, patients with other primary or secondary headache (except MOH), patients using opioid medication, or patients with metal/electric implants in the head, cardiac pacemaker, ICD, and WCD patients. On top of that, Mann excludes patients with migraine aura without headache, brainstem aura migraine, or patients with migraine prophylaxis modification in prior three months, and patient who abuse alcohol/illicit drugs [15]. Chou et al. exclude pregnant patients, temporal/occipital headache patients, or patients who used abortive medication in past three hours, who are oversensitive to pain, or who have a complicated migraine diagnosis [10, 14].

Study characteristics and results of included studies are displayed in Table A-1 to A-4 and in the evidence profile in Tables 7-1 and 7-2.

6.3 Results

Patient safety

C0008 – How safe is e-TNS in comparison to the comparator(s)?

Prevention

Präventionstherapie:

No SADE's occurred in the *preventive* studies.

keine schwerwiegenden Nebenwirkungen (NW)

In terms of ADEs, two studies reported that there were none [9, 12], while intolerance to paraesthesia (burning sensation) was reported in 34.3% of patient in [13]. Furthermore, headache after stimulation as well as neck tension were reported in one study [11], where headache occurred in 8.7% of patients, while neck tension in 4.3%.

sonstige NW: Intoleranz gegenüber Parästhesien, Kopfschmerzen, Nackenverspannungen

In one study, 10.8% of patients experienced technical issues with the e-TNS device [13].

technische Schwierigkeiten mit e-TNS

Acute treatment

Akutbehandlung:

No SADEs occurred in *acute treatment* studies.

keine schwerwiegenden NW

In terms of ADEs, one study reported that there were none [14]. Intolerance to paraesthesia was documented in two *acute treatment* studies in 5.8% (IG n=52) vs. 1.9% (CG n=54) [10] and 11.9% of patients [15]. Nausea after stimulation was reported in two studies in 1.9% (IG n=52) vs. 0% (CG n=54) [10] and 3.5% of patients [15].

sonstige NW: Intoleranz gegenüber Parästhesien, Übelkeit

Furthermore, arousal changes (insomnia, sleepiness/fatigue, drowsiness), dizziness, vomiting, pain in the jaw, discomfort in teeth, pain in eyes, and cold feet occurred in one study all in 1.7% of patients [15]. In the same study, 18.3% of patients reported skin allergy/irritation.

1 Studie: Sensibilitätsveränderungen, Schwindel, Erbrechen, Kieferschmerzen, etc.

C0002 – Are the harms related to dosage or frequency of applying e-TNS?

No relationship between dosage and frequency of applying e-TNS was found. The only point of concern is the increase in ADEs in Mann, where the higher *acute treatment* pulse frequency of 100 Hz was applied [15]. An increased number of ADEs was, however, not confirmed in the other two *acute treatment* studies with the same pulse frequency [10, 14].

Zusammenhang zwischen erhöhter Impuls-frequenz und vermehrten NW nicht eindeutig

C0004 – How does the frequency or severity of harms change over time or in different settings?

Due to the short length of follow-up, there is no data to answer this question.

keine Daten aufgrund der kurzen Nachbeobachtungszeit

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of e-TNS?

C0007 – Are e-TNS and comparator(s) associated with user-dependent harms

The patient groups that are most susceptible to be harmed by e-TNS are those patients who can be influenced by the ADEs present. Those are patients who can be unduly influenced by fatigue and the related lack of attention such as car drivers. Also, patients who have mental or physical difficulty operating a device that used electric impulses or patients in whom the allergic reaction to the electrode on their forehead may cause personal or professional challenges such as first point of personal contact people.

Konzentrationsfähigkeit (z. B. Autofahrer), Probleme mit Elektro-Stimulation, persönliche/ berufliche Unannehmlichkeiten durch Hautirritationen (Aussehen)

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of e-TNS and the comparator(s)?

größere RCTs und prospektive Registerdaten mit längerer Nachbeobachtungszeit

Larger RCTs and prospective registry data are needed to monitor the use of e–TNS and thus provide a longer follow-up data.

7 Quality of evidence

The risk of bias (RoB) for individual studies was assessed with the Cochrane Collaboration's tool for randomised trials [32] as well as with the Institute of Health Economics (IHE) checklist for single-arm studies [33]. Both assessments are presented in Tables A-5 and A-6 in the Appendix. The *preventive* RCT [9] was rated with a moderate RoB, whereas the *acute treatment* RCT [10] was rated with a high RoB. In both cases it was unclear whether the randomization sequence was adequate. Furthermore, in the *acute treatment* RCT [10], the method of concealment was not described to allow a definite judgement. Selective outcome reporting was unclear in both studies as it was assumed that not all ADEs were reported. Also, there was a conflict of interests present in the *acute treatment* study [10] as it was funded by the manufacturer.

RoB-Assessment:
1 RCT moderater RoB:
Randomisierungssequenz,
1 RCT hoher RoB:
Randomisierungssequenz,
Geheimhaltung
Randomisierung,
selektives Berichten,
etc.

In the prospective case series studies used for the assessment of safety, one study was rated with low RoB [12], three studies were rated as moderate [11, 14, 15], and one study was rated with high RoB [13]. The reasons for downgrading were mainly non-consecutive selection of patients, lack of clarity concerning the reporting on co-interventions, lack of blinding, lack of the use of parametric statistics, and lack of reporting of the sources of funding.

prospektive Fallserien:
1 Studie niedriger RoB,
3 Studien moderater RoB,
1 Studie hoher RoB

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [36] for each endpoint individually. Each study was rated by three independent researchers. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [36].

Evaluierung der Evidenzstärke mittels GRADE

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

4 Kategorien für Evidenzstärke:
hoch,
moderat
niederig
sehr niedrig

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Overall the strength of evidence for the effectiveness and safety of e-TNS for *prevention* in comparison to the sham e-TNS device is low and very low in outcomes of satisfaction, ADEs, and SADEs. Concerning *acute treatment*, the strength of evidence is very low overall.

Evidenzstärke Prävention: niedrig und sehr niedrig, akute Therapie: sehr niedrig

For the comparison of e-TNS with the standard practice comparators such as triptans, NSAIDs/paracetamol for *acute treatment*, and propranolol and topiramate for *prevention*, no evidence was found.

keine Evidenz zum Vergleich mit präventiven und akuten Standardtherapien

Table 7-1: Summery of findings table: efficacy and safety of e-TNS for the prevention of episodic/chronic migraine patients

Outcomes	Anticipated absolute effects* (97.5% CI)	Relative effect (97.5% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Reduction in monthly migraine attacks assessed with: mean number of days	The mean reduction in the number of monthly migraine attacks in the IG was 0.67 more.	-	67 (1 RCT)	⨁⨁◯◯ LOW a)b)	Statistically significant (p = 0.044)
Reduction in monthly migraine days assessed with: mean	The mean reduction in the number of monthly migraine days in the IG was 1.74 more.	-	67 (1 RCT)	⨁⨁◯◯ LOW a)b)	Statistically not significant (p = 0.054)
Reduction of monthly headache days assessed with: mean	The mean reduction in the number of monthly headache days in the IG was 2.28 more.	-	67 (1 RCT)	⨁⨁◯◯ LOW a)b)	Statistically significant (p = 0.041)
Reduction in the number of monthly acute antimigraine drug intake	The mean reduction in the number of monthly acute antimigraine drug intake in the IG was 4.24 more.	-	67 (1 RCT)	⨁⨁◯◯ LOW a)b)	Statistically significant (p = 0.0072)
High or moderate Satisfaction	70.6% (IG, n=34) vs.39.4% (CG, n=33)	-	67 (1 RCT)	⨁◯◯◯ VERY LOW a)b)	Patient reported outcome
Serious Adverse Events	0/34 (IG) vs. 0/33 (CG)	-	67 (1 RCT)	⨁◯◯◯ VERY LOW a)b)	-
Adverse Events	0/34 (IG) vs. 0/33 (CG)	-	67 (1 RCT)	⨁◯◯◯ VERY LOW a)b)	-

* *The risk in the IG (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: *CG = Control group, CI = Confidence interval, IG = Interventional group, n= number, pts = Patients, RCT = Randomised controlled trial, VAS = Visual Analogue Scale*

Explanations: *a) Wrong comparator, b) Small sample size*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Table 7-2: Summary of findings table: efficacy and safety of e-TNS for the acute treatment of episodic/chronic migraine patients

Outcomes	Anticipated absolute effects* (97.5% CI)	Relative effect (97.5% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Reduction in pain score units on VAS scale compared to baseline at 1 hr follow up	The mean improvement in reduction in pain score units on VAS scale compared to baseline at 1 hr was 1.68.	-	106 (1 RCT)	⊕◯◯◯ VERY LOW[a)b)c)d)e)]	Statistically significant (p_{Group} = 0.0001)
Reduction in pain score units on VAS scale compared to baseline at 2 hr follow up	The mean improvement in reduction in pain score units on VAS scale compared to baseline at 2 hr was 1.02.	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	Statistically significant (p_{Group} = 0.028)
Reduction in pain score units on scale compared to baseline at 24 hrs	The mean improvement in reduction in pain score units on VAS scale compared to baseline at 24 hrs was 1.08.	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	Statistically not significant (p_{Group} = 0.062)
Patients on acute medication at 2 hrs follow up	3/52(IG) vs. 2/54 (CG)	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	-
Patients on acute medication at 24 hrs	18/52 (IG) vs. 21/54 (CG)	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	-
Serious Adverse Events: follow-up 1 day	0/52 (IG) vs. 0/54 (CG)	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	-
Adverse Events: follow-up 1 day	Intolerance to paresthesia in 3/52 (IG) vs. 1/54(CG) pts Nausea after stimulation in 1/52 (IG) vs. 0/54 (CG) pts	-	106 (1 RCT)	⊕◯◯◯ VERY LOW [a)b)c)d)e)]	-

* *The risk in the IG (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Abbreviations: *CG = Control group, CI = Confidence interval, hr = hour, IG = Interventional group, n= number, pts = Patients, RCT = Randomised controlled trial, VAS = visual analogue scale*

Explanations: *a) Funded by the manufacturer b) Insufficient information about sequence generation process c) Method of concealment in not described to allow definitive judgment d) Wrong comparator e) Small sample size*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

8 Discussion

To our knowledge, this is the first systematic review on the *preventive* and *acute treatment* use of e-TNS in episodic (EM) as well as chronic migraine (CM) patients.

Summary of evidence from prospective clinical studies

We included two RCTs for the analysis of clinical effectiveness:

- 1 RCT with 67 patients for prevention, of which 34 received the e-TNS intervention and
- 1 RCT with 106 patients for *acute treatment*, of which 52 received the e-TNS intervention, and

additional five prospective case series complementing the analysis of safety:

- 84 *preventive* patients and 95 *acute* patients receiving the e-TNS intervention.

vorliegende Evidenz: 2 RCTs + 5 prospektive Fallserien mit insgesamt 118 Pts (Prävention) und 147 Pts. (akute Behandlung)

Concerning *prevention*, the results from the RCT (34 e-TNS patients) show statistically significant differences between e-TNS and sham treatment in EM patients with respect to reduction of migraine attacks (0.67 less migraine attacks per month), migraine days (1.74 less migraine days per month), responder rate (26.2% more response to treatment), headache days (2.28 less headache days per month), acute antimigraine drug intake (4.24 less instances of acute drug intake per month), and satisfaction (31.2% difference in satisfaction with the CG).

Prävention (1 RCT): e-TNS vs. Sham → Reduktion der Migräneattacken, -tage, Anti-Migräne-Medikamenteneinnahme, etc.

Concerning *acute treatment*, the RCT (52 patients) shows statistically significant differences between e-TNS and sham treatment suggesting more improvement in pain reduction than sham on a VAS scale (out of 11 points) at 1/2/24 hours post-*acute treatment* (1.68/1.02/1.08 improvement, respectively).

akute Therapie (1 RCT): e-TNS vs. Sham → Schmerzreduktion

The size of the difference measured on VAS scale, however, is of questionable clinical relevance as concerning the MCID, the results oscillate around the lower end of the clinically meaningful benefit threshold [16]. There was also an increase of one IG patient in acute antimigraine drug intake at two hours post-*acute treatment* compared to CG, but a decrease of three IG patients compared to CG at 24 hours.

klinische Relevanz der Effekte ist unklar

Concerning safety, no SADEs occured neither in the RCTs nor in the case series. The reporting of AEDs, however, remains to be a point of concern as the largest treatment case series study with 60 patients reports several AED's that are unreported in all the remaining studies (dizziness, vomiting, pain in the jaw, discomfort in teeth, and pain in eyes). Each occurred only in 1/60 patients.

keine schwerwiegenden NW, größte Fallstudie berichtet zahlreiche NW, die in keinen anderen Studien erwähnt wurden

Efficacy data from the three *preventive* prospective case series suggest a better efficacy profile than the *preventive* RCT [9], namely that e-TNS reduced the number of monthly migraine attacks by 2.5 instances [12], monthly migraine days by 3.5 days [12] and by 31% [11], and monthly headache days by two days [13]. Also, responder rate in migraine days was 75% in one study [12]. Furthermore, monthly acute antimigraine drug intake was reduced by 40.7%, 49.6%, and 46.3%, respectively [11-13]. In terms of satisfaction, 83.3% [12] and 65.7% [13] of patients were satisfied. Furthermore, a survey with 2,313 EM patients who used e-TNS concludes that 54.4% were satisfied and thus were willing to continue the e-TNS treatment [17].

Prävention (3 Fallserien) – besseres Wirksamkeitsprofil als in RCT

akute Therapie (2 Fallserien) besseres Wirksamkeitsprofil als in RCT: Kopfschmerzfreiheit, Freiheit von Migräne-assoziierten Symptomen, Schmerzreduktion und Verminderung der Anti-Migräne-Medikamenteneinnahme

Efficacy data from the two *acute treatment* prospective case series also suggest a better efficacy profile than the *acute treatment* RCT, namely that 35.4%/ 25% of patients were headache pain free at 2/24 hours post-*acute treatment*, respectively, and 36.7% were free from nausea, vomiting, and sensitivity to light and sound at 2 hours [15]. On the VAS scale, there was a 3.22/2.98 decrease of pain at 1/2 hours, respectively [14], and 34.6% and 50% of patients were on acute medication at 24 hours post-*acute treatment*, respectively [14, 15].

Internal and external validity

Qualität der Evidenz für Wirksamkeit niedrig bis sehr niedrig, für Sicherheit von hoch bis sehr niedrig

Concerning the effectiveness (RCTs) of *prevention* and *acute treatment* with e-TNS, the quality of evidence was low to very low. The main reasons were the small sample size, uncertainty about sufficient reporting of AEDs, and the wrong comparator. Concerning safety, the quality of evidence ranged from high, moderate, to low and very low (see ROB Tables A-5 and A-6). Furthermore, two studies (case-series) were judged to have a high risk of confounding as co-interventions were either not clearly described [13], or it was clearly stated that *preventive* as well as *acute treatments* for chronic migraine were not changed during the study [11].

2 Studien zur akuten Therapie: keine Daten zu am Stärksten belastenden Migränesymptomen;

Pts.-Berichte haben hohe Subjektivität

Challenges with interpreting the data arise when in the *acute treatment* use of e-TNS, Mann outlines the baseline most bothersome migraine symptoms (nausea, vomiting, sensitivity to light and sound) [15], but these baseline symptoms are not outlined in the remaining two *acute treatment* studies, thus undermining their internal validity [10, 14]. Furthermore, the role of patients' reports is key in the assessment of antimigraine treatments, yet it is subject to a high level of subjectivity as seen on the exclusion criteria in Mann, where patients were excluded upon having difficulty distinguishing migraine attacks from tension-type headaches [15].

Daten generalisierbar basierend auf Herkunftsländern, jedoch akute Therapie-Studien: Krankenhaus-Setting anstatt Real-Life-Setting

In terms of external validity, the data is considered generalizable to other contexts. The studies were conducted in Belgium, Italy, Greece, and the US, and these contexts are similar to the Austrian one. At the same time, however, the differences between inclusion and exclusion criteria undermine the generalizability. The *prevention* studies represent the real clinical context, as the patients used the e-TNS in their homes, but the *acute treatment* studies were conducted in the hospital setting, yet the e-TNS should be used in the home setting for *acute treatment* as well.

große Unterschiede in den Compliance-Raten zwischen den Studien

in RCTs nur ca. ½ Pts compliant

Compliance is considered to be one of the key issues. In the *preventive* studies, compliance ranged in the case series from 81.8% to 83.3% [11-13], and in the *preventive* RCT [9], it was 61.7% (IG) vs. 54.4% (CG). It was not reported in the *acute treatment* RCT [14], but in the *acute treatment* case series of Mann, it was 82.7% [15]. In the survey with 2,313 patients, 46.6% of patients were unsatisfied who, in terms of compliance, used the device for the recommended period of time only in 48.6% of cases [17]. The real-life compliance with e-TNS is put into question because the relatively high case series compliance data are contrasted with lower RCT and survey data.

Missverhältnis zwischen Frauen und Männern

Also, there is a disproportion in the presence of the female population in the studies as 75-91% of the whole patient population were women and 9-25% were men. However, the epidemiologic data suggest that EM and CM is only three times more prevalent in women than in men [1].

In all studies included in the analysis (except for one, where drug refractory patients are included [13]), the alternative treatment option to e-TNS is drug therapy. Other non-invasive neuromodulation techniques (TMS, DCS, VNS), which are recommended as additional or alternative to drug therapy [23], aim at a similar target population in which drug therapy may be replaced [1]. In terms of invasive neuromodulation techniques (ONS), chronic refractory patients are the target population [34].

Alternativtherapien meist Medikamente; für nicht invasive Neuromodulations-behandlungen

Given the small size of the selective sample of patients included in the evidence base (as compared to the large burden of disease that migraine creates), the conclusions about effectiveness and the positive safety profile are considered to be inflated. Larger controlled trials with best practice interventions as comparators are necessary for potentially considering e-TNS to be part of the standard practice.

selbe Zielpopulation; kleine Stichprobengröße, Wirksamkeits- und Sicherheitsergebnisse vermutlich überschätzt

Limitations of evidence

The evidence base found was only partly relevant in answering the research question. Both RCTs identified were relevant for excluding placebo effects, but RCT comparing e-TNS to best practice interventions (such as propranolol and topiramate for *prevention*, and triptans, NSAIDs/paracetamol for *acute treatment*) should be used as comparators. The reason being that the target population of e-TNS are not only patients refractory to medication, but also drug responsive patients, which makes e-TNS aim to replace the use of medication. That is why a controlled trial comparing e-TNS to either of the above outlined (*preventive* or *acute*) treatments is necessary.

Evidenz nur teilweise relevant: Komparator in RCTs war eine Scheinbehandlung, nicht jedoch best practice Standard

Furthermore, outcomes measured in the studies were judged to be relevant to patient's experience, but a standardized evaluation of satisfaction was lacking (especially in the RCTs). It is important to note, however, that the patient relevant endpoint of QoL was not measured or reported in any of the studies. Also, in most *acute treatment* studies with medication, patients are followed for 48 hours for the purpose of measuring headache recurrence. For that reason, the follow-up of 24 hours that is applied to all three *acute treatment* studies is considered to be too short [10, 14, 15]. Also, consistency of the effect of e-TNS is undermined because in medication studies, several attacks must be treated in one person to prove that the acute therapy works and that was not the case.

keine QoL-Daten, kein standardisiertes Maß für Zufriedenheit, Follow-up von 24h für Akuttherapien sehr kurz – in den meisten Studien Follow-up von 48h, Bestätigung des Effekts von e-TNS geschwächt – 1 Pts. sollte mehrmals mit e-TNS behandelt worden sein

Socio-economic and ethical considerations, conclusion

When considering socio-economic and ethical aspects of this new intervention e-TNS, the effects have to be reflected over against the principles of beneficence, non-maleficence, autonomy, distribute justice, and uncertainty. On the one hand, by being applied in the home setting (thus securing patient autonomy and easy access), e-TNS claims to reduce the burden on the in-/outpatient sector by reducing the pharmacological and other healthcare spending associated with the use of the current *preventive* and *acute treatment* options for EM and CM patients (freeing of resources an accordingly distribute justice). And, if proven to be more effective than the best practice comparators, it may also reduce the economic loss associated with decreased economic productivity of migraine patients [18]. E-TNS also claims to be associated with less side effects than the current pharmacological therapy and thus, it may better protect the principles of medical beneficence and patient's autonomy.

Wohltätigkeit, Schadensvermeidung, Autonomie, gerechte Verteilung von Ressourcen, Unsicherheit; Potential: da e-TNS im Privathaushalt – Verminderung der Gesundheitsausgaben und des Produktivitätsverlusts am Arbeitsmarkt

Unsicherheit bezügl. positives NW-Profil – Langzeitdaten notwendig, zur Schadensverminderung größere RCTs im Verhältnis zur Zielpopulation notwendig

On the other hand, however, the lack of clarity behind the mechanism of action of e-TNS casts doubts over its positive safety profile [19-21, 35]. This is further coupled by the location of the device placed at the patient's forehead as any possible long-term ADEs, not yet measured by the current evidence, may be found crucial (with respect to non-maleficence). It is not clear to what extent the electrical field applied in such close proximity to the brain for such an extended period of time influences the brain. As outlined above, to prevent breaching the principle of non-maleficence, larger controlled trials are needed to match the size of the population that e-TNS targets. Currently, there is only one ongoing RCT for the *acute treatment* use of e-TNS that aims to recruit 600 patients with an estimated primary completion date of October 2018, however, it lacks the measurement of any longer-term outcomes (more than 24 hours) (NCT03465904).

e-TNS – Stärkung der Autonomie der Pat. + verminderte Medikamenteneinnahme, jedoch Langzeitsicherheitsprofil notwendig, mögliche Kosteneffektivität von e-TNS vs. geringe Schmerzeffekten (VAS) und geringe Pat.-Anzahl in den Studien

While e-TNS has the potential to improve patients' autonomy and reduce the total medication intake, its non-invasive nature needs to be put in the context of the paucity of knowledge about its mechanism of action and thus its long term safety profile. Furthermore, the potential cost-effectiveness of e-TNS needs to be contrasted with the small effects measured by the VAS and the small sample size included in the studies with the large real life target population.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions.**
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence indicates that the assessed technology e-TNS in episodic and chronic migraine patients is more effective and equally safe as the comparator sham Cefaly® device. The quality of the body of evidence suggesting this is, however, low to very low. Because there is no evidence base that would compare e-TNS to best practice standard treatment, new study results with standard practice comparators will influence the effect estimate considerably. Also, concerning safety, an RCT with a larger sample size will influence the safety profile considerably.

Due to the lack of ongoing studies that could sufficiently broaden the evidence base, no specific date for re-evaluation is recommended.

10 References

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: e-TNS: Results from randomised controlled trials for prevention of episodic and chronic migraine

	Schoenen et al. [9] (2013)
Country	Belgium
Sponsor	Walloon Region[1]
Study design	Multi-centre, prospective, double-blinded, randomised, sham-controlled trial
Conducted in	09/2009 – 09/2011
Indication	***Preventive*** treatment in pts with episodic migraine with and without aura
Intervention (I)	e-TNS (pulse frequency 60 Hz, pulse width 250 µs, max intensity 16 mA, **20 min/day**)
Comparator (C)	Sham Cefaly® device (pulse frequency 1 Hz, pulse width 30 µs, max intensity 1 mA, **20 min/day**)
Number of pts (I vs. C)	34 vs. 33
Inclusion criteria	Pts 18-65 yrs, migraine with or without aura meeting ICHD-II code 1.2.1 or 1.1 criteria, **episodic migraine of ≤2 attacks per mo**
Exclusion criteria	*Preventive* antimigraine treatment in prior 3 mos, failure of ≥3 antimigraine medications, medication overuse headache, frequent/chronic tension type headache, severe neurologic or psychiatric disorders
Primary outcome measure	Change in monthly migraine days and 50% responder rate
Secondary outcome measure	Change in monthly frequency of any headache, change in mean headache severity per migraine day (4 points scale), change in monthly acute antimigraine drug use, percentage of patients stating satisfaction
Baseline patient characteristics (I vs. C) (intention-to-treat)	
Mean age, yrs (SD)	34.59 (11.01) vs. 39.06 (9.87)
Sex, female:male, n	31:3 vs. 30:3
Migraine with aura, n (%) Migraine without aura, n (%) Migraine duration, yrs (SD) Migraine attack duration in hrs, median (IQR) Pts on acute medication, n	10 (29.4) vs. 10 (30.3)[2] 24 (70.6) vs. 23 (69.7) 14.71 (9.39) vs. 18.17 (11.68) NA NA

[1] The manufacturer STX Med provided the Cefaly® devices

[2] While all pts had migraine without aura, 20 pts had occasional visual aura preceding the attack.

	Schoenen et al. [9] (2013)
Follow-up time, days	90
Loss to follow-up, n (%)	8 (11.9)
Efficacy	
Reduction in monthly migraine attacks, mean n (SD) Difference between I and C	4.37 (1.87)/3.55 (2.94) with p = 0.058 vs. 4.04 (1.52)/3.89 (1.89) with p = 0.516 (baseline/90 days) p = 0.044
Reduction in monthly migraine days, mean n (SD) Difference between I and C	6.94 (3.04)/4.88 (3.46) with p = 0.023 vs. 6.54 (2.61)/6.22 (2.99) with p = 0.082 (baseline/90 days) p = 0.054
Reduction in monthly headache days, mean n (SD) Difference between I and C	7.78 (4.00)/5.27 (3.55) with p = 0.011 vs. 6.72 (2.63)/6.49 (3.2) with p = 0.674 (baseline/90 days) p = 0.041
Reduction in the number of monthly acute antimigraine drug intake, mean n (SD) Difference between I and C	11.45 (8.35)/7.25 (7.31) with p = 0.0057 vs 9.24 (4.75)/9.28 (5.69) with p = 0.822 (baseline/90 days) p = 0.0072
Responder rate, reduction in migraine days, baseline vs. follow-up, n (%)	12 (40) vs. 4 (13.8)
QoL	NA
Satisfaction, n (%) (very/moderately/not at all satisfied/NA)	29.4 (10)/41.2 (14)/21.2 (7)/8.8 (3) vs. 18.2 (6)/21.2 (7)/51.5 (17)/9.1 (3)
Compliance, mean n of sessions out of 90 (%)	55.54 (61.7) vs. 49 (54.4)
Safety	
SADEs , n (%) Pain/intolerance to paresthesia (burning sensation), n (%) Arousal changes (insomnia, sleepiness/fatigue), n (%) Headaches after stimulation, n (%) Nausea after stimulation, n (%) Skin allergy/irritation , n (%)	0 0 0 0 0 0

C – comparator, e-TNS – external trigeminal nerve stimulation, ICD – implantable cardioverter defibrillator, ICHD – International Classification of Headache Disorders, IHS – International Headache Society, I – intervention, IQR – inter-quartile range, hrs – hours, mos – months, min – minutes, NA – data not available, pts – patients, QoL – quality of life, SADEs – serious adverse device effects, SD – standard deviation, yrs – years, VAS – visual analogue scale, WCD – wearable cardioverter defibrillator

Table A-2: e-TNS: Results from randomised controlled trials for acute treatment of episodic and chronic migraine

	Chou et al. [10] (2018)
Country	United States
Sponsor	STX Med – Cefaly® Technology
Study design	Multi-centre, prospective, double-blinded, randomised, sham-controlled trial (NCT02590939)
Conducted in	02/2016 – 03/2017
Indication	***Acute treatment*** in pts with acute migraine (episodic or chronic) with or without aura
Intervention (I)	e-TNS (pulse frequency 100 Hz, pulse width 250 µs, max intensity 16 mA, **60 min**)
Comparator (C)	Sham Cefaly® device (pulse frequency 3 Hz, pulse width 250 µs, max intensity NA, **60 min**)
Number of pts (I vs. C)	52 vs. 54
Inclusion criteria	Pts 18-65 yrs, **episodic/chronic migraine** with or without aura meeting ICHD-III criteria, 3 hrs long attack, pain intensity stabilized for 1 hr, frontal-retro-peri-orbital headache
Exclusion criteria	Pregnancy, Botox in past 4 mos, supra-orbital nerve blocks in past 4 mos, other primary/secondary headache (except medication overuse), temporal/occipital headache pts, opioid medication use, migraine abortive medications in past 3 hrs, allodynia (oversensitivity to pain), metal or electric implants in head, cardiac pacemaker, ICD, WCD, previous Cefaly® pts, pts with complicated migraine (hemiphlegic, basilar-type, ophthalmoplegic, migranous infarction)
Primary outcome measure	Mean change in pain score at 1 hr after intervention
Secondary outcome measure	Mean change in pain score at 2 hrs/24hrs compared to baseline (VAS scale), pts' used rescue medication after 2/24 hrs
Baseline patient characteristics (I vs. C) (intention-to-treat)	
Mean age, yrs (SD)	39.71 (13.62) vs. 40.09 (12.65)
Sex, female:male, n	43:9 vs. 49:5
Migraine with aura, n (%) Migraine without aura, n (%) Migraine duration, yrs Migraine attack duration in hrs, median (IQR) Pts on acute medication, n	12 (23.1) vs. 5 (9.3) 40 (76.9) vs. 49 (90.7) NA 7 (4-48) vs. 6 (4.63-20.75) 17 vs. 14
Follow-up time, days	1
Loss to follow-up, n (%)	5 (9.6) vs. 2 (3.7)[3]

[3] In the IG and the CG, 3 and 1 subjects withdrew and 2 and 1 subjects failed nociceptive test, respectively.

	Chou et al. [10] (2018)
Efficacy	
QoL	NA
Satisfaction, n (%)	NA
Reduction in pain score units on VAS scale compared to baseline at 1 hr, mean n (SD)	-3.46 (2.32); p = 0.0001 vs. -1.78 (1.89); p = 0.0001 p_{Group} = 0.0001
Reduction in pain score units on VAS scale compared to baseline at 2 hrs, mean n (SD)	-2.87 (2.24); p = 0.0001 vs. -1.85 (1.96); p = 0.0001 p_{Group} = 0.028
Reduction in pain score units on VAS scale compared to baseline at 24 hrs, mean n (SD)	-3.46 (2.65); p = 0.0001 vs.-2.38 (2.27); p = 0.0001 p_{Group} = 0.062
Pts on acute antimigraine medication at 2/24 hrs, n (%) Difference between I and C	3 (5.8)/18 (34.6) vs. 2 (3.7)/21 (38.9)[4] 0.66/1
Compliance, mean n of sessions out of 90 (%)	NA
Safety	
SADEs , n (%)	0 vs. 0
Pain/intolerance to paresthesia (burning sensation), n (%)	3 (5.8) vs. 1 (1.9)[5]
Arousal changes (insomnia, sleepiness/fatigue), n (%)	NA
Headaches after stimulation, n (%)	NA
Nausea after stimulation, n (%)	1 (1.9) vs. 0
Skin allergy/irritation , n (%)	NA

C – comparator, e-TNS – external trigeminal nerve stimulation, ICD – implantable cardioverter defibrillator, ICHD – International Classification of Headache Disorders, IHS – International Headache Society, I – intervention, IQR – inter-quartile range, hrs – hours, mos – months, min – minutes, NA – data not available, pts – patients, QoL – quality of life, SADEs – serious adverse device effects, SD – standard deviation, yrs – years, VAS – visual analogue scale, WCD – wearable cardioverter defibrillator

[4] The data on the use of rescue medication was not available for 9.6%/13.5% vs. 3.7%/5.6% of pts at 2/24 hrs.

[5] Before completion of the 1 hr of e-TNS session.

Table A-3 e-TNS: Results from observational studies for prevention of episodic and chronic migraine

	Russo et al. [12] (2015)	DiFiore et al. [11] (2017)	Vikelis et al. [13] (2017)
Country	Italy	Italy	Greece
Sponsor	unclear[6]	unclear[6]	STX Med-Cefaly® Technology and Brain Therapeutics Greece
Study design	Prospective single-arm, interventional trial	Prospective single-arm, interventional, open label preliminary trial	Multi-centre, prospective, single-arm, interventional trial (NCT03125525)
Conducted in	01/2013 – 10/2014	04/2014 – 12/2014	NA
Indication	***Preventive*** treatment in pts with episodic migraine without aura	***Preventive*** treatment in pts with chronic migraine with or without medication overuse	***Preventive*** treatment in pts with episodic or chronic migraine refractory or intolerant to Topiramate/Phrophylaxe
Intervention (I)	e-TNS (pulse frequency 60 Hz, pulse width 250 µs, max intensity 16 mA, **20 min/day**)	e-TNS (pulse frequency 60 Hz, pulse width 250 µs, max intensity 16 mA, **20 min/day**)	e-TNS **(20 min/day)**
Comparator (C)	none	none	none
Number of pts (I vs. C)	24[7]	23	37[8]
Inclusion criteria	Migraine without aura meeting ICHD-III criteria, **episodic migraine of ≤5 attacks per mo**	Pts 18+ yrs, **chronic migraine** with or without medication overuse headache+ meeting ICHD-III criteria, chronic migraine for 1+ yrs, not part of withdrawal program to stop medication overuse, normal neurological exam, normal neuroimaging findings	Pts refractory/intolerant to topiramate, **episodic/chronic** (≥15 days headache/mo) **migraine** according to ICHD-III criteria, stop topiramate 3 mos prior
Exclusion criteria	Other type of headache, somatic and psychosomatic conditions, daily medication intake, migraine drug-naïve pts, no structural brain abnormality confirmed by MRI	Pregnancy, major neurological, systemic or psychiatric illness	NA
Primary outcome measure	Change in monthly migraine days and migraine attacks, % of pts having ≥50% reduction of monthly migraine attacks and migraine days	50% or more reduction in both headache days per month, and in consumption of acute headache relief medications per month	Change in total headache days and days with acute medication use
Secondary outcome measure	Average of pain intensity during migraine attacks (VAS scale), intake of rescue medication during migraine attacks, satisfaction, compliance, HIT-6 score	NA	NA

[6] STX Med provided the Cefaly® devices, but it is stated that the study was not industry sponsored.

[7] Baseline data on 20 pts.

[8] 2 pts dropped out before using e-TNS device. Baseline data on 35 pts.

	Russo et al. [12] (2015)	DiFiore et al. [11] (2017)	Vikelis et al. [13] (2017)
Baseline patient characteristics (I vs. C)			
Mean age, yrs (SD)	32.9 (2.3)	43.7 (13.6)	45 (median), 22-62 (range)
Sex, female:male, n	15:5	18:5	31:4
Migraine with aura, n (%)	0 (0)	NA	NA
Migraine without aura, n (%)	24 (100)	NA	NA
Migraine duration, mean n of yrs (SD)	8.3 (1.7)	26.4 (12.8)[9]	NA
Migraine attack duration in hrs, median (IQR)	NA	NA	NA
Follow-up time, days	60	120	90
Loss to follow-up, n (%)	4 (16.7)[10]	4 (17.4)[11]	8 (21.6)
Efficacy			
Reduction in monthly migraine attacks, mean n	4.6/2.1[12] (baseline/60 days)	NA	NA
Difference, mean (p-value)	2.5 (<0.001)	NA	NA
Reduction in monthly migraine days, mean n	6.6/3.1 [12] (baseline/60 days)	20.7/ 14.3[13] (baseline/120 days)	NA
Difference, mean n (p-value)	3.5 (<0.001)	31.0% (NA)	NA
Reduction in monthly headache days, mean (SD)	NA	NA	8.9 (4.7)/6.3 (3.5) (baseline/90 days)
Difference, mean n (p-value)	NA	NA	2 (<0.001)
Reduction in monthly acute anti-migraine drug intake, (n of times per month), mean (SD)	5.6 (0.4)/2.2 (0.3)[14] (baseline/60 days)	20.2/10.2 [13] (baseline/120 days)	8.2 (4.6)/4.4 (3.3) (baseline/90 days)
Difference, mean n [%] (p-value)	3.4 [40.7] (<0.001)	49.6% (NA)	46.3% (NA)

[9] Mean duration of the chronic phase was 10.7 (8.7).

[10] Pts excluded from the analysis for non-compliance (compliance defined in the study as ≥2/3 of total 60 treatment days).

[11] 1 pt due to keratoconjunctivitis, 3 pts due to inability to tolerate e-TNS. Efficacy reported for 19 pts who fulfilled 4-months treatment schedule.

[12] Translated from figure, as values were not explicitly reported on in the text. Unclear if mean or median.

[13] Analysis based on 19 pts.

[14] Unclear if it refers to monthly intake because the text states “total intake”.

	Russo et al. [12] (2015)	DiFiore et al. [11] (2017)	Vikelis et al. [13] (2017)
Responder rate, reduction in migraine days, baseline vs. follow-up, %	75	NA	NA
QoL	NA	NA	NA
Satisfaction, n (%)	20 (83.3)[15]	NA	23 (65.7)
Compliance, n (%)	20 (83.3)[16]	19 (82.6)	27 (81.8)
Safety			
SADEs, n	0	0	0
Pain/intolerance to paresthesia (burning sensation), n (%)	0	0	12 (34.3)
Arousal changes (insomnia, sleepiness/fatigue), n (%)	0 (0)	0 (0)	NA
Headaches after stimulation, n (%)	0 (0)	1 (4.3)	NA
Nausea after stimulation, n (%)	0 (0)	0 (0)	NA
Skin allergy/irritation, n (%)	0 (0)	0 (0)	NA
Neck tension, n (%)	NA	2 (8.7)	NA

e-TNS – external trigeminal nerve stimulation, ICD – implantable cardioverter defibrillator, ICHD – International Classification of Headache Disorders, IQR – inter-quartile range, hrs – hours, min – minutes, mITT – modified intention-to-treat, mos – months, MRI – magnetic resonance imaging, NA – data not available, pts – patients, QoL – quality of life, SADEs – serious adverse device effects, SD – standard deviation, yrs – years, VAS – visual analogue scale, WCD – wearable cardioverter defibrillator

[15] Not measured, but defined by willingness to continue using e-TNS. Patients excluded due to non-compliance are part of this analysis.

[16] 4 pts (16.7%) were considered non-compliant as they did not finish with ≥ 800 min of e-TNS treatment in the 60 days trial period.

Table A-4: e-TNS: Results from observational studies for acute treatment of episodic and chronic migraine

	Chou et al. [14] (2017)	Mann et al. [15] (2018)
Country	United States	United States
Sponsor	STX Med -Cefaly® Technology	STX Med -Cefaly® Technology
Study design	Prospective single-arm, interventional, open label trial (NCT02411513)	Single center, prospective, open-label, phase 1 trial (NCT03217968).
Conducted in	04/2015 – 10/2015	08/2017 – 01/2018
Indication	***Acute treatment*** in pts with acute migraine attack (episodic or chronic) with or without aura	***Acute treatment*** in pts with single moderate or severe migraine attack (Grade 2 or 3) at home, pts with episodic migraine
Intervention (I)	e-TNS (pulse frequency 100 Hz, pulse width 250 µs, max intensity 16 mA, **60 min**)	e-TNS (pulse frequency 100 Hz, pulse width 250 µs, max intensity 16 mA, **120 min**)
Comparator (C)	none	none
Number of pts (I vs. C)	35[17]	60[18]
Inclusion criteria	Pts 18-65 yrs, **episodic/chronic migraine** with or without aura meeting ICHD-III criteria, 3+ hrs long attack, pain intensity stabilized for 1 hr, frontal-retro-peri-orbital headache	Pts 18-65 yrs, ≥ 1-year history of **episodic migraine with or without aura** meeting ICHD-III criteria, migraine onset before 50 yrs of age, 2-8 moderate-severe migraine attacks/mo in each of the 2 mos prior to screening, pts' consent
Exclusion criteria	Pregnancy, Botox in the head in past 4 mos, supra-orbital nerve blocks in past 4 mos, other primary/secondary headache (except medication overuse), temporal/occipital headache pts, opioid medication use, migraine abortive medications in past 3 hrs, allodynia (oversensitivity to pain), metal or electric implants in head, cardiac pacemaker, ICD, WCD, pts with complicated migraine (hemiphlegic, basilar-type, ophthalmoplegic, migranous infarction)	Pts' difficulty distinguishing migraine from tension-type headache, >15 headaches per month (**chronic migraine pts**), migraine aura without headache, hemiplegic migraine and brainstem aura migraine, pts with supraorbital nerve blocks or Botox in the head in the prior 4 mos, migraine prophylaxis modification in prior 3 mos, other primary/secondary headache disorders (medication overuse), pts with opioid, alcohol or illicit drugs abuse, metallic or electric device in head, cardiac pacemaker, ICD, WCD, prior experience with Cefaly®, participation in other study in past 30 days, pts unable to self-service or bear the e-TNS stimulation
Primary outcome measure	Mean change in pain intensity after one-hour *acute treatment* compared to baseline	Freedom from pain and from most bothersome migraine-associated symptoms (photophobia, phonophobia, nausea, vomiting) at 2 hrs post-*acute treatment* with e-TNS
Secondary outcome measure	Change in pain intensity after two-hour *acute treatment* compared to baseline (VAS scale), percentage of pts not requiring rescue medication at 2 hrs/24 hrs	Reduction of moderate to severe migraine headache and percentage of pts with absence of photophobia, phonophobia, nausea, vomiting at 2 hrs from baseline. Measured at baseline, 2 hrs, 24 hrs, on the scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain
Baseline patient characteristics (I vs. C)		
Mean age, yrs (SD)	39.4 (12.5)	46.85 (10.2)

[17] Baseline data on 30 pts.

[18] mITT analysis with 48 pts.

	Chou et al. [14] (2017)	Mann et al. [15] (2018)
Sex, female:male, n	24:6	43:5
Migraine with aura, n (%)	NA	15 (25)
Migraine without aura, n (%)	NA	33 (55)
Migraine duration, yrs	NA	>1[19]
Migraine attack duration in hrs, median (IQR)	NA	NA
Pts on medication, mean (SD)	NA	NA
Other baseline symptoms: (n (%)		
❁ Nausea	NA	11 (18.3)
❁ Vomiting	NA	1 (1.66)
❁ Sensitivity to light	NA	27 (45)
❁ Sensitivity to sound	NA	9 (15)
Follow-up time, days	1	1
Loss to follow-up, %	5[20]	12[21]
Efficacy		
QoL	NA	NA
Satisfaction, n (%)	NA	NA
Headache pain free pts at 2/24 hrs post-*acute treatment*, n (%)	NA/NA	17 (35.4)/12 (25)
Freedom from nausea, vomiting, sensitivity to light and sound at 2 hrs, n (%)	NA	22 (36.7)[22]
Reduction in pain score units on VAS scale compared to baseline at 1 hr, mean n (SD)	-3.22 (2.4) p<0.001)	NA
Reduction in pain score units on VAS scale compared to baseline at 2 hrs, mean n (SD)	-2.98 (2.31) p<0.001	34 (NA) [23]
Pts on rescue medication at 2/24 hrs, n (%)	0 (0)/17 (48.6)[24]	NA/ 24 (40)[25]

[19] Not specified.

[20] 1 pt due to opioid use in past 3 mos, 4 pts due to inability to tolerate e-TNS.

[21] 1 pt failed the training test, 4 pts withdrew from the study, 1 pt was lost to follow-up and 6 pts did follow the study protocol.

[22] From the results document it is unclear if 22 or 29 patients were free from the most bothersome symptoms.

[23] Number (%) of pts with pain relief at 2 hrs, not measured on VAS scale.

[24] 34.6% out of 26 pts as 4 pts were lost to follow-up (not reachable at 24hrs).

	Chou et al. [14] (2017)	Mann et al. [15] (2018)
Compliance, n (%)	NA	49 (81.7)[26]
Safety		
SADEs , n (%)	0 (0)	0 (0)
Pain/intolerance to paresthesia (burning sensation), n (%)	0 (0)	7 (11.9)
Arousal changes (insomnia, sleepiness/fatigue, drowsiness), n (%)	0 (0)	1 (1.7)[27]
Headaches after stimulation, n (%)	0 (0)	NA
Nausea after stimulation, n (%)	0 (0)	2 (3.5)[27]
Dizziness, n (%)	NA	1 (1.7)
Vomiting, n (%)	NA	1 (1.7)
Pain in the jaw, n (%)	NA	1 (1.7)
Discomfort in teeth, n (%)	NA	1 (1.7)
Pain in eyes, n (%)	NA	1 (1.7)
Cold feet, n (%)	NA	1 (1.7)
Skin allergy/irritation, n (%)	NA	1 (1.7)
Neck tension, n (%)	0 (0)	11 (18.3)
	0 (0)	NA

e-TNS – external trigeminal nerve stimulation, ICD – implantable cardioverter defibrillator, ICHD – International Classification of Headache Disorders, IQR – inter-quartile range, hrs – hours, min – minutes, mITT – modified intention-to-treat, mos – months, MRI – magnetic resonance imaging, NA – data not available, pts – patients, QoL – quality of life, SADEs – serious adverse device effects, SD – standard deviation, yrs – years, VAS – visual analogue scale, WCD – wearable cardioverter defibrillator

[25] 50 out of 48 pts as 12 were lost to follow-up.

[26] Defined as withdrawal, loss to follow-up, or violation of protocol.

[27] ADEs reported out of 59 pts

Risk of bias tables

Internal validity of the included studies was judged by three independent researchers. All disagreements were solved through discussion. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [38] and in the Guidelines of EUnetHTA [39].

Table A-5: Risk of bias – study level (randomised studies), see [32]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Schoenen et al. [9] (2013)	Unclear[28]	Yes	Yes	Yes	Unclear[29]	Yes	Moderate
Chou et al. [10] (2018)	Unclear[28]	Unclear[30]	Yes	Yes	Unclear[31]	No[32]	High

[28] Insufficient information about sequence generation process.

[29] Even though it was reported that no adverse events or side effects occurred during the trial in both treatment arms, it seems unlikely.

[30] Method of concealment is not described to allow a definite judgement.

[31] Considering the sample size, there are reasons to think that not all ADEs s and SADEs were reported.

[32] Conflict of interest: study sponsored by the manufacturer.

Table A-6: Risk of bias – study level (case series), see [33]

Study reference/ID	Russo et al. [12] (2015)	DiFiore et al. [11] (2017)	Vikelis et al. [13] (2017)	Chou et al. [14] (2017)	Mann et al. [15] (2018)
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes
Study design					
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes	Yes	No	No
4. Were patients recruited consecutively?	Yes	Yes	Unclear	Unclear	Unclear
Study population					
5. Were the characteristics of the participants included in the study described?	Yes	Yes	Partial	Partial	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the studyclearly stated?	Partial[33]	Partial[34]	Partial[34]	Yes	Yes
7. Did participants enter the study at similar point in the disease?	Yes	Yes	No	No	Yes
Intervention and co-intervention					
8. Was the intervention clearly described?	Yes	Yes	No[35]	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	No[36]	No	Yes	Yes
Outcome measure					
10. Were relevant outcome measures established a priori?	Yes	Partial[37]	Partial	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear[38]	Unclear[38]	Unclear[38]	Unclear[38]	Unclear[38]
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes[39]	Partial	Partial	Partial	Partial
13. Were the relevant outcomes measured before and after intervention?	Yes[40]	Yes[40]	Yes[40]	Yes[40]	Yes[40]

[33] Only the exclusion criteria were clearly stated in the study.

[34] Exclusion criteria were not explicitly mention in the study.

[35] Information on pulse frequency, pulse width and maximal intensity was missing.

[36] "Preexisting *preventive* and *acute treatments* for CM were not changed" was an insufficient explanation of co-interventions present.

[37] Only the primary endpoints were mentioned a priori.

[38] No information is given if the outcome assessors were blinded to the intervention.

[39] However, the validity of used methods to measure outcomes was unclear.

[40] Satisfaction was not measure before the intervention in any of the studies.

Study reference/ID	Russo et al. [12] (2015)	DiFiore et al. [11] (2017)	Vikelis et al. [13] (2017)	Chou et al. [14] (2017)	Mann et al. [15] (2018)
Statistical Analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes[41]	No[42]	No[43]	Yes	No[44]
Results and Conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	No[45]	No[45]	No[45]	No[45]	No[45]
16. Was the loss to follow-up reported?	Yes	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial	No	Partial	No
18. Were adverse events reported?	Yes[46]	Yes	Yes	Partial	Yes
19. Were the conclusions of the study supported by results?	No[47]	No[48]	No[47]	No[47]	No[47, 49]
Competing interest and source of support					
20. Were both competing interest and source of support for the study reported?	Yes	Yes	Yes	Partial[50]	Partial[50]
Overall Risk of bias	**Low**	**Moderate**	**High**	**Moderate**	**Moderate**

[41] It is not stated at what point or where parametric (*paired t-test*) and non-parametric (*Wilcoxon sign-rank test*) measures have been applied.

[42] Only descriptive statistics were used.

[43] Fisher's exact test and the Mann-Whitney test are mentioned in the methods section, but the results fail to present any results from these tests.

[44] Only descriptive statistics were used.

[45] Unclear if of follow-up is enough for the effect of *preventive* treatment. It is taken for granted that TENs machines should have minor ADEs and SADEs even if applied onto the head.

[46] It was reported that no adverse events occurred in the study population, yet it is assumed otherwise.

[47] The study design cannot meet the conclusions about effectiveness.

[48] The study design cannot meet the conclusions about effectiveness and the conclusions are only made on the basis of a subgroup of patients from the results.

[49] Study not published yet, data available only at clinicaltrials.gov.

[50] Source of support for the study is unclear.

GRADE Evidence profile tables

Table A-7: Evidence profile table: efficacy and safety of e-TNS for the prevention of episodic/chronic migraine patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	e-TNS	Placebo	Relative (95% CI)	Absolute (95% CI)		
Reduction in monthly migraine attacks (assessed with: mean number of days)												
1	randomised controlled trial	not serious	not serious	serious[a]	serious[b]	none	The mean reduction in the number of monthly migraine attacks in the IG (n=34) was 0.67 more than in the CG (n=33). Difference between IG and CG was p = 0.044.				⨁⨁◯◯ LOW	IMPORTANT
Reduction in monthly migraine days (assessed with: mean)												
1	randomised controlled trial	not serious	not serious	serious[a]	serious[b]	none	The mean reduction in the number of monthly migraine days in the IG (n=34) was 1.74 more than in the CG (n=33). Difference between IG and CG was p = 0.054.				⨁⨁◯◯ LOW	CRITICAL
Reduction of monthly headache days (assessed with: mean)												
1	randomised controlled trial	not serious	not serious	serious[a]	serious[b]	none	The mean reduction in the number of monthly headache days in the IG (n=34) was 2.28 more than in the CG (n=33). Difference between IG and CG was p = 0.041.				⨁⨁◯◯ LOW	IMPORTANT
Reduction in the number of monthly acute antimigraine drug intake												
1	randomised controlled trial	not serious	not serious	serious[a]	serious[b]	none	The mean reduction in the number of monthly acute anti-migraine drug intake in the IG (n=34) was 4.24 more than in the CG (n=33). Difference between IG and CG was p = 0.072.				⨁⨁◯◯ LOW	CRITICAL
High or moderate satisfaction												
1	randomised controlled trial	serious [c]	not serious	serious [a]	serious [b]	none	70.6% (IG, n=34) vs.39.4% (CG, n=33)				⨁◯◯◯ VERY LOW	CRITICAL
Serious Adverse device effects												
1	randomised controlled trial	serious [c]	not serious	serious [a]	serious [b]	none	0/34 (IG) vs. 0 /33(CG)				⨁◯◯◯ VERY LOW	CRITICAL
Adverse device effects												
1	randomised controlled trial	serious [c]	not serious	serious [a]	serious [b]	none	0/34 (IG) vs. 0/33 (CG)				⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations: *CG = Control group, CI = Confidence interval, IG = Interventional group, n= number, pts = Patients, RCT = Randomised controlled trial, VAS = Visual Analogue Scale*

Explanations: *[a] Wrong comparator, [b] Small sample size, [c] Uncertainty about sufficient reporting of adverseevents*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table A-8: Evidence profile table: efficacy and safety of e-TNS for the acute treatment of episodic/chronic migraine patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	e-TNS	Placebo	Relative (95% CI)	Absolute (95% CI)		
Reductionin pain score units on scale compared to baseline at 1 hr												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	The mean improvement of IG (n=52) over CG (n=54) in reduction in pain score units on VAS scale compared to baseline at 1 hr was 1.68 (p_{Group} = 0.0001).				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in pain score units on scale compared to baseline at 24 hrs												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	The mean improvement of IG (n=52) over CG (n=54) in reduction in pain score units on VAS scale compared to baseline at 1 hr was 1.02 (p_{Group} = 0.028).				⨁◯◯◯ VERY LOW	IMPORTANT
Reduction in pain score units on scale compared to baseline at 24 hrs												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	The mean improvement of IG (n=52) over CG (n=54) in reduction in pain score units on VAS scale compared to baseline at 1 hr was 1.08 (p_{Group} = 0.062).				⨁◯◯◯ VERY LOW	CRITICAL
Patients on acute medication at 2 hrs												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	3/52 (IG) vs. 2/54 (CG)				⨁◯◯◯ VERY LOW	CRITICAL
Patients on acute medication at 24 hrs												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	18/52 (IG) vs. 21/54 (CG)				⨁◯◯◯ VERY LOW	IMPORTANT
Serious Adverse device effects												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	0/52 (IG) vs. 0/54 (CG)				⨁◯◯◯ VERY LOW	CRITICAL
Adverse device effects												
1	randomised controlled trial	serious [a,b,c]	not serious	serious [d]	serious [e]	none	Intolerance to paresthesia in 3/52 (IG) vs. 1/54 (CG). Nausea after stimulation in 1/52 (IG) vs. 0/54 (CG)				⨁◯◯◯ VERY LOW	IMPORTANT

Abbreviations: *CG = Control group, CI = Confidence interval, IG = Interventional group, n= number, pts = Patients, RCT = Randomised controlled trial, VAS = Visual Analogue Scale*

Explanations: [a] *Funded by the manufacturer,* [b] *Insufficient information about sequence generation process,* [c] *Method of concealment is not described to allow a definite judgement* [d] *Wrong comparator,* [e] *Small sample size*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Applicability table

Table A-9: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population enrolled in the studies is similar to the target population of the intervetion in that both episodic as well as chronic migraine patients are included, patients are of simialr age, and the proportion of women is similar. However, there is a number of differences in inclusion and exclusion criteria between both *preventive* as well as *acute treatment* studies. The main ones are that some studies include while others exclude chronic migraine patients, some require treatment-naïve patients, while others treatment refractory, or some include while others exclude patients with medication overuse headche.
Intervention	External trigeminal nerve stimulation (e-TNS) (previously called also Supraorbital transcutaneous nerve stimulation (s-TNS) – original name changed after GMDN code to e-TNS) is the intenvention under assessment. Its product name is Cefaly®.
Comparators	Comparators differ for the *acute treatment* vs. *prevention* use of e-TNS. For prevention, topiramate, propranolol or placebo were considered comparators, while for *acute treatment*, triptans + NSAIDs/ Paracetamol were considered as comparators.
Outcomes	For the *preventive* use of e-TNS, the crucial outcomes considered were Reduction in monthly migraine days, Reduction in monthly acute antimigraine drug intake, and Satisfaction. Further outcomes considered were Reduction in monthly migraine attacks, Reduction in monthly headache days, QoL, and Compliance. For the *acute treatment* use of e-TNS, the crucial outcomes comsidered were Change in pain score units on VAS scale compared to baseline at 1/2/24 hours, Patients on acute antimigraine medication at 2/24 hours, and Satisfaction. Furhter outcomes considered were Headache pain free patients at 2/24 hours post-*acute treatment*, Improvement in nausea, vomiting, sensitivity to light and sound at 2 hours, QoL, and Compliance. Crucial safety outcomes considered were Serious adverse device effects, while further outcomes considered were Pain/intolerance to paraesthesia (burning sensation), Arousal changes (insomnia, sleepiness/fatigue), Headaches after stimulation, Skin allergy, Neck tension, Nausea after stimulation, Dizziness, Vomiting, Pain in the jaw, Discomfort in teeth, Pain in eyes, and Cold feet.
Setting	All of the studies included were either single-centre or multi-centre studies, with clinical centres based in Europe and the United States. The studies were specifically conducted in Belgium, Italy, Greece, and the US, and these contexts are considered similar to the Austrian one. Clinical settings were not described in all of the studies, but it is likely that all patients received-standard care at university hospitals.

List of ongoing randomised controlled trials

Table A-10: List of ongoing randomised controlled trials of e-TNS

Identifier/ Trial name	Patient population	Estimated enrolment	Intervention	Comparison	Primary Outcomes	Primary completion date	Sponsor
NCT03465904/ A Phase III Trial of e-TNS for the *Acute Treatment* of Migraine (TEAM)	Episodic migraine patients with or without aura	600	e-TNS (Cefaly®) device	Sham e-TNS (Cefaly®) device	Pain Freedom at 2 hours. Most bothersome migraine-associated symptom freedom at 2 hours	October 2018	STX Med – Cefaly® Technology

Literature search strategies

Search strategy for Cochrane

Search Name: External nerve stimulation for migraine	
Search Date: 07/05/2018	
ID	Search
#1	MeSH descriptor: [Migraine Disorders] explode all trees
#2	migrain* (Word variations have been searched)
#3	#1 or #2
#4	MeSH descriptor: [Electric Stimulation] explode all trees
#5	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#6	neurostimul* (Word variations have been searched)
#7	neuro-stimul* (Word variations have been searched)
#8	electrostimul* (Word variations have been searched)
#9	electro-stimul* (Word variations have been searched)
#10	neuromodulat* (Word variations have been searched)
#11	neuro-modulat* (Word variations have been searched)
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Trigeminal Nerve] explode all trees
#14	(trigemin* or tri-gemin* or supraorb* or supra-orb*) near nerve* (Word variations have been searched)
#15	#13 or #14
#16	#12 and #15
#17	(transcutaneous* or trans-cutaneous* or extern*) near ((trigemin* or tri-gemin* or supraorb* or supra-orb*) near (stimul* or neurostim* or neuro-stim*)) (Word variations have been searched)
#18	e-TNS (Word variations have been searched)
#19	eTNS (Word variations have been searched)
#20	s-TNS (Word variations have been searched)
#21	sTNS (Word variations have been searched)
#22	t-SNS (Word variations have been searched)
#23	tSNS (Word variations have been searched)
#24	Cefaly (Word variations have been searched)
#25	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#3 and #25
#27	supraorbital transcutaneous near (nerve stimul* or neurostimul* or neuro-stimul*):ti,ab,kw (Word variations have been searched)
#28	#26 or #27
Total: 23 Hits	

Search strategy for CDR

Search Name: External nerve stimulation for migraines (MS/SW/HJ)	
Search Date:07/05/2018	
ID	Search
#1	MeSH DESCRIPTOR Migraine Disorders EXPLODE ALL TREES
#2	(migrain*)

#3	#1 OR #2
#4	MeSH DESCRIPTOR Electric Stimulation EXPLODE ALL TREES
#5	MeSH DESCRIPTOR Electric Stimulation Therapy EXPLODE ALL TREES
#6	(neurostimul*)
#7	(neuro-stimul*)
#8	(electrostimul*)
#9	(electro-stimul*)
#10	(neuromodulat*)
#11	(neuro-modulat*)
#12	((trigemin* OR tri-gemin* OR supraorb* OR supra-orb*) NEAR nerve*)
#13	MeSH DESCRIPTOR Trigeminal Nerve EXPLODE ALL TREES
#14	((transcutaneous* OR trans-cutaneous* OR extern*) NEAR ((trigemin* OR tri-gemin* OR supraorb* OR supra-orb*) NEAR (stimul* OR neurostim* OR neuro-stim*)))
#15	(e-TNS)
#16	(eTNS)
#17	(s-TNS)
#18	(sTNS)
#19	(t-SNS)
#20	(tSNS)
#21	(Cefaly)
#22	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#3 AND #22
#24	(supraorbital transcutaneous neurostimulation):TI
Total:8 Hits	

Search strategy for Medline

Search Name: External nerve stimulation for migraines (MS/SW/HJ)	
Search Date: 03/05/2018	
ID	Search
#1	exp Migraine Disorders/ (24860)
#2	migrain*.mp. (35408)
#3	1 or 2 (35428)
#4	exp Electric Stimulation/ (123832)
#5	exp Electric Stimulation Therapy/ (71107)
#6	neuro?stimul*.mp. (2965)
#7	electro?stimul*.mp. (3271)
#8	neuro?modulat*.mp. (14238)
#9	4 or 5 or 6 or 7 or 8 (206462)
#10	exp Trigeminal Nerve/ (16014)
#11	((tri?geminal* or supra?orbital*) adj3 nerve*).mp. (14604)
#12	10 or 11 (21127)
#13	9 and 12 (1889)
#14	((trans?cutaneous* or extern*) adj5 ((tri?geminal* or supra?orbital*) adj3 (stimul* or neuro?stim*))).mp. (53)
#15	e?TNS.ti,ab. (26)

#16	s?TNS.ti,ab. (142)
#17	t?SNS.ti,ab. (52)
#18	Cefaly.ti,ab. (14)
#19	13 or 14 or 15 or 16 or 17 or 18 (2120)
#20	3 and 19 (175)
#21	remove duplicates from 20 (175)
Total: 175 hits	

Search strategy for Embase

Search Name: External nerve stimulation for migraines (MS/SW/HJ)	
Search Date: 03/05/2018	
ID	Search
#1	'migraine'/exp
#2	migrain*:ti,ab
#3	#1 OR #2
#4	'nerve stimulation'/exp
#5	'electrostimulation'/exp
#6	'electrotherapy'/exp
#7	'neuromodulation'/exp
#8	electrostimul*:ti,ab
#9	'electro stimul*':ti,ab
#10	'neurostimul*':ti,ab
#11	(neuro-modulat*)
#12	'neuro-stimul*':ti,ab
#13	'neuro-modulat*':ti,ab
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	'trigeminal nerve'/exp
#16	'supraorbital nerve'/exp
#17	((trigeminal* OR 'tri geminal*' OR supraorbital* OR 'supra orbital*') NEAR/3 nerve*):ti,ab
#18	#15 OR #16 OR #17
#19	#14 AND #18
#20	((transcutaneous* OR 'trans cutaneous*' OR extern*) NEAR/5 (trigeminal* OR 'tri geminal*' OR supraorbital* OR 'supra orbital*')):ti,ab
#21	(transcutaneous* OR 'trans cutaneous*' OR extern*) NEAR/5 (trigeminal* OR 'tri geminal*' OR supraorbital* OR 'supra orbital*') NEAR/3
#22	'e tns':ti,ab
#23	#3 AND #22
#24	'etns':ti,ab
#25	's-tns':ti,ab
#26	't-sns':ti,ab
#27	'tsns':ti,ab
#28	cefaly:ti,ab
#29	cefaly:dn
#20	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31	#3 AND #30
Total: 350 hits	

Search strategy for ClinicaTrials.gov

Date: 22/05/2018

(Cefaly OR stimul* OR Electric Stimulation OR electrostim* OR electro-stim* OR neurostim* OR neuro-stim* OR neuromodulat* OR neuro-modulat* OR trigemin* OR tri-gemin* OR supraorb* OR supra-orb* OR e-TNS OR eTNS OR s-TNS OR sTNS OR t-SNS OR tSNS) AND Migraine [DISEASE]

Total: 23 hits

Search strategy for WHO-ICTRP

Date: 22/05/2018

Condition: Migraine

AND

Intervention: Cefaly OR stimul* OR Electric Stimulation OR electrostim* OR electro-stim* OR neuro-stim* OR neuro-stim* OR neuromodulat* OR neuro-modulat* OR trigemin* OR tri-gemin* OR supra-orb* OR supra-orb* OR e-TNS OR eTNS OR s-TNS OR sTNS OR t-SNS OR tSNS

Total: 50 (37 further) hits

Search strategy for EU Clinical Trials (EUdraCT)

Date: 22/05/2018

migrain* AND (Cefaly OR stimul* OR electric OR electrostim* OR neurostim* OR neuromodulat* OR trigemin* OR supraorb* OR transcutaneous* OR extern* OR electro-stim* OR neuro-stim* OR neuro-modulat* OR tri-gemin* OR supra-orb* OR e-TNS OR eTNS OR s-TNS OR sTNS OR t-SNS OR tSNS)

Total: 10 studies hits

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Health Technology Assessment