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SUMMARY WITH CRITICAL APPRAISAL

Non-invasive Nerve Stimulation Modalities for Migraine Pain: A Review of Clinical Effectiveness and Cost-effectiveness

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CRD	University of York Centre for Reviews and Dissemination
eTNS	External Trigeminal Nerve Stimulation
HIT-6	Headache ImpacT scale
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICH	International Classification of Headache Disorders.
NINS	Non-Invasive Nerve Stimulation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Years
RCT	Randomized Control Trials
rTMS	repetitive Transcranial Magnetic Stimulation
sTMS	single pulse Transcranial Magnetic Stimulation
tONS	transcutaneous Occipital Nerve Stimulation
tSNS	transcutaneous Supraorbital Neurostimulation
VAS	Visual Analog Scale
YLD	Years of Life lived with Disability

Context and Policy Issues

Migraine is a common debilitating neurological condition characterized by the presence of unilateral pulsatile headaches with or without an aura lasting up to 72 hours.[1] Globally, migraine was found to be the second most leading cause of years lived with disability (YLDs) amounting to 45.1 million, after low back pain.[2] Statistics Canada reports that approximately 8.3% of Canadians have been diagnosed with migraine based on the 2010/11 Canadian Community Health Surveys. [3] In 2017, migraine accounted for about 770 Years Lived with Disability (YLD) per 100,000 in Canada.[4]

Based on the number of average headache attacks per month, the disorder can be grouped into episodic and chronic migraine. Episodic migraine is diagnosed when the number of migraine days per month are 14 or less whereas a migraine disorder is classified as chronic if headache symptoms are present at least 15 days per month, of which at least eight days fulfill the migraine criteria set by the International Classification of Headache Disorders (ICH). [1]

Migraines are treated prophylactically (before an attack occurs) and abortive (for acute treatment of attacks) using various pharmacological and non-pharmacological interventions. Non-invasive Nerve Stimulation (NINS) modalities are neuromodulation methods which

involve stimulating central or peripheral nervous system with a non-painful magnetic field or an electric current using electrodes/devices applied on top of skin at strategic positions over the nerves involved. [5,6] There are several NINS devices available for migraine treatment and prevention. The modalities discussed in the current report include external trigeminal nerve stimulation (e-TNS), repetitive transcranial magnetic stimulation (rTMS) and transcutaneous occipital nerve stimulation (tONS).

e-TNS is a modality also known as Transcutaneous Supraorbital Neurostimulation (tSNS) under the brand name Cefaly®. e-TNS devices are applied on the forehead to stimulate the bilateral supraorbital nerves which are a branch of trigeminal nerve.[6,7] TMS devices generate magnetic pulses applied directly to the back of the neck over the occipital cortex to stimulate the cerebral cortex directly. Single pulse (sTMS) and repetitive pulse (rTMS) are different types of TMS. [6,8] tONS are relatively new NINS devices that stimulate the bilateral occipital nerve and are applied over the occipital areas of the neck. [6]

The objective of this rapid response report is to summarize the evidence regarding the clinical effectiveness and cost effectiveness of NINS modalities for prophylactic and abortive treatment for episodic and chronic migraine pain.

Research Questions

1. What is the clinical effectiveness of non-invasive nerve stimulation modalities for adult patients with migraine pain?
2. What is the cost-effectiveness of non-invasive nerve stimulation modalities for adult patients with migraine pain?

Key Findings

This report included two health technology assessments (HTAs) and two systematic reviews (SRs) that identified one unique primary study, in addition to two randomized controlled trials (RCTs) regarding the clinical effectiveness of various non -invasive nerve simulation (NINS) modalities for the treatment of migraine pain. However, of the included HTAs and SRs, only one of the SRs included a relevant primary study.

There is a lack of evidence on the effectiveness of NINS modalities compared to standard of care. The limited comparative clinical evidence suggests that migraine prophylaxis with NINS devices such as transcutaneous Supraorbital Neurostimulation (tSNS), transcutaneous Occipital Nerve Stimulation (tONS) and repetitive Transcranial Magnetic Stimulation (rTMS) were not different compared to standard of care (pharmacological and non-pharmacological interventions) in improving clinical symptoms. However, the findings should be interpreted with caution, in light of the limited available evidence and the quality and generalizability of included studies. The modalities were found to be effective in improving symptoms and safe with few adverse events. No evidence was found for the clinical effectiveness of NINS devices in abortive treatments of acute migraine attacks. No evidence regarding the cost effectiveness of NINS devices compared to standard of care were identified. No evidence on the clinical and cost effectiveness of other available NINS devices were found.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were migraine and non-invasive neurostimulation. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and March 11, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with migraine pain (e.g., chronic, episodic)
Intervention	Any type of non-invasive nerve stimulation modality (NINS), [e.g., TMS (rTMS, stMS, paied pulse TMS, dTMS,) TBS, tCDS, sTNS, eTNS, vagal nerve stimulation] applied as a prophylactic or abortive migraine treatment method
Comparator	Standard of care, which may include pharmacological interventions (e.g., triptans, nonsteroidal anti-inflammatory drug, acetaminophen, other migraine medications) or non-pharmacological interventions (e.g., behavioural therapy, physical therapy)
Outcomes	Q1: Clinical effectiveness (e.g., headache frequency, duration, intensity, pain symptoms, functional performance, health-related quality of life, safety) Q2: Cost-effectiveness (e.g., cost per QALY, cost per benefit gained)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations.

dTMS = deep Transcranial Magnetic Stimulation; eTNS= external Trigeminal Nerve Stimulation; NINS = non-invasive nerve stimulation modality; QALY= Quality Adjusted Life Years; r-TMS = repetitive Transcranial Magnetic Stimulation; sTMS = single pulse Transcranial Magnetic Stimulation; TBS = Theta Burst magnetic Stimulation;; tCDS = transcranial Direct Current Stimulation; tSNS = transcutaneous Supraorbital Neuro Stimulation

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlines in Table 1, they were duplicate publications or were published prior to 2015. Original research articles with combined NINS and pharmacological interventions were excluded.

Critical Appraisal of Individual Studies

The included HTAs and SRs were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews II (AMSTAR II) [9] and the RCTs were critically appraised using Downs and Black Checklist [10]. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 298 studies were identified by the literature search. Following screening of titles and abstracts, 236 citations were excluded and 62 potentially relevant reports from the electronic search were retrieved for full text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these 66 articles, 60 were excluded for various reasons and six publications met the inclusion criteria and were included in this report. These comprised two HTAs [11,12], two SRs [13,14] and two RCTs. [15,16] Appendix 1 presents the PRISMA [17] flow chart of the study selection. Additional references for potential interests are provided in Appendix 5.

Summary of Study Characteristics

Six publications were identified and included in this report. They comprised two HTAs [11,12], two SRs [13,14] and two RCTs.[15,16] No relevant non-randomized studies or economic evaluations not already included in the SRs were identified. The details regarding the characteristics of included publications are provided in Appendix 2, Table 2 and Table 3.

Among the included publications, two HTAs and one SR had a broader scope and selection criteria, than the current report. The HTA by Brown et al. (2018)[11] aimed to synthesize the evidence on the clinical effectiveness of all neuromodulation methods in cancer and non-cancer pain, while the HTA by Skelly et al. (2017)[12] and the SR by Stilling et al. (2019)[14] included studies of patients with migraine as well as other headache disorders. Only the characteristics and results of primary studies that are relevant to this report are summarized and described here.

Study Design

The systematic review by Stilling et al (2019) [14] included randomized and non-randomized studies, and searched for studies published up to September 2018. The SR included 34 studies, among which one RCT was relevant to the current report. [18] The HTA by Brown et al. [11] searched for publications between 2015 to May 2018 to supplement the literature search of a National Institute for Health and Care Excellence (NICE) interventional procedure guideline published previously (Citation not provided in the publication). The authors searched for a broad range of neuromodulation interventions for cancer and non-cancer pain. None of the included studies were relevant to the current report. The HTA by Skelly et al. (2017) [12] included 35 RCTs and economic evaluations that were published up to November 2016, none of which were relevant to the current report. Lastly, the SR by Stanak et al. [13] searched for randomized and non-randomized studies published up to May 2018. The SR included seven RCTs, none of which were relevant to the current report. The SR was based on a detailed evidence report published in 2019 by the same authors.[19]

The two included primary studies were single center prospective RCTs. [15] [16]

Country of Origin

The HTAs were conducted in Canada [11] and the United States.[12] The SRs were by authors in Canada [14] and Austria.[13] The country of origin for the included primary study [18] was not reported in the SR. Both RCTs [15,16] were conducted in China.

Patient Population

One of the HTAs[11] included patients with cancer and non-cancer pain. Relevant to the current report, the authors reviewed studies that involved adult patients with non-cancer pain. The second HTA[12] evaluated adults with migraine and other types of headaches. They excluded studies that involved pediatric patients, those with acute migraine attack, episodic migraine, medication overuse headache, menstrual migraines, other primary and secondary headaches and pregnant and lactating women. The SR by Stanak et al. colleagues[13] included studies with adult patients with episodic and chronic migraine . Lastly, the other SR[14] included all studies of patients with primary or secondary headaches

The two RCTs [15,16] recruited participants diagnosed with migraine based on the International Classification of Headache Disorder (ICHD) third edition beta [20]. One of the RCTs [15] enrolled adult patients aged 18 to 65 years diagnosed with episodic migraine headaches at least twice a month. The other RCT [16] included adult patients aged 18 to 65 years with a diagnosis of migraine without aura, with a minimum of one year history of migraine with at least four attacks per month in the three months preceding the study and a pain intensity of five or more on a Visual Analog Scale (VAS) pain score scale.

Regarding the number of participants, the primary study[18] included in the SR by Stilling et al. [14] enrolled 14 patients in the rTMS group and 15 in the comparator group. The Jiang et al. RCT [15] recruited 51 patients in the tSNS group and 52 in the comparator group. Lastly, the RCT by Liu et al.[16] enrolled 88 patients, 22 in each of the relevant study arm.

Interventions and Comparators

One HTA[11] reviewed the evidence on the clinical effectiveness of all neuromodulation methods. Relevant to this report, the intervention was Transcutaneous Electric Nerve Stimulation (TENS) of the supraorbital nerve for non-cancer pain. No specific comparators were described. The second HTA[12] assessed the evidence for clinical effectiveness and safety of several non-pharmacological interventions for migraine prevention compared to standard of care, sham/placebo, no treatment or waitlist. Neither HTAs found any relevant primary studies.

In terms of the SRs, one [13] examined the effects of external Trigeminal Nerve Stimulation (eTNS) previously known as transcutaneous supraorbital nerve stimulation (tSNS) (Brand name: Cefaly ®) compared to pharmacological interventions or placebo for the acute treatment and prevention of migraine. None of the included primary studies were relevant to this current report due to irrelevant comparators or study design. The SR by Stilling et al[14] compared various types of Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tCDS) used in preventative or abortive treatment of migraine compared to an alternative standard of care (pharmacological intervention, botulinum toxin) or sham. The included primary study [18] compared the effects of repetitive TMS (rTMS) with Botulinum toxin (Botox). The rTMS was of 80% motor threshold (APB) with a frequency of 10Hz. 100 pulses of 20 trains with 10s ITI (2000 total pulses) were applied with a Figure 8 coil for 3 days a week, for a total of 12 sessions over 1 month. In the comparator group,155 to 195 of Botulinum toxin (Botox®) units were injected at 31 sites across seven specific head and neck muscles at about eight sites.

The two RCTs [15,16] compared the effects of different NINS devices to pharmacological interventions. In one study [15], transcutaneous Supraorbital Nerve Stimulation (tSNS) was the NINS device used and was compared to flunarizine. Participants were divided into three groups, 1) tSNS 2) flunarizine and 3) tSNS and flunarizine. Relevant to this report, the tSNS

group received stimulation using tSNS (Pulse width 250µs; frequency 60Hz; maximum intensity 16mA) for 20 minutes daily for a duration of 90 days. The flunarizine group received the medication orally, 5mg daily for the same duration. In the RCT by Liu et al.[16], the NINS device used was transcutaneous Occipital Nerve Stimulation (tONS) and was compared with topiramate. Participants were divided into five groups: three arms received tONS treatment in various frequencies, the fourth arm received sham and the fifth arm received topiramate treatment. Relevant to the current report, the tONS groups received stimulation of various frequencies using a HANS-200A machine with two self-adhesive electrodes placed over the occipital area, over bilateral occipital nerves. The frequencies were as follows: Group A: tONS 2Hz, Group B: tONS100Hz and Group C: tONS 2/100Hz (Waves at 2Hz applied for 3 seconds followed by 100Hz for another 30 seconds). In the comparator group, oral topiramate was administered with a starting dose of 25 mg per day. Dose was increased 25 mg per day weekly to a maximum of 50 mg twice daily.

Outcomes

The HTAs [11,12], and SRs [13,14] identified in this report described several outcomes related to clinical effectiveness of NINS. One of the HTAs[11] reviewed the evidence on the clinical effectiveness on various methods of neuromodulation. The outcomes relevant to this report were pain assessment (measured using the VAS), Health Related Quality of Life (HRQoL), adverse events and serious adverse events, healthcare utilization (intake of medications for pain) and patient satisfaction. The outcomes of interest in the HTA by Skelly et al.(2017)[12] were proportion of responders, headache prevention (mean number of episodes and headache days), functional outcomes, harms, adverse events and QoL. Economic outcomes addressed were cost effectiveness, cost utility measured by Quality Adjusted Life Years (QALY) and Incremental Cost Effectiveness Ratio (ICER). The outcomes of interest for the included SRs [13,14] were improvement in clinical symptoms like migraine days, migraine frequency, use of abortive medications and quality of life. The Stanak et al [13] SR included outcomes related to the safety of eTNS (e.g., serious adverse effects, intolerance, allergies) as well.

The included RCTs [15,16] reported change in monthly migraine days, migraine intensity (measured using VAS), patient satisfaction and responder rate as the outcomes of interest. The responder rate is defined as the percentage of participants reporting at least 50% reduction in migraine days. The RCT by Jiang et al.[15] also examined the use of rescue medications and adverse effects, whereas the RCT by Liu et al.[16] examined headache duration, change in duration after treatment, changes in score of the self-rating depression score (SDS) and self-rating anxiety scale (SAS) and the Headache impact Scale (HIT-6) for QoL assessment.

Visual Analog Scale is a validated patient reported outcome measure to measure pain intensity. A scale that ranges from 0 to 10, 10 being the highest pain intensity is a commonly used outcome measure for pain in acute and chronic settings. [21] The SDS [22] and SAS [23] are validated self-rated outcome measures for depression and anxiety respectively. HIT-6 is also a validated measure of the impact of headache on normal activity, among individuals with migraine [24].

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Health technology assessments and Systematic Reviews

The two HTAs[11,12] included in this report had clearly defined objectives, and a comprehensive search of multiple databases was conducted for identifying studies. The study selection process using a PRISMA flowchart was shown and was done by two independent reviewers. The characteristics of the included studies was reported in detail. The HTA by Skelly et al.[12] selected study designs with low risk of bias, and the list of excluded studies with the reason to exclude were reported. Risk of bias was assessed by validated tools.

As for the limitations of the included HTAs, it was unclear whether the review methods were established prior to the assessment in the form of a protocol increasing the risk of selective reporting. Additionally, the Brown et al **[11]** HTA did not handsearch for additional references and bibliographies, and a list of excluded studies were not provided. It was unclear whether the data extraction from selected studies in duplicate in the other HTA. [12]

The two included SRs[13,14] had clearly defined objectives and the inclusion exclusion criteria for study selection were described in detail. The inclusion and exclusion criteria for both reviews were described in detail and included components of population, intervention, comparators and outcomes. Comprehensive searching of multiple databases was done to identify eligible studies, and the detailed search strategy was reported. Study selection was done in duplicate by more than one reviewer. The characteristics of included studies were reported in detail, and risk of bias were assessed using validated tools. Lastly, potential conflicts of interest were reported, even though there were none to disclose.

As for methodological limitations, the SRs did not report any structured search for grey literature outside the databases. The reviews did not include a list of excluded studies. It was not clear if one of the SRs [13] established a protocol for review methods beforehand. Only one primary study[18] was included from the SRs. The setting and country of the study was not reported, thereby making the generalizability to Canadian settings unclear.

Randomized Controlled Trials

The two RCTs[15,16] included in this report were designed as single center prospective randomized controlled trials and had some strengths common to both. The objectives of the study, inclusion and exclusion criteria for participant selection, intervention, comparators and outcomes were clearly described. Sample size calculations were reported to provide adequate statistical power. The studies had large enough sample sizes to meet these estimates. Computerized randomization was done to assign participants to different study groups. Follow up time was the same for all study groups. Appropriate statistical tests were done to analyze the data. The main findings for primary outcome were described along with corresponding standard deviations (accounting for random variability). The authors also described potential conflicts of interests (there were none). Additionally, the RCT by Liu et al.(2017)[16] were conducted following a pilot study and was a registered trial.

The RCTs[15,16] were not free from methodological limitations. Because of the nature of intervention and comparator (NINS vs pharmacological interventions), neither studies were double blinded. In one of the RCTs [16], participants in the tONS groups were blinded whereas in the other[15], the researchers measuring the outcome were blinded. In both studies, the number and characteristics of patients who dropped out after the baseline period were unclear and intention to treat analyses were not conducted. In the RCT by Jiang et al.[15], the outcome of satisfaction and adverse effects were measured through open ended self-reported questionnaires. It was unclear whether those questionnaires were

validated. In the second RCT by Liu et al. (2017)[16], the diagnosis (episodic vs chronic migraine) of the participants was not clear. Actual effect sizes and confidence intervals were not reported in the study. Comparative findings were presented graphically, which can be unclear while drawing conclusions. Lastly, both RCTs were conducted in China, which may not be generalizable to Canadian settings.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions. A summary of relevant findings is presented below.

Clinical Effectiveness of Non-Invasive Nerve Stimulation modalities

Headache frequency

The primary study included in one of the SRs [14], and the two RCTs [15,16] reported the effects of various NINs devices on migraine headache frequency. The SR included a primary study[18], which reported a 75% improvement in 71.4 % patients with rTMS treatment. There were no significant difference between the groups. The Jiang et al. (2019) [15] RCT found that patients who received tSNS prophylaxis experienced a reduction in migraine days which was not significantly different to the flunarizine group (P=0.90). The other RCT [16] found a reduction in headache days in the tONS groups, but the comparison between tONS groups and the topiramate group was not reported. Overall, the included studies showed that the use NINS devices like tONS, rTMS and tSNS reduce the monthly headache days, but are not significantly different when compared to the pharmacological interventions or Botulinum toxin that were assessed in these studies.

Headache duration

One RCT[16] by Liu et al. reported the results of NINS modalities on headache duration compared to topiramate therapy. One of the three groups who received tONS therapy (Group B: tONS100 Hz) reported a significant improvement in headache duration. The improvement between tONS groups and the topiramate group were not compared.

Headache intensity

One SR[14], and the two RCTs[15,16] reported the effects of various NINs devices on headache intensity measured using the VAS. The SR included a primary study[18], which reported a 75% improvement in 71.4 % patients with rTMS treatment. Compared to Botox, the effects were not significant. The Jiang et al.(2019)[15] RCT found that headache intensity was improved after tSNS prophylaxis. However, when the groups were compared, Flunarizine was superior to tSNS. (P<0.01). The second RCT[16] similarly found that headache intensity was improved in all tONS groups, but the difference was not significant compared to topiramate. Overall, NINS modalities may improve headache intensity in migraine patients, but not enough evidence available to suggest an improvement compared to pharmacological prophylaxis.

Responder rates

Responder rates are defined as the percentage of patients reporting at least 50 % improvement after treatment. Two RCTS[15,16] reported results on the responder rates of tSNS and tONS compared to pharmacological standard of care. The Jiang et al. (2019) [15] RCT found that 39.22% of the tSNS group and 46.15% of the flunarizine group reported at least 50% improvement after treatment. There was no significant difference between the two groups. The other RCT [16] reported that on average 38% of the patients treated with

tONS, and 68% of the patients treated with topiramate felt at least a 50% improvement. There was no significant difference between the two groups. To summarize, the responder rates of NINS modalities like tSNS and tONS are comparable to the pharmacologic standard of care.

Functional performance and Health related quality of life

One SR [14], and one RCT[16] reported the effects of NINS modalities on HRQoL and functional performance in migraine patients measured using HIT-6 [24]. The primary study[18] from the SR reported that patients had improved HIT-6 scores after rTMS treatments. Compared to Botox group the differences were not significant. The RCT by Jiang et al.[16] also reported improved HIT-6 scores across all groups after tONS. The effects compared with the topiramate group was not reported. Thus, NINS may improve functional performance and HRQoL but there is not enough evidence to suggest a difference over standard of care.

Safety

The two RCTs [15,16] reported the results of safety of tSNS and tONS respectively. Among the 51 patients treated with tSNS, three (5.88%) patients experienced mild adverse effects (paresthesia, pressure feeling at the site and somnolence)[15]. In the 66 patients treated with tONS, one patient reported intolerance, which was subsided by reducing the intensity of tONS[16]. These results suggest that NINs modalities like tSNS and tONS are safe.

Cost Effectiveness of Non-Invasive Nerve Stimulation modalities

No relevant evidence regarding the cost effectiveness of NINS modalities for migraine was identified; therefore, no summary can be provided.

Limitations

The main limitation of this report is the lack of clear evidence to address the research questions. Among the two HTAs[11,12] and two SRs[13,14] included in this report, only one relevant primary study[18] was identified. Most of the studies found by these reviews were either sham controlled or small single arm prospective studies. Such studies cannot provide clear evidence on the effectiveness of just NINS on migraine. The HTA by Skelly et al.[12] found no studies that met their inclusion criteria. Additionally, for many of the NINS modalities, no relevant primary studies were identified. No studies evaluating the cost effectiveness of NINS only therapy compared to standard of care were found. This lack of evidence shows a gap in research on the clinical effectiveness and safety of NINS compared to standard of care among patients with migraine. The two recent RCTs[15,16] included in this report are done in Chinese population and may not be generalizable to the Canadian context.

Conclusions and Implications for Decision or Policy Making

Six publications including two HTAs, two SRs and two RCTS were identified to address the evidence of clinical effectiveness and cost effectiveness of NINS compared to standard of care (pharmacological or non-pharmacological interventions) Overall, the limited evidence suggests that migraine prophylaxis with NINS modalities like tONS, tSNS and rTMS were not different from pharmacological and non-pharmacological interventions. NINS modalities may be effective in improving clinical symptoms and were found to be safe with fewer adverse effects. However, the lack of well-designed comparative trials makes the evidence

uncertain. No evidence on the clinical and cost effectiveness of other available NINS devices were found Future research addressing NINS therapy alone compared to standard of care may help to fill in the existing research gaps and reduce uncertainty. Additional research examining the clinical effectiveness of other NINS devices as well as cost effectiveness studies are also warranted.

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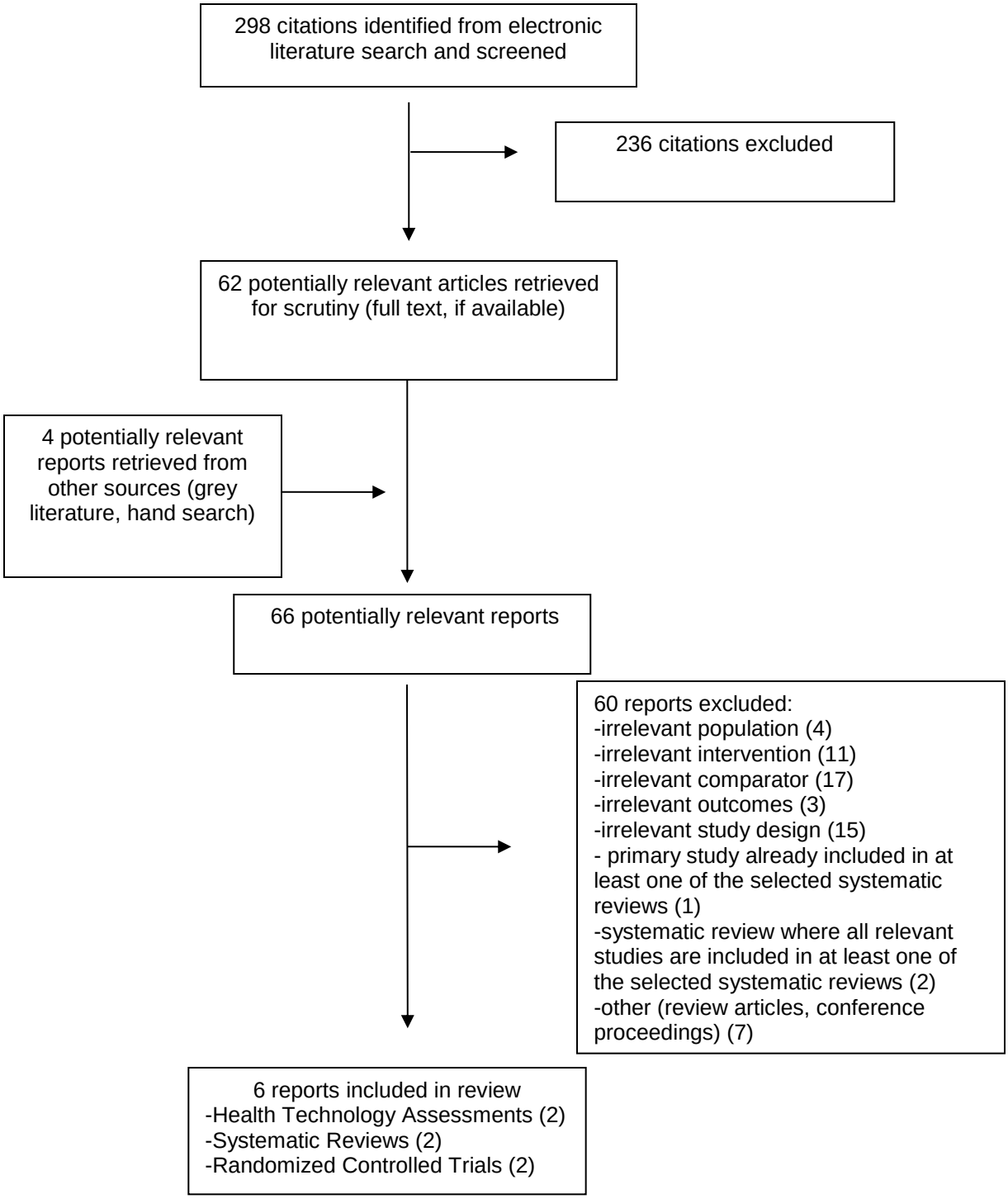
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding source	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Technology Assessments				
Brown 2018[11] **Country:** Canada **Funding source:** Health Technology Assessment Office (HTAO), British Columbia	**Study Design:** HTA **Objective:** To review and synthesize the evidence on clinical effectiveness and policy implications of neuromodulation for patients with cancer and non-cancer pain. **Search Strategy:** Studies found during the search of a NICE interventional procedure guideline was included in this review (citation not reported) An electronic search of Medline, Embase, PsycINFO, CINAHL and the Cochrane central register of controlled trials was done from 2015 to May 2018 to supplement that. **Number of primary studies included:** The number of primary studies included varied for each population group and intervention as follows: Spinal cord Stimulation for Cancer pain – 0 studies Spinal cord Stimulation for non-cancer pain – 15 studies Peripheral Nerve Stimulation for Non- Cancer pain- 10 studies Intrathecal pumps for Cancer and non-cancer pain- 8 studies **TENS for Non-Cancer pain: 1 study** The included study was not relevant to this report. **Quality Assessment tool:** RCT- Cochrane Collaborations tool for Assessing risk of bias.	**Population:** Patients with Cancer or non-cancer pain undergoing neuromodulation. **Relevant inclusion criteria:** TENS supra orbital nerve stimulation for non-cancer pain, English of French studies, All study designs, Adult population. **Relevant exclusion criteria:** Other neuromodulation technologies, Animal studies, does not report original data, case reports.	**Intervention of interest:** TENS of the supra-orbital nerve for non-cancer pain. **Comparator:** No specific comparators were described	Clinical effectiveness and safety. **Outcomes of interest:** Pain assessment (VAS, or McGIll pain questionnaire), Health related Quality of Life, Adverse events and serious adverse events, healthcare utilization, satisfaction.
Skelly, 2017[12] **Country:** United States	**Study Design**: HTA **Objective**: To systematically review and assess the evidence on efficacy, safety and cost effectiveness of several non-pharmacological interventions (trigger point injection, botulinum toxin injection, transcranial magnetic stimulation,	Adults with migraine, tension type headache and chronic daily headache.	**Intervention:** Transcranial Magnetic Stimulation, Botulinum toxin injection, Trigger point injection,	**Clinical outcomes:** Proportion of responders, headache prevention (including

First Author, Publication Year, Country, Funding source	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Funding source: Washington State HealthCare Authority**.**	acupuncture, manipulation and massage) in the prevention of chronic migraine and chronic tension-type headache in adults. **Search Strategy:** Electronic search was conducted in PubMed, Embase, Cochrane Central Register for Controlled Trials, Cochrane database for systematic review, and National Guidelines Clearinghouse (Inception to November 2016) Reference lists and bibliographies of relevant studies were hand searched. **Number of primary studies included:** A total of 35 publications including RCT and economic analyses were included. None of the primary studies were relevant to the current report. **Quality Assessment Tools:** Risk of bias in primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias, GRADE, and AHRQ guidelines. Economic studies were evaluated using The Quality of Health Economic Studies (QHES) instrument.	**Excluded:** Age <18y, acute migraine attacks. Episodic migraine, medication overuse headaches, menstrual migraine, hospitalized patients, other primary and secondary headaches, pregnant and lactating women.	acupuncture, manipulation/manual therapy, massage. **Comparator:** Standard of Care, Sham/placebo, No treatment, waitlist.	reduction in mean number of episodes and/or headache days), headache days and frequency, functional outcomes (based on validated outcome measures), harms and adverse events, Quality of life. **Economic outcomes**: cost effectiveness, cost utility (eg: Quality Adjusted Life Years (QALY), Incremental cost effectiveness ratio (ICER)). **Length of follow up:** Varied by primary study. The HTA focused on intermediate (>6months) and long term (>12 months) for outcomes for efficacy. No timeframe limit was set for harms.
Systematic Reviews				
Stanak, 2020[13]	**Study Design**: A systematic Review of randomized and non-randomized studies.	Adult patients with episodic and chronic migraine who could benefit	**Intervention:** External trigeminal nerve stimulation (e-	**Efficacy of e-TNS:** Improvement in clinical

First Author, Publication Year, Country, Funding source	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Country: Austria **Funding source:** Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria	**Objective:** To assess if e-TNS, when used as preventative or acute treatment, was effective in improving clinical symptoms (migraine days, anti-migraine drug usage, satisfaction, change in pain score episodes, quality of life) and safe regarding side effects in patients with episodic and chronic migraine. **Literature search strategy**: Electronic search were conducted in MEDLINE via Ovid, Embase, the Cochrane library and CRD. No date restriction was imposed, but search was limited to English and German language. **Number of studies included**: A total of 7 RCTs were included in the quantitative analysis. None of the included primary studies were relevant to this current report. **Quality Assessment tool:** Risk of bias in the included studies were done using Cochrane Collaboration's tool for RCTS and the Health Economics' quality appraisal checklist for case series.	from prophylactic or acute treatment using eTNS.	TNS) previously known as Supraorbital transcutaneous nerve stimulation. Brand name: Cefaly® **Comparator:** Pharmacological therapy or placebo for the acute treatment and prevention of migraine.	symptoms including migraine days, migraine frequency, usage of abortive drug, change in pain, QoL and compliance. **Safety of e-TNS:** Serious Adverse device effects, pain/intolerance, allergies, and other adverse effects**.** **Follow-up**: Varied by individual study and ranged from 1 to 120 days.
Stilling, 2019[14] **Country:** Canada **Funding source:** Not funded.	**Study Design**: A systematic Review of randomized and non-randomized studies. **Objective**: The use of TMS and tDCS for the treatment of headache disorders including migraine, cluster headache, tension headache and post-traumatic headache. **Literature search strategy**: Electronic search were conducted in Ovid MEDLINE, Cochrane Central Register for Clinical Trials, Embase, Scopus and PsycINFO. No date or human restrictions were imposed, but search was limited to English language. First search was done in June 2017 and was repeated after 14 months. Study authors were not contacted. **Number of studies included**: A total of 34 studies were included in the quantitative analysis (one[18] of which were relevant to the current report). Only information from the relevant primary study were extracted.	Adults with primary or secondary headaches.	**Intervention:** Various types of TMS and tCDS used in prophylactic or abortive headache treatment method. **Comparator**: Sham or another alternative Standard of care including pharmacological intervention and botulinum toxin. Relevant primary study[18] compared rTMS to Botox.	**Outcomes**: Headache frequency, duration, intensity, use of abortive medications, quality of life anxiety and depression. **Follow up:** Varied by primary study. Study relevant to this report had a follow up of one month after intervention.

First Author, Publication Year, Country, Funding source	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Quality assessment tool: Risk of bias in primary studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias.			

AHRQ = Agency for Healthcare Research and Quality; CENTRAL = Cochrane Central Register of Controlled Trials; ; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; e-TNS = external Trigeminal Nerve Stimulation; GRADE= Grading of Recommendations Assessment, Development and Evaluation; HTA = Health Technology Assessment; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SR = systematic review; tDCS= Transcranial Direct Current Stimulation; TENS= Transcutaneous Electrical Nerve Stimulation; TMS= Transcranial Magnetic Stimulation; rTMS = repetitive TMS; VAS = Visual Analog Scale.

Table 3: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country, Funding source	Objective, Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Control Trials				
Jiang, 2018[15] **Country:** China **Funding source:** Support was received from the following sources- Chongqing Municipal Commission of Health and Family Planning; Chongqing Municipal Education Commission; Chongqing Science and	**Objective:** to assess the effectiveness of combined tSNS and flunarizine in migraine prophylaxis. **Study Design:** Single center Randomized Control Trial Study participants were randomly assigned to one of three groups 1) tSNS, 2) Flunarizine and 3) tSNS + flunarizine. The groups relevant to this report are: 1) tSNS group and 2)	**Inclusion criteria:** Adults (age 18-65y), diagnosed with **episodic migraine**, who experienced migraine headaches at least twice per month. **Exclusion criteria:** Individuals who 1) used prophylactic drugs for migraine, 2) diagnosed with depression, Parkinson disease or other neurological/psychiatric conditions, 3) have implanted cardiac pacemaker, defibrillator or other metallic /electrical device and 4) are pregnant, lactating or have a child bearing potential without adequate contraception. **Number of participants in the relevant groups:** N = 154 tSNS group, n=51 Flunarizine group, n=52 **Mean age, years (SD)** tSNS group 29.67 (9.24) Flu group 30.96 (9.40) **Sex**: 74.7% females	**Intervention:** tSNS group: delivered 20 min daily. Pulse width 250µs; frequency 60Hz; maximum intensity 16mA. Flu group: 5 mg daily orally.	**Outcomes**: Primary outcome: changes in monthly migraine days; responder rate (percentage of participants reporting at least 50% reduction in migraine days) Secondary outcomes: migraine intensity; use of rescue medications; satisfaction and adverse effects. **Follow up:** Baseline period: 30 days Treatment period: 90 days.

First Author, Publication Year, Country, Funding source	Objective, Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Technology Commission	flu group. The information pertaining to only the relevant study arms were extracted.	**Clinical features of the relevant groups at baseline:** 87 participants (84.5%) had migraine without aura. **Mean migraine duration in days (SD)** tSNS group: 6.21 (4.80) Flu group: 5.12 (4.03) **Mean migraine days per month (SD)** tSNS groups: 5.92 (1.04) Flu group: 5.68 92.51) **VAS Score (SD)** tSNS group: 6.75 (1.35) Flu group: 6.98 (1.10) **Acute anti-migraine drug intake (SD)** tSNS group: 4.88 (2.29) Flu group: 4.96 (2.56)		Patients were seen and assessed every 30 days.
Liu, 2017[16] **Country:** China **Funding sources:** National Scientific Research Fund (grant number 81471147)	**Objectives:** to assess the clinical effectives and tolerability of transcutaneous Occipital Nerve Stimulation (tONS) compared with topiramate in migraine patients. **Study design**: Prospective Single Center randomized control trial. Study participants were assigned to 5 groups, with 3 arms receiving tONS treatment in various frequencies, 4th arm receiving sham and the 5th arm on topiramate	**Inclusion criteria**: Adult patients (18-65 years of age) with a diagnosis of migraine without aura, who had a minimum of one year history of migraine headaches with at least 4 attacks per month in the 3 months preceding the study, and a pain intensity of 5 cm of more on a VAS pain score were included. **Exclusion criteria:** Patients were excluded if they 1) were prescribed preventative treatment in the previous 3 months, 2) used any non-pharmacological treatment in the previous year, or 3) had a history of cardiac pacemaker implantation, epilepsy, severe anxiety or depression, 4) had paresthesia or any other type of headache including medication overuse headache or 5) were <18 y or over 65 years of age. **Number of participants in the relevant groups**, N= 88 tONS 2Hz, tONS 100Hz, tONS 2/100 Hz and the TPM group all had 22 participants each. **Mean age (SD)** Group A (tONS 2Hz): 37.55 (10.49) Group B tONS 100 Hz: 35.91 (9.94)	**Intervention:** **Group A, B and C** tONS treatment was done using a HANS-200A machine with two self-adhesive electrodes placed over the occipital area, over bilateral occipital nerves. **Frequency:** Once daily for 30 min. Group A tONS 2Hz Group B tONS 100Hz Group c tONS 2/100Hz (Waves at 2Hz applied for 3 seconds followed by 100Hz for another 30 seconds).	**Primary outcomes**: 50% responder rates, change in headache days, headache intensity (measured using VAS), headache duration and change in duration after treatment. **Secondary outcomes:** 1)Changes in score of the self-rating depression score (SDS) and self-rating anxiety scale (SAS) 2) Headache impact test (HIT-6) assessing quality of life

First Author, Publication Year, Country, Funding source	Objective, Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	treatment. The information pertaining to only the relevant study arms were extracted. (Information on sham group excluded)	Group C tONS 2/100 HZ: 39.45 (10.99) Group E TPM : 41.45 (10.13) **Sex:** 78.4% female **Clinical features of the relevant groups at baseline** **Mean Disease duration (SD) in years** Group A: 12.59 (9.10) Group B: 12.00 (5.09) Group C: 14.82 (7.00) Group E: 14.27 (9.94) **Mean score of VAS (SD)** Group A: 6.54 (1.30) Group B: 6.98 (1.46) Group C: 6.87 (1.53) Group E: 7.19 (1.35) **Mean headache duration (SD) in hours** Group A: 9.45 (3.84) Group B: 14.35 (7.65) Group C: 11.11 (6.16) Group E: 13.78 (10.71)	**Group E (TPM)** Oral topiramate oral topiramate, with a starting dose of 25 mg per day. Dose was increased 25 mg per day weekly to a maximum of 50 mg twice daily.	3) Percentage of satisfiers **Follow up time:** One month baseline period after which the participants were randomized. Outcome measures assessed after 1 month of intervention and follow up at 3 months.

SD = Standard Deviation; tSNS = transcutaneous Supraorbital Nerve Stimulation; tONS = transcutaneous Occipital Nerve Stimulation; TPM = Topiramate; VAS = Visual Analog Scale

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews using AMSTAR II[9]

Strengths	Limitations
Health Technology Assessments	
Brown, 2018[11]	
• The objectives of this HTA were clearly described. • A comprehensive search of multiple electronic databases including MEDLINE, Embase, PsycINFO, CINAHL and Cochrane register for clinical trials was completed to supplement a previously published NICE guideline search. Detailed search strategy was reported in appendix. Publication restrictions are justified. • A PRISMA flowchart showing the study selection was presented. • Study selection and data extraction was done in duplicate and selection process is well described. Any discrepancies between reviewers are addressed through discussion and consensus. • The study characteristics of the included study are described in detail including population, intervention, and study setting.	• The inclusion and exclusion criteria for the relevant intervention was described, but the PICO was unclear. • It was unclear whether the review methods were established in the form of a protocol. • The rationale for the selection of study designs was unclear. • It was unclear whether the additional references/bibliographies were hand searched. • A list of excluded studies was not provided. • The characteristics results of the included study was not presented in tabular form, and the author and citation to the included study was not given. • The risk of bias for the included study was not completed using a validated tool, and source of funding was not reported.
Skelly, 2017[12]	
• The objectives of the HTA were clearly described. The inclusion and exclusion criteria for the review were described in detail and included components of population, intervention, comparators and outcomes. • The selection of study designs for the inclusion in the review was clearly mentioned. The review included only low Risk of Bias study designs. • A comprehensive search of multiple electronic databases including PubMed, Embase, Cochrane register for clinical trials, National guidelines Clearinghouse was completed. Additionally, references were hand searched. Detailed search strategy was reported in appendix. Publication restrictions are justified. • Study selection was done by two independent reviewers, and selection process is well described. • A list of excluded studies along with the reason to exclude are reported. • The study characteristics of included studies are described in detail including population, intervention (with doses if applicable), study setting and follow up time. • The risk of bias and quality of evidence from each of the included studies are assessed using a valid tool. • The funding sources for included studies were reported. • Potential sources of conflict of interest were not disclosed.	• The review did not report that the methods were published prior to the conduct of the review. No review protocol was mentioned. • It is unclear whether the data extraction from included studies were done by two independent reviewers. • Publication bias were not assessed and was not considered in determining the quality of evidence.

Strengths	Limitations
Systematic reviews	
Stanak 2020[13]	
• The objectives of the systematic review were clearly described. The inclusion and exclusion criteria for the review were described in detail and included components of population, intervention, comparators and outcomes. • A comprehensive search of multiple databases (Ovid MEDLINE, Embase, Cochrane Library, and CRD) and clinical trial registries was done, without imposing a date or human restrictions. Publications submitted by the device manufacturer was included. Hand searching for additional publications was also done. • A detailed search strategy for one database and publication restriction (language) was reported • Study selection was done by three independent reviewers, and discrepancies were solved by discussion. Data extraction form the selected studies was done by one reviewer, and cross checked by two others. • The included studies were described in adequate detail in terms or population, intervention, comparators, outcomes, follow up time, and study design. • The risk of bias and quality of evidence from each of the included studies are assessed using a valid tool. • Sources of funding for the included studies were reported. • Potential conflict of interests were reported (there were none to disclose).	• The review did not report that the methods were published prior to the conduct of the review. No review protocol was mentioned. • A grey literature search, as well as references lists/bibliographies were not completed. • A list of excluded studies was not provided but the reasons for exclusion were reported in the PRISMA diagram.
Stilling, 2019[14]	
• The objectives of the systematic review were clearly described. The inclusion and exclusion criteria for the review were described in detail and included components of population, intervention, comparators and outcomes. • The review methods were established prior to the systematic review in the form of a published registered protocol. • A comprehensive search of multiple databases (Ovid MEDLINE, PsycINFO, Embase, CENTRAL, Scopus) was done, without imposing a date or human restrictions. Databases were re-searched a few months later and within 24 months of completion of the review to include any studies published in the meantime. • A detailed search strategy for one database and publication restriction (language) was reported. • Study selection and quality assessments were completed by two independent reviewers. (Conflicts were resolved through a third independent reviewer) • A PRISMA flow diagram for study selection was provided.	• The rationale for the selection of study designs was unclear. • A grey literature search, as well as references lists/bibliographies were not completed. • Data extraction from the included studies were done by only one reviewer. • A list of excluded studies was not provided but the reasons for exclusion were reported in the PRISMA diagram. • The sources of funding for included primary studies were not reported.

Strengths	Limitations
• The included studies were described in adequate detail in terms or population, intervention, comparators, outcomes, follow up time, and study design. • The risk of bias of the included studies was assessed using the Cochrane collaborations tool for assessing risk of bias. • The Risk of bias and the level of evidence was reported for individual studies. • Source of funding for the review was reported (there was no funding received). • Potential conflict of interests were reported (there were none to disclose).	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; CRD = University of York Centre for Reviews and Dissemination; EMBASE = Excerpta Medica database; HTA = Health Technology Assessment; NICE = National Institute for Health and Care Excellence; PRISMA = Preferred Reporting Items for Systematic Reviews and MetaAnalyses

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[10]

Strengths	Limitations
Randomized control trials	
Jiang, 2018[15]	
• The objectives of the study were clearly described. • The main outcomes and the outcome measures were clearly described. • The characteristics of participants at baseline were described and were tested for significant differences between across the treatment groups. • The interventions of interest were reported in detail including doses, timing and frequency. • The main findings of the study for all outcomes of interest were clearly described. • Standard deviation for all results were reported, accounting for random variability. The actual P values were reported except when they were <0.001. • Adverse events were captured and reported including frequency of them in each group. • Participants in all treatment groups were recruited from a medical university hospital and were representative of the population and study setting. • Researchers assessing the outcome measures of interest were blinded to the treatment. • The statistical analysis to compare groups were appropriate and were describe in detail in the methods section. The follow up time was the same for all patients. • Sample size calculations were reported to provide an 85% power, α of 0.05. The study had enough N to meet these estimates. • Conflict of interests of the authors were declared (there were none to disclose).	• 6.7% (11) patients were not included in the final analysis, because of non-compliance and adverse effects. But their characteristics were not reported. Intention to treat analysis was not performed. • Participants were recruited from a medical university hospital. The method of recruitment or proportion of source population from which they were recruited were unclear. • Study participants were not blinded to the intervention. • Characteristics of patients who dropped out after baseline period were unclear. No intent to treat analysis was done • The outcome of satisfaction and adverse effects were recorded through open-ended questions which were not validated. • The time period over which the participants were recruited are not reported. • Study was done in China so may not be generalizable to a Canadian setting

Strengths	Limitations
Liu 2017[16]	
• The trial was registered in the Chinese Clinical Trial Registry and was done following a pilot study. • The objectives of the study were clearly described. • The primary and secondary outcomes were clearly described. The outcome measures used were validated. • Inclusion and exclusion criteria for the study are described clearly. • The study interventions including frequency of administration, type of device and dosing were clearly described for all groups. • Standard deviations were reported wherever appropriate accounting for random variability. • The outcome measures were self-reported. • The statistical analysis to compare groups were appropriate and were describe in detail in the methods section. The follow up time was the same for all patients. • Participants were randomized to different study arms suing a computerized randomization system. Study participants were blinded in the tONS groups and sham group. • Sample size calculations were reported to provide 80% power, α of 0.05 with 10% attrition rate. The study had enough N to meet these estimates. • Conflict of interests of the authors were declared (there were none to disclose).	• It was not clear if the study recruited episodic or chronic migraine patients or both. Some baseline characteristics of participants were not well defined. • Numerator and denominator data for results of some primary and secondary outcomes were not reported. The findings were presented graphically. • List of possible adverse effects were not described. • Actual P values, for probabilities over 0.001 were not always reported. • Participants were recruited from a medical university hospital. The method of recruitment or proportion of source population from which they were recruited were unclear. • Characteristics of patients who dropped out after baseline period were unclear. No intent to treat analysis was done. • Study was done in China so may not be generalizable to a Canadian setting.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Health Technology Assessments	
Brown 2018[11]	
This Technology Assessment report aimed to evaluate and synthesize the evidence on the use of neuromodulation for patients with cancer and non-cancer pain. Relevant to this report, the clinical effectiveness of TENS for of the supraorbital nerve for non-cancer pain was assessed. The review found one study for this research question. It was not relevant to this current report.	"The evidence for clinical effectiveness and safety of TENS of the supraorbital nerve in noncancer chronic pain is limited and of non-RCT quality".[11] (*pp95*)
Skelly, 2017[12]	
The technology assessment report aimed to review and synthesize evidence for the clinical effectiveness and cost effectiveness of non-pharmacological interventions including Transcranial Magnetic Stimulation, Botulinum toxin injection, trigger point injection, acupuncture, manipulation and massage in chronic migraine and chronic tension type headache. The review found no studies relevant to the current report. No trials were identified that assessed the clinical effectiveness of TMS compared to Standard of care. No economic studies that compared TMS with standard of care were identified.	"**Transcranial Magnetic Stimulation versus Active Control for Chronic Migraine:** No studies were identified that met the inclusion criteria for this comparison".[12] (*p9*)
Systematic reviews	
Stanak 2020[13]	
This systematic review was done to assess the clinical effectiveness and safety of eTNS, used as preventative or abortive therapy in patients with episodic and chronic migraine. The review included seven studies including two RCTs and 5 prospective case series. None of the included studies were relevant to this report.	"While e-TNS has the potential to improve migraine symptoms (in terms of migraine attacks, migraine days, and headache days), improve patients' autonomy, and reduce the total medication intake, its noninvasive nature needs to be put in the context of paucity of knowledge about its mechanism of action and the lacking long-term safety profile. With regards to short-term safety, no serious adverse events occurred in any of the studies. Furthermore, the potential cost-effectiveness of e-TNS needs to be contrasted

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td></td><td>with the small effects measured by the VAS, the question of the clinical importance of these effects, and the small sample size included in the studies. For its establishment in the standard practice, high quality comparative data, studies with larger sample sizes, studies with standard primary outcome parameters, patient relevant outcome parameters, and precise reporting is needed". [13] (p10)</td></tr>
<tr><td colspan="2">Stilling, 2019 [14]</td></tr>
<tr><td>This systematic review aimed to assess the use of TMS and tCDS for the treatment of various headache disorders including migraine, cluster headache, tension headache and post-traumatic headache compared to sham or alternative standard of care. Outcomes were measured in symptomatic relief of headache, use of medications, quality of life, anxiety and depression.

This study included one primary study relevant to this report.[18] No meta-analysis was conducted.

<table>
<tr><th>Primary study citation</th><th>Summary of relevant results</th><th>Statistical significance[a]</th></tr>
<tr><td colspan="3">Outcome: Headache frequency and severity</td></tr>
<tr><td>Shehata et al, 2016[18] (N = rTMS: 14, Botulinum toxin: 15)</td><td>In rTMS group, headache severity (VAS) and frequency deceased by 75% in 71.4% of the participants, after 4-5 session. In the BTX group, headache severity decreased by 75% in 73.3% of the participants, but not in headache frequency.

All outcome measures reduced in both groups at end of treatment with no significant difference between groups (p=0.84).

At 2 wk and 4-week follow-up, the effects persisted in BTX group.

At 2week and 4 week follow up, effects was non-significant in rTMS group compared to after intervention.</td><td>

NS

S

NS</td></tr>
</table>
[a]The threshold for statistical significance was set to P < 0.05.
N = number of participants; NS = non-significant; S = significant.</td><td>"Of all TMS and tDCS modalities, rTMS is most promising with moderate evidence that it contributes to reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment. However, only few studies reported changes greater than sham treatment. Further high-quality RCTs with standardized protocols are required for each specific headache disorder to validate a treatment effect." [14] (p1)</td></tr>
</table>

BTX= Botulinum Toxin; e-TNS = external Trigeminal Nerve Stimulation; RCT = randomized controlled trial; tDCS= Transcranial Direct Current Stimulation; TENS= Transcutaneous Electrical Nerve Stimulation; TMS= Transcranial Magnetic Stimulation; rTMS = repetitive TMS; VAS = Visual Analog Scale.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Control Trials	
Jiang, 2018[15]	
This single-centre randomized control study compared the clinical effectiveness of tSNS with flunarizine after a 3-month preventive treatment in patients with migraine. tSNS group n=51; flu group n=52 **Summary of relevant findings:** Participants in the tSNS group and flu group both reported statistically significant improvement in migraine days, severity of migraine and acute antimigraine drug intake after 3 months of intervention. Compared to flu group, patients in the tSNS group reported less improvement in the severity of migraine days (P<0.05). Improvement in other outcomes were not statistically significant across the groups. • **Migraine days (SD)** ➢ Baseline ○ tSNS group: 5.92 (2.04) ○ flu group: 5.68 (2.51) ➢ Third month ○ tSNS group: 3.73 (2.13) ○ flu group: 3.43 (2.56) ➢ Change from baseline to third month ○ tSNS group: 2.20 (2.43), P <0.001 ○ flu group: 2.25 (2.08), P <0.001 ➢ Comparison between TSNS and flu groups ○ P =0.90 • **Percentage of responders after treatment period (≥ 50% reduction in migraine days)** ➢ Responders ○ tSNS group: 39.22% ○ Flu group: 46.15 % ➢ Comparison between TSNS and flu groups ○ P = 0.55 • **Severity of migraine days (SD) (measured using VAS)** ➢ Baseline ○ tSNS group: 6.75 (1.35) ○ Flu group: 6.96 (1.10) ➢ Third month ○ tSNS group: 5.53 (2.05) ○ flu group: 4.82 (1.70) ➢ Change from baseline to third month ○ tSNS group: 1.22 (1.46), P<0.001 ○ flu group: 2.14 (1.52), P <0.001 ➢ Comparison between TSNS and flu groups ○ P = 0.01 • **Acute anti-migraine drug intake (SD)** ➢ Baseline ○ tSNS group: 4.88 (2.30) ○ Flu group: 4.96 (2.56) ➢ Third month	"tSNS is effective and safe for migraine treatment and can be a valid option for migraineurs who are reluctant to take oral medications or for patients who experience a low migraine frequency and/or intensity that prophylactic therapy is not indicated but desire to acquire medical intervention".[15] (*p282*)

Main Study Findings	Authors' Conclusion
○ tSNS group: 2.78 (2.19) ○ flu group: 2.89 (2.67) ➢ Change from baseline to third month ○ tSNS group: 2.10 (2.22), P<0.001 ○ flu group: 2.0.7 (2.37), P <0.001 ➢ Comparison between TSNS and flu groups ○ P = 0.91 • **Safety:** Three (5.88%) of participants in the tSNS group experienced some adverse effects including somnolence (1), pressure on the stimulation site (1) and forehead paresthesia (1). In the flu group 18 (34.62%) of the participants experienced at least one adverse event, including somnolence (9), fatigue (1), insomnia (1), dizziness (1) and weight gain (6). • **Satisfaction:** 54.9% of the tSNS group were satisfied with the treatment compared to 50% of the participants in flu group.	
Liu, 2017[16]	
This single-centre randomized control study compared the clinical effectiveness of different frequencies of tONS with oral topiramate among adults with migraine. Group A – tONS 2Hz; Group B – tONS 100 HZ; Group C – tONS 2/100 Hz; Group E – TPM. 22 participants each in al groups. The results relevant to the current report are summarized below. **Summary of relevant findings.** Study found no significant differences between tONS groups and TPM group for any primary or secondary outcome. Participants in tONS groups and TPM group did not differ in the primary outcome of fifty percent responder rates. All groups had improved headache days from the baseline which was significant (p<0.05). • **Fifty Percent Responder Rates (%)** ○ Group A: 8 (36.36) ○ Group B: 9 (40.91) ○ Group C: 8 (36.36) ○ Group E: 15 (68.18) ➢ tONS groups and TPMS group showed no differences. (P value not reported) • **Headache days (SD)** ➢ tONS groups and TPM group reported reduction in headache days when compared to baseline(P<0.05). Data values not reported. ➢ Comparison between tONS group and TPM groups was not reported • **Headache intensity (SD) (measured using VAS)** ➢ Baseline ○ Group A: 6.54 (1.30) ○ Group B: 6.98 (1.46) ○ Group C: 6.87 (1.53) ○ Group E: 7.19 (1.35) ➢ One month ○ Group A: 4.13 (1.68) ○ Group B: 4.82 (1.77) ○ Group C: 4.44 (1.27) ○ Group E: 4.77 (1.95) ➢ Change from baseline to one month ○ Group A: P <0.01 ○ Group B: P <0.01	"We found that tONS effectively treated frequent migraines, especially in terms of the 50% responder rate and headache intensity, but different frequencies exerted similar effects. With infrequent and mild adverse events, tONS shows a promising application in the future. The devices will become even safer, more portable, and inexpensive, and patients may be able to use them at home. Furthermore, it is essential to determine the precise mechanisms involved, and larger sample sizes, and longer follow-up periods are urgently needed in the further studies".[16] (*p1013*)

Main Study Findings	Authors' Conclusion
○ Group C: P <0.01 ○ Group E: P <0.01 ➢ Comparison between tONS and TPM groups ○ tONS groups did not differ from TPM group. (P value not reported) • **Headache duration (SD) hours** ➢ Baseline ○ Group A: 9.45 (3.84) ○ Group B: 14.35 (7.65) ○ Group C: 11.11 (6.16) ○ Group E: 13.78 (10.71) ➢ One month ○ Group A: 7.70(3.92) ○ Group B: 8.55 (6.27) ○ Group C: 7.98 (3.83) ○ Group E: 7.71 (4.50) ➢ Change from baseline to one month ○ Group A: P = Non-significant ○ Group B: P <0.05 ○ Group C: P Non-significant ○ Group E: P <0.05 ➢ Comparison between tONS and TPM groups ○ Results not reported • **Secondary outcomes** ➢ SDS and SAS score were significantly improved in all tONS groups and TPM group compared to baseline. P<0.01 ○ Comparison between tONS and TPM groups: Results not reported ➢ HIT-6 scores were significantly different compared to baseline in all tONS groups and TPM group. P<0.05 ➢ **Satisfaction at one month (%)** ○ Group A: 14 (63.64) ○ Group B: 14 (63.64) ○ Group C: 17 (77.27) ○ Group E: 17 (77.27) ➢ **Satisfaction at 3 month follow up (%)** ○ Group A: 12 (54.55) ○ Group B: 11 (50.0) ○ Group C:15 (68.18) ○ Group E: 12 (54.55) • **Safety:** One patient in tONS group (group A) experienced intolerance which subsided on reducing the intensity of tONS. 9 patients in TPM group experienced paresthesia.	

Flu = flunarizine; HIT-6 = Headache Impact Scale; SAS = Self rating Anxiety Scale; SD = Standard Deviation; SDS = Self rating Depression Scale; tONS = transcutaneous Occipital Nerve Stimulation; TPM = Topiramate; tSNS = transcutaneous Supraorbital Nerve Stimulation; VAS = Visual Analog Scale

Appendix 5: Additional References of Potential Interest

NICE Reports

NICE. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine [*Interventional procedures guidance 559*]. London (UK): National Institute for Health and Care Excellence; 2016 May: https://www.nice.org.uk/guidance/ipg559/resources/transcutaneous-electrical-stimulation-of-the-supraorbital-nerve-for-treating-and-preventing-migraine-pdf-1899871995657157 Accessed 2020 Apr 08.

NICE. Interventional procedure overview of transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine. London (UK): National Institute for Health and Care Excellence; 2015 Jul: https://www.nice.org.uk/guidance/ipg559/documents/overview Accessed 2020 Apr 08.

Economic Evaluation

Strickland I, Mwamburi M, Davis S, et al. Noninvasive vagus nerve stimulation in a primary care setting: effects on quality of life and utilization measures in multimorbidity patients with or without primary headache. *Am J Manag Care*. 2018 Dec;24(24 Suppl):S517-s526. PubMed: PM30543269

Mwamburi M, Tenaglia AT, Leibler EJ, Staats PS. Cost-effectiveness of noninvasive vagus nerve stimulation for acute treatment of episodic migraine - and role in treatment sequence strategies. *Am J Manag Care*. 2018 Dec;24(24 Suppl):S527-s533. PubMed: PM30543270

Protocol

Araújo M, Souza J, Araújo F, DeSantana J. Effect of Transcutaneous Electric Nerve Stimulation (TENS) in patients with migraine: a systematic review. PROSPERO. 2017 CRD42017055820. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017055820 Accessed 2020 Apr 08.