| Policy Number | SUR701.046 |
|---|---|
| Policy Effective Date | 12/15/2025 |

# Remote Electrical Neuromodulation for Migraines

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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Coverage

**Acute Treatment**
Remote electrical neuromodulation for acute migraine **is considered experimental, investigational and/or unproven**.

**Preventive Treatment**
Initiation of Use-Adult
Remote electrical neuromodulation (REN [e.g. Nerivio]) for the prevention of migraine **may be considered medically necessary** in individuals when the following criteria are met:

- Individual is 18 years of age or older; AND
- Headaches meet the International Classification of Headache Disorders (ICHD-3) diagnostic criteria for migraine with or without aura (see Policy Guidelines); AND
- The REN device will be used in the following clinical scenario:
  - For the prevention of migraine in individuals with 6 to 24 headache days (defined as a calendar day with headache regardless of severity or duration) per 28-day period in each of the 3 months preceding use of the REN device); AND
- One of the following additional criteria must also be met:

- Insufficient response, contraindication, or intolerance to 2 or more guideline-recommended preventive headache medications (e.g., anticonvulsants, antihypertensives, antidepressants, CGRP inhibitors); or
- Pregnancy, breastfeeding, or planning to conceive; or
- At risk for or have a history of medication overuse headache; or
- At risk for drug-drug interactions with medications for comorbid conditions.

Initiation of Use-Pediatric

Remote electrical neuromodulation (REN [e.g. Nerivio]) for the prevention of migraine **may be considered medically necessary** in individuals when the following criteria are met:

- Individual is 8-17 years of age; AND
- Headaches meet the International Classification of Headache Disorders (ICHD-3) diagnostic criteria for migraine with or without aura (see Policy Guidelines); AND
- The REN device will be used in the following clinical scenario:
  - For the prevention of migraine in individuals with 6 to 24 headache days (defined as a calendar day with headache regardless of severity or duration) per 28-day period in each of the 3 months preceding use of the REN device).

Continuation of Use

Continued use of the REN device and/or accessories for the prevention of migraine **is considered medically necessary** in individuals when the following criteria are met:

- Compliance with ongoing use; AND
- Documentation of clinical benefit (see Policy Guidelines).

Remote electrical neuromodulation for prevention of migraine outside of the above criteria **is considered experimental, investigational and/or unproven**.

## Policy Guidelines

**Remote Electrical Neuromodulation Contraindications**

Nerivio is contraindicated in patients with uncontrolled epilepsy and patients with an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device. Nerivio has not been evaluated in patients with congestive heart failure, severe cardiac or cerebrovascular disease, pregnancy, or patients under the age of 8 years.

**Criteria for Migraine**

The International Classification of Headache Disorders ICDH-3 criteria for migraine with and without aura can be accessed at <https://ichd-3.org>.

**Clinical Benefit for Continuation of Use**

Documentation of clinical benefit for continuation of use may include a clinician attestation regarding any of the following outcomes:

- Improvements in pain relief or freedom, particularly for acute use;

- Reduction in headache frequency, duration, or severity;
- Reduction in functional disability;
- Reduction in absenteeism;
- Reduction in concomitant headache medications.

Based on observed outcomes of pivotal studies of Nerivio and study duration recommendations from the International Headache Society concerning migraine neuromodulation trial designs, assessment for clinical benefit is reasonable after a minimum of 8-12 weeks for preventive treatment.

## Description

Migraine attacks due to episodic or chronic migraine require acute management. Some individuals may also require preventive migraine therapy. Current first-line therapy for treatment and prevention of acute migraine involves use of various pharmacologic interventions. Regular use of pharmacologic interventions can result in medication overuse and increased risk of progression from episodic to chronic migraine. Nonpharmacologic remote electrical neuromodulation (REN) may offer an alternative to pharmacologic interventions for patients with migraine.

**Migraine**

Migraine is a neurologic disease characterized by recurrent moderate to severe headaches with associated symptoms that can include aura, photophobia, nausea, and/or vomiting. (1) Overall migraine prevalence in the United States is about 15% but varies according to population group. (2) Prevalence is higher in women (21%), among American Indian/Alaska Natives (22%), and among 18- to 44-year-olds (19%). Social determinants including low education level (18%), use of Medicaid (27%), high poverty level (23%), and being unemployed (22%) are also associated with higher rates of migraine.

Migraine is categorized as episodic or chronic depending on the frequency of attacks. Generally, episodic migraine is characterized by 14 or fewer headache days per month and chronic migraine is characterized by 15 or more headache days per month. (3) Specific International Classification of Headache Disorders (4) diagnostic criteria are as follows:

- Episodic migraine:

1. Untreated or unsuccessfully treated headache lasting 4 to 72 hours
2. Headache has at least 2 of the following characteristics:
    a. Unilateral location
    b. Pulsating quality
    c. Moderate or severe pain intensity
    d. Aggravation by or causing avoidance of routine physical activity
3. At least 1 of the following during headache:
    a. Nausea and/or vomiting
    b. Photophobia or phonophobia.

- Chronic migraine:

1. Migraine-like or tension-type headache on 15 or more days per month for more than 3 months
2. At least 5 headache attacks without aura meet episodic migraine criteria 1 to 3, and/or at least 5 headache attacks with aura meet episodic migraine criteria 2 to 3
3. On more than 8 days per month for more than 3 months, fulfilling any of the following criteria:
    a. For migraine without aura, episodic migraine criteria 2 and 3
    b. For migraine with aura, episodic migraine criteria 1 and 2
    c. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

Migraine attacks, whether due to episodic or chronic migraine, require acute management. The goal of acute treatment is to provide pain and symptom relief as quickly as possible while minimizing adverse effects, with the intent of timely return to normal function. Pharmacologic interventions for treatment of acute migraine vary according to migraine severity. First-line therapy for an acute episode of mild or moderate migraine includes oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Moderate to severe migraine can be treated through the use of triptans or an NSAID-triptan combination. Antiemetics can be added for migraine accompanied by nausea or vomiting, though certain antiemetic medications used as monotherapy can also provide migraine relief. Other pharmacologic interventions used to treat acute migraine include calcitonin-gene related peptide antagonists, which can be used in patients with an insufficient response or contraindications to triptans, lasmiditan, and dihydroergotamine. Migraine can be managed at home, although acute migraine is a frequently cited reason for primary care and emergency department visits. (5) Regular use of pharmacologic interventions can result in medication overuse, which in turn could lead to rebound headache and increased risk of progression from episodic to chronic migraine. (4)

Many individuals who suffer from migraine may also benefit from preventive migraine therapy, including those with frequent or long-lasting migraines, migraine attacks that diminish quality of life or cause significant disability despite acute treatment, contraindications to or failure of acute therapies, and risk of medication overuse headache. (6-8) The main goals of preventive therapy are to reduce future attack frequency, severity, and duration, improve responsiveness to acute treatments, improve function and reduce disability, and prevent progression of episodic migraine to chronic migraine. For most adults with episodic migraines who may benefit from preventive therapy, initial therapy with an antiepileptic drug (divalproex sodium, sodium valproate, topiramate) or beta-blockers (metoprolol, propranolol, timolol) is recommended. Frovatriptan may be beneficial as initial therapy for prevention of menstrually associated migraine. Antidepressants (amitriptyline, venlafaxine), alternative beta-blockers (atenolol, nadolol), and additional triptans (naratriptan, zolmitriptan for menstrually associated migraine prevention) may be considered if initial therapy is unsuccessful. For preventive treatment of pediatric migraine, many children and adolescents who received placebo in clinical trials improved and most preventive medications were not superior to placebo. Possibly effective

preventive treatment options for children and adolescents may include amitriptyline, topiramate, or propranolol.

**Remote Electrical Neuromodulation**

Remote electrical neuromodulation (REN) may offer an alternative to pharmacologic interventions for patients with acute migraine or it may decrease the use of abortive or preventive medications and the risk of medication overuse to treat or prevent acute migraines. The only currently available REN device (Nerivio™) cleared for use by the Food and Drug Administration (FDA) is worn on the upper arm and stimulates the peripheral nerves to induce conditioned pain modulation (CPM). The conditioned pain in the arm induced by the Nerivio REN device is believed to reduce the perceived migraine pain intensity. (9) Control of the REN device is accomplished through Bluetooth communication between the device and the patient's smartphone or tablet. For acute treatment, at onset of migraine or aura and no later than within 1 hour of onset, the user initiates use of the device through their mobile application. When used for preventive treatment, the device should be used every other day, controlled by the individual through their smartphone or tablet application. Patient-controlled stimulation intensity ranges from 0% to 100%, corresponding to 0 to 40 milliamperes (mA) of electrical current. Patients are instructed to set the device to the strongest stimulation intensity that is just below their perceived pain level. The device provides stimulation for up to 45 minutes before turning off automatically. The Nerivio manufacturer indicates that the device can be used instead of or in addition to medication.

**Regulatory Status**

In May 2019, Nerivio Migra™ (Theranica Bio-Electronics Ltd.) was granted a de novo classification by the FDA (class II, special controls, product code: QGT). (10) This new classification applied to this device and substantially equivalent devices of this generic type. Nerivio Migra was initially cleared for treatment of acute migraine in adults who do not have chronic migraine.

In October 2020, Nerivio was cleared for marketing by the FDA through the 510(k) process (K201824). FDA determined that this device was substantially equivalent to Nerivio Migra for use in adults. (11) The device name changed to just “Nerivio” and the exclusion of chronic migraine patients was removed. The Nerivio device can provide more treatments than the predicate Nerivio Migra (12 treatments vs. 8 treatments) and has a longer shelf life (24 months vs. 9 months). In January 2021, the Nerivio device was cleared for use in patients aged 12 to 17 years. (12) In February 2023, Nerivio's indication was expanded to include preventive treatment of migraine with or without aura in individuals 12 years and age or older and was cleared for marketing through the 510(k) process (K223169). (13) In October 2024, the Nerivio and rechargeable Nerivio Infinity devices were cleared for marketing (K241756) with an expanded indication for acute and/or preventive treatment of migraine with or without aura in patients 8 years and older. (14)

## Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Acute Migraine due to Episodic or Chronic Migraine**

Clinical Context and Therapy Purpose

The purpose of remote electrical neuromodulation (REN) in individuals who have acute migraine attacks due to episodic or chronic migraine is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

***Populations***

The relevant population of interest is individuals with acute migraine due to episodic or chronic migraine.

***Interventions***

The therapy being considered is REN with the Nerivio device.

***Comparators***

The following therapies are currently being used to treat acute migraine due to episodic or chronic migraine: medical management or no treatment. A number of medications are used to treat migraine. First-line therapy for mild or moderate migraine includes oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. More severe migraine can be treated through the use of triptans or an NSAID-triptan combination through a variety of routes (e.g. oral, nasal spray or powder, subcutaneous). Antiemetics can be added for migraine accompanied by

nausea or vomiting. Other pharmacologic interventions used to treat acute migraine include calcitonin-gene related peptide antagonists, which can be used in patients with an insufficient response or contraindications to triptans, lasmiditan, and dihydroergotamine. Pharmacologic therapies have not been extensively studied in adolescent and pediatric populations. Options in this population have typically focused on use of ibuprofen, acetaminophen, and select triptans.

***Outcomes***

The general outcomes of interest are: symptoms, functional outcomes, quality of life, and treatment-related morbidity. Specific important health outcomes include freedom from migraine pain and bothersome symptoms, restored function (e.g., return to normal activities), and patient-assessed global impression of treatment. Examples of relevant outcome measures appear in Table 1. In adolescent and pediatric populations, functional disability can also be captured as changes in missed days of school.

Follow-up over several hours is needed to monitor for treatment effects.

**Table 1. Health Outcome Measures Relevant to Acute Migraine Attack (3, 15, 16)**

| Outcome | Description |
|---|---|
| Pain free | No pain at defined assessment time (e.g., 2 hours) |
| Pain relief | Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g., 2 hours) |
| Sustained pain free | No pain at initial assessment (e.g., 2 hours) and remains at follow-up assessment (e.g., 1 day) with no use of rescue medication or relapse (recurrence) within that time frame |
| Sustained pain relief | Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g., 2 hours) and remains improved at follow-up assessment (e.g., 1 day) with no use of rescue medication or relapse (recurrence) within that time frame |
| Symptom relief | Improvement of most bothersome symptom(s) from moderate to severe at baseline to mild or none at defined assessment time (e.g., 2 hours) |
| Function relief | Improvement of function from moderate to severe at baseline to mild or none at defined assessment time (e.g., 2 hours) |
| Restored function | No restriction to perform work or usual activities at a defined assessment time (e.g., 2 hours) |
| Global impact of treatment | Patient assessment of functional disability and health-related quality of life using a Likert or other validated scale at a defined assessment time (e.g., 2 hours) |

| | |
|---|---|
| Global evaluation of treatment | Patient assessment of overall treatment effect (pain, symptom relief, adverse events) using a Likert or other validated scale at a defined assessment time (e.g., 2 hours) |

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Use of REN for the treatment of migraine has been assessed in 2 RCTs (Yarnitsky et al., 2017 [17] and 2019 [18]) comparing an active REN device (Nerivio Migra) with a sham device in patients with an acute migraine attack due to episodic migraine (Table 2).

A pilot, crossover trial conducted by Yarnitsky et al. (2017) included data from 71 (of 86 randomized) patients who received active or sham REN. (17) All patients were given an identical REN device that was preprogrammed to deliver in random order 4 active treatment sessions ranging from 80 to 120 hertz (Hz), corresponding to pulse widths of 50 to 200 milliseconds, and 1 sham session of 0.1 hertz (45 millisecond pulse width). Both active and sham treatments were programmed for a duration of 20 minutes each. Most patients were women (80%) in their mid-40s (mean age: 46 years), with a mean of 5 migraine attacks per month with a mean pain intensity of 8.8, corresponding to severe pain. Race and/or ethnicity were not reported. In the trial, treatment with active REN was more frequently associated with reduction in, and freedom from, migraine pain than sham REN at 2-hour follow-up (Table 3). When the device was programmed to deliver an active treatment session, it was most effective at reducing pain when used within 20 minutes of migraine onset. Treatment response to active REN diminished over time of initiation following migraine onset, and no active REN participants reported complete pain relief if the device was initiated more than 1 hour from onset. No adverse events were reported, though patients were more likely to rate their treatment perception of the active REN sessions as painful (11%) or unpleasant (28%) compared with sham REN sessions (1% painful; 13% unpleasant). Other outcomes were not reported in this study. Study limitations appear in Tables 4 and 5.

A second, larger (N=252) RCT was conducted by Yarnitsky et al. in 2019 (Table 2). (18) The mean age of study participants was 43 years, 81% were female. Most participants were of White race (88%); 7% were Black and less than 1% were Asian. Time since migraine diagnosis was not reported; participants experienced a mean of 7 migraine days per month. Seventy-one percent

of participants managed migraines with the use of acute medication, but important details about type and dosage were not provided. At baseline, 50% of participants reported that light sensitivity was their most bothersome symptom apart from migraine pain, followed by nausea (27%) and sound sensitivity (19%). After a 2 to 4-week run-in during which study participants kept a headache diary, participants were randomized to 4 to 6 weeks of at-home active or sham REN. The frequency was 100 to 120 Hz for the active device and less than 0.1 Hz for the sham device. The pulse width was 400 microseconds for the active device, and ranged from 40 to 550 microseconds for the sham device, with the intent of mimicking a similar sensation as that delivered by the active device. At the time of randomization, participants were instructed on how to determine their optimal REN intensity, but this was unclearly defined as a threshold that was "perceptible not painful" (e.g., no specific measure of intensity was described) and no data on the actual intensities used during the study were reported. Participants were instructed to treat their migraine with the REN device as soon as possible following migraine onset, and no later than within 1 hour of onset. Participants who initiated device use more than 1 hour following onset were excluded from the outcome analyses. Study results are summarized in Table 3. Patients treated with active REN were more likely to report freedom from pain and pain relief at 2-hour follow-up, and sustained freedom from pain and pain relief at 48-hour follow-up compared with the sham REN group. There was no statistical between-group difference in the proportions of patients reporting freedom from their most bothersome symptom (MBS) at 2-hour follow-up, but a greater proportion of active REN patients reported MBS relief at 2 hours relative to sham REN. Device-related adverse events were reported in 5% of active REN and 2% of sham REN participants (p=.49). At the conclusion of the study, participants were asked whether they believed they had received active or sham treatment as a measure of blinding. Half as many active participants correctly identified their device as did sham participants (23% in the active group vs. 50% in the sham group), although statistical analyses determined the treatment outcome differences between groups were not affected by participants perceived treatment group.

Relevance and methodological limitations of the study are detailed in Tables 4 and 5. Several critical limitations were identified, primarily related to study design and conduct. The most significant limitations pertain to the 1) selection and measurement of outcomes and 2) imbalances in baseline characteristics that are potentially important confounders and 3) absence of statistical adjustments to account for these confounders. These limitations are detailed next.

*Outcome Selection and Assessment*

Contemporary best practices in migraine research emphasize the importance of aligning study endpoints with outcomes that matter most to patients- complete resolution of pain and most bothersome migraine-associated symptom (MBS). (19) Instead, Yarnitsky et al. (2019) measured pain relief as the primary endpoint relegating pain-free status and freedom from MBS to secondary outcomes. Pain-free status, which reflects total resolution of pain, is more consistent with patient expectations and real-world therapeutic goals. In contrast, pain relief is a subjective measure that may not fully restore functional capacity. Similarly, while MBS relief

targets the symptom most disruptive to quality of life, its clinical relevance is diminished if it does not translate into improved daily functioning.

Migraine trials typically focus on individuals with moderate to severe pain as it reflects the typical clinical presentation. Only 10% of participants reported severe pain, and 51% reported moderate pain at baseline. Remaining 39% of patients reported mild pain at the baseline. Further, the primary outcome was a composite of improvement from severe/moderate pain to mild/ none, or improvement from mild pain to none. It is unclear whether the observed pain relief in 67% (66 of 99) of treated patients was primarily driven by clinically meaningful improvement (i.e., severe/moderate pain to mild/none), or merely resolution of mild pain to none. It is important to recognize that only 7 patients with severe pain at baseline were treated with Nerivio.

To assess precision, we calculated 95% confidence intervals for two key outcomes: pain-free status and MBS relief at two hours. In the treatment group, 37.4% of participants were pain-free (95% CI: 27.8-46.9), compared to 18.4% in the sham group (95% CI: 10.9-25.9). Although the 19% between group difference was statistically significant, the wide confidence interval (7% to 30%) indicates substantial uncertainty. No significant effect was observed for MBS resolution.

*Imbalances in Baseline Characteristics*
A second major limitation was the lack of stratified randomization for potentially important confounders that could influence treatment response, including duration of migraine, response to triptans, and current use of preventive medication. Despite randomization, the treatment and sham groups differed in triptan use (52% vs. 44%) and preventive medication use (29% vs. 37%). Migraine duration was not reported. Additionally, there were intra-group differences in baseline pain severity: mild (35% vs. 42%), moderate (58% vs. 45%), and severe (7% vs. 14%) in the treatment and sham groups, respectively.

*Lack of Adjusted Analysis*
Despite these imbalances, the study did not include adjusted analyses to control for key covariates such as triptan response (responder, insufficient responder, or naive), preventive medication use, or baseline headache severity. This omission limits the interpretability of the findings and raises concerns about residual confounding.

*Conclusion*
In the light of these major limitations, the results of Yarnitsky et al. (2019) cannot be interpreted at face value due to the potential for confounding. An adequately powered randomized, double-blind, placebo-controlled trial is necessary to clearly ascertain the net health outcome for Nerivio in treatment of acute migraine in individuals with moderate to severe headache.

A post-hoc analysis of the Yarnitsky 2019 RCT retrospectively compared the effectiveness of acute migraine treatment with the Nerivio device with usual care (i.e., pharmacologic acute

migraine management) used during the 2- to 4-week run-in phase of the trial. (20) Pharmacologic treatment used during the run-in phase consisted of NSAIDs, acetaminophen (alone, or in combination with aspirin and caffeine) or triptans. In analysis of a subset of 99 trial participants, the rate of freedom from pain was similar for Nerivio (37.4% [37/99]) and usual care (26.3% [26/99]; p=.099) at 2-hour follow-up. Results were similar for achievement of pain relief (66.7% [66/99] vs. 52.5% [52/99]; p=.034). Randomized controlled trials directly comparing REN with pharmacologic management are needed to confirm these pain findings and to compare the effect of REN versus pharmacologic management on other outcomes.

**Table 2. Summary of Key RCT Characteristics**

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | *Active* | *Comparator* |
| Yarnitsky et al. (2017) (17) | Israel | 1 | 2016-2016 | Adults (18 to 75 years) with ICHD-3 migraine 2 to 8 days/month with no preventive medication use 2 months prior to enrollment | n=86<br>Active REN device; 4/5 preprogrammed treatment sessions | NA; crossover trial<br>Sham REN device; 1/5 preprogrammed treatment sessions |
| Yarnitsky et al. (2019) (18) | U.S., Israel | 12 | 2017-2018 | Adults (18 to 75 years) with ICHD-3 migraine 2 to 8 days/month but <12 days/month, with no or stable preventive medication use 2 months prior to enrollment | n=126<br>Active REN (Nerivio) device | n=126<br>Sham REN device |

ICHD: International Classification of Headache Disorders; NA: not applicable; RCT: randomized controlled trial; REN: remote electrical neuromodulation; U.S.: United States.

**Table 3. Summary of Key RCT Results**

| Study | Pain Free[1], 2 hours | Pain Relief[2], 2 hours | Sustained Pain Free, 48 hours | Sustained Pain Relief, 48 hours | MBS Free, 2 hours | MBS Relief[3], 2 hours |
|---|---|---|---|---|---|---|
| **Yarnitsky et al. (2017) (17)** | | | | | | |
| Active REN | 44.1% (19/43) | 76.7% (33/43) | NR | NR | NR | NR |
| Sham REN | 5.9% (1/17) | 23.5% (4/17) | NR | NR | NR | NR |
| p value | .005 | .005 | NR | NR | NR | NR |

| Yarnitsky et al. (2019) (18) | | | | | | |
|---|---|---|---|---|---|---|
| Active REN | 37.4% (37/99) | 66.7% (66/99) | 20.7% (18/87) | 39.1% (34/87) | 40.7% (33/81) | 46.3% (44/95) |
| Sham REN | 18.4% (19/103) | 38.8% (40/103) | 7.9% (7/89) | 16.9% (15/89) | 36.4% (32/88) | 22.2% (22/99) |
| p value | .003 | <.001 | .014 | .001 | .55 | .001 |

MBS: most bothersome symptom; NR: not reported; RCT: randomized controlled trial; REN: remote electrical neuromodulation.

[1] Change in headache severity from mild, moderate, or severe at baseline, to none.

[2] Change in headache severity from moderate, or severe at baseline, to none or mild, or a reduction in headache severity from mild to none.

[3] Subjective (undefined) relief of most bothersome symptom.

**Table 4. Study Relevance Limitations**

| **Study** | Yarnitsky et al. (2017) (17) | Yarnitsky et al. (2019) (18) |
|---|---|---|
| **Population**[a] | 1, 2. Intended use population is unclear (e.g., treatment naive, those with contraindications to medication, or those who have failed pharmacologic treatment); time since migraine diagnosis and details about current migraine management regimen not reported | 1, 2. Intended use population is unclear (e.g., treatment naive, those with contraindications to medication, or those who have failed pharmacologic treatment); time since migraine diagnosis and details about current migraine management regimen not reported |
| **Intervention**[b] | 4. Predicate device not commercially marketed. | 1, 5. Details about the mean timing of device initiation and mean, recommended or optimal device intensity (in mA) were not reported; a clinically relevant device intensity threshold has not been established |
| **Comparator**[c] | 2. Comparison versus an acute treatment with established efficacy would be preferred | 1, 2. Details and subgroup analysis on the effect of preventive medication use in 29% of active and 37% of sham participants were not reported; comparison versus an acute treatment with established efficacy would be preferred |
| **Outcomes**[d] | 1, 5. Functional and quality of life outcome measures not addressed | 1, 5. Functional and quality of life outcome measures not addressed |
| **Duration of Follow-up**[e] | | |

mA: milliamperes.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 5. Study Design and Conduct Limitations**

| **Study** | Yarnitsky et al. (2017) (17) | Yarnitsky et al. (2019) (18) |
|---|---|---|
| **Allocation[a]** | 3. Method of allocation to active or sham treatment session not reported | |
| **Blinding[b]** | | 4. 23% of REN vs. 50% of sham participants correctly identified their treatment allocation; however, ad-hoc statistical analyses determined between-group treatment differences were not affected by perceived treatment group |
| **Selective Reporting[c]** | | |
| **Data Completeness[d]** | 1. No data reported for 17% (15/86) of enrolled participants | 1. 19% (49/252) of randomized participants not accounted for in analysis described as intention to treat |
| **Power[e]** | 1. This was a pilot study; no sample size rationale or power calculations were reported | |
| **Statistical[f]** | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other

Avoiding medication overuse has been postulated as a potential benefit of REN treatment of acute migraine. Marmura et al. (2020) (21) reported the results of an observational 8-week open-label extension study following the double-blind phase of the Yarnitsky 2019 trial. The Marmura study compared within-subject data (N=117) from the trial run-in phase with data from the open-label phase, finding that a higher proportion of patients avoided medication use during the open-label phase (when the REN device was available for use; 89.7%) than in the run-in phase (when the REN device was not available for use; 15.4%). Although these results suggest that use of the REN device could result in less medication use and therefore reduce the risk of medication overuse, confirmatory studies designed to directly assess the role of REN in populations at risk of medication overuse are needed.

Nonrandomized Studies

Numerous nonrandomized, uncontrolled studies have been conducted examining the effectiveness of REN with the Nerivio device for acute migraine. (22-28) The most relevant studies are discussed below.

Three single-arm, open-label clinical trials of the Nerivio device were used to inform U.S. Food and Drug Administration (FDA) approval for use in patients other than those with acute migraine due to episodic migraine (Table 6). This includes 2 studies (25, 27) in patients with chronic migraine and 1 study (24) in adolescents. In the 2 studies (25, 27) of patients with chronic migraine, the mean age was 42 and 44 years, and was 15 years in the study of adolescents. (24) In all 3 studies most participants were female (60% to 83%) and of White race (86% to 100%). In the study by Hershey et al. (2021) (24) conducted in adolescents, patients with episodic and chronic migraine were eligible for study inclusion. The studies reported on the effectiveness of the Nerivio device for acute migraine at 2 and 24 hours; study results are summarized in Table 7. The Nerivio device was associated with improvements in pain, symptoms, and function in all 3 studies. Adverse events related to the Nerivio device occurred in 1.0% to 2.0% of study participants across the 3 studies; no serious adverse events were reported in any of the studies. Results from these studies are limited due to their open-label study design, lack of control groups, and variable follow-up.

**Table 6. Summary of Key Nonrandomized Clinical Trial Characteristics**

| Study | Country | Dates | Participants | Treatment | Follow-Up |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Nierenburg et al. (2020) (25) | U.S., Israel | 2019-2020 | N=42 adults (18 to 75 years) with ICHD-3 chronic migraine | REN (Nerivio) | 24 hours |
| Grosberg et al. (2021) (27) | U.S. | 2019-2020 | N=126 adults (18 to 75 years) with ICHD-3 chronic migraine | REN (Nerivio) | 24 hours |
| Hershey et al. (2021) (24) | U.S. | 2019-2020 | N=45 adolescents (12 to 17 years) with ICHD-3 migraine ≥3 attacks/month | REN (Nerivio) | 24 hours |

ICHD: International Classification of Headache Disorders; REN: remote electrical neuromodulation; U.S.: United States.

**Table 7. Summary of Key Nonrandomized Clinical Trial Results**

| Study | Pain Free, 2 hours | Pain Relief, 2 hours | Sustained Pain Free, 24 hours | Sustained Pain Relief, 24 hours | Symptom Free, 2 hours | Functional improve-ment, 2 hours | Return to normal function, 2 hours |
|---|---|---|---|---|---|---|---|
| **Nieren-burg et al. (2020) (25)** | N=38 | N=38 | N=20 | N=32 | N=31 | N=35 | N=35 |
| Proportion (n/N) | 26.3% (10/38)[1] | 73.7% (28/38)[1] | 45.0% (9/20)[1] | 84.4% (27/32)[1] | Nausea/ vomiting: 58.3% (14/24)<br><br>Photo-phobia: 35.5% (11/31)<br><br>Phono-phobia: 40.0% (10/25) | 45.7% (16/35) | 28.6% (10/35) |
| **Grosberg et al. (2021) (27)** | N=99 | N=99 | NR | N=54 | N=82 | N=40 | NR |
| Proportion (n/N) | 19.2% (19/99)[2] | 54.5% (54/99)[3] | NR | 53.7% (29/54) | Nausea/ vomiting: 40.8% (20/49)<br><br>Photo-phobia: | 47.5% (19/40) | NR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | 36.6% (30/82)<br><br>Phono-phobia: 39.7% (129/73) | | |
| **Hershey et al. (2021) (24)** | N=39 | N=39 | N=11 | N=22 | N=31 | N=33 | NR |
| Proportion (n/N) | 35.9% (14/39)[2] | 71.8% (28/39)[3] | 90.9% (10/11) | 90.9% (20/22) | Nausea/ vomiting: 54.5% (12/22)<br><br>Photo-phobia: 41.9% (13/31)<br><br>Phono-phobia: 40.0% (10/25) | 69.7% (23/33) | NR |

NR: not reported.
[1]Pain free and pain relief for at least 50% of treated attacks.
[2]Change in headache severity from mild, moderate, or severe at baseline to none.
[3]Change in headache severity from moderate or severe at baseline to none or mild; or a reduction in headache severity from mild to none.

A post-hoc analysis of the Hershey et al. (2021) study, conducted in adolescents, compared the effect of Nerivio use (during the study phase) versus medication use (during the run-in phase) based on within-subject data. (23) Thirty-five adolescents who used medication during the 4-week run-in phase and who had Nerivio use data from the study phase were included in the post-hoc analysis. Nerivio users were more likely to report freedom from pain than medication users (p=.004) but there was no difference between Nerivio and medication in the proportions of patients who achieved pain relief (p=.225). Studies designed to directly compare the Nerivio device with medication are needed to adequately assess comparative effectiveness.

A real-world study (Ailani et al., 2021) sponsored by the Nerivio manufacturer collected data from 23,151 treatments from 5,805 Nerivio users between October 2019 and May 2021. (22) This study is unique in including data on use of the Nerivio device as monotherapy and in combination with medications. Nerivio users reported use of medications (over-the counter, triptans, or other medications) in addition to the Nerivio device for about one-third of the

treatment sessions. For use of Nerivio as monotherapy at 2-hour follow-up, the proportion of patients with freedom from pain, pain relief, return to normal function, and functional disability improvement was 20.3%, 55.6%, 24.9%, and 51.2%, respectively. When the Nerivio device was used in conjunction with medication, proportions ranged from 10.1% to 15.5% for freedom from pain, 38.5% to 51.3% for pain relief, 11.0% to 19.7% for return to normal function, and 39.8% to 49.6% for functional disability improvement, depending on the drug class used. While these results suggest that REN with the Nerivio device is efficacious in a highly selected group of individuals, additional evidence from well-designed RCTs is needed to thoroughly assess comparative effectiveness.

Pediatric Experience

The FDA 510(k) summary for the 2024 expanded approval of acute use of Nerivio in pediatric patients (ages 8-11) was based on a retrospective real-world analysis of 293 children, aged 6-11 at their first use of the device. (14) Median patient age was 11 (73.7% female). Safety data were primarily collected via self-reported customer service complaints, which indicated no adverse events. Effectiveness was assessed in patients who completed voluntary pre- and post-treatment surveys. Available efficacy data was only available in 18 participants, of which consistent headache relief was reported by 72.2% (13/18), consistent freedom from headache by 83.3% (15/18), and consistent functional disability freedom by 38.9% (7/18). Additional controlled studies are required to confirm efficacy in this population. Patients in this population used REN as a standalone treatment, with over-the-counter medications, and with prescribed headache medications, in 45.4%, 34.4%, and 20.9% of treatments, respectively. (29)

In 2024, Hershey et al. published the results of a survey of 332 students aged 7-17 (80.4% female). (30) After being prescribed REN, the percentage of students reporting having their headaches treated at school increased by 11.5%. The most common reasons given for preferring REN treatment at school are the ability to avoid going to the nurse's office (42.5%) and the ability to treat discreetly (39.2%). Barriers to treatment included concerns about standing out (42.2%), and permission to use a smartphone in class to control the REN device (22.9%).

Coverage with Evidence Development Study

In 2025, Synowiec and coworkers published the outcomes of a real-world postmarketing coverage with evidence development study conducted in partnership with Highmark Inc. (31) Members aged 12-75 years who were diagnosed with migraine were prescribed REN. Eligibility criteria included: 1) at least 1 standard-of-care acute migraine therapy had failed for 1 or more of the following reasons: contraindication, lack of sufficient efficacy, or intolerability of adverse effects; 2) were at risk of drug-drug interaction with other medications; 3) were a pregnant woman, woman trying to conceive, or breastfeeding woman; 4) had chronic migraine and were at risk of or diagnosed with medication overuse headache (MOH); or 5) were younger than 18 years. Efficacy was assessed by changed in Migraine Disability Assessment (MIDAS) score from baseline to 3 months of treatment and by prospective pain and disability reports 2 hours post treatment. Device utilization was assessed through prescription fulfillment rates. A total of 381 patients (mean age, 40.5; 91.1% female) participated in the study. Change in MIDAS

score was calculated for all participants who answered the questionnaire twice (n=116), indicating a statistically and clinically meaningful improvement of -12.1 point (p =.014). Pain relief, pain freedom, functional disability relief, and functional disability freedom were reported in 77.8%, 33.3%, 70.6%, and 50.0% of participants, respectively Three minor adverse events were reported and patients used a mean of 4.0 (SD, 3.1) devices annually. Generalizability of outcomes is limited due to lack of a control group and high degree of missing data (70%).

Section Summary: Acute Migraine due to Episodic or Chronic Migraine

Evidence from 2 small RCTs found REN with the Nerivio device was more effective than a sham device for measures of pain and symptom relief at 2-hours post-treatment. Patients treated with the Nerivio device were also more likely than those treated with a sham device to report 48-hour freedom from pain and pain relief based on 1 RCT. No significant between-group difference in functional disability or quality of life was noted in a post-hoc analysis of the pivotal RCT. The remaining evidence from post-hoc and nonrandomized studies suggests that REN with the Nerivio device may provide improvements in acute pain and symptomatology. Controlled studies in adolescent and pediatric populations are lacking.

**Prevention of Migraine**

Clinical Context and Therapy Purpose

The purpose of REN as preventive therapy in individuals who have acute migraine attacks due to episodic or chronic migraine is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

*Populations*

The relevant population of interest is individuals who may benefit from preventive migraine therapy, including those with frequent or long-lasting episodic or chronic migraines, migraine attacks that diminish quality of life or cause significant disability despite acute treatment, contraindications to or failure of acute therapies, and risk of medication overuse headache.

*Interventions*

The therapy being considered is REN with the Nerivio device.

*Comparators*

The following therapies are currently being used to prevent acute migraine due to episodic or chronic migraine: medical management or no treatment. A number of medications are used as prevention for migraine. For most adults with episodic migraines who may benefit from preventive therapy, initial therapy with an antiepileptic drug (divalproex sodium, sodium valproate, topiramate) or beta-blockers (metoprolol, propranolol, timolol) is recommended. Frovatriptan may be beneficial as initial therapy for prevention of menstrually associated migraine. Antidepressants (amitriptyline, venlafaxine), alternative beta-blockers (atenolol, nadolol), and additional triptans (naratriptan, zolmitriptan for menstrually associated migraine prevention) may be considered if initial therapy is unsuccessful. For preventive treatment of

pediatric migraine, many children and adolescents who received placebo in clinical trials improved and most preventive medications were not superior to placebo. Possibly effective preventive treatment options for children and adolescents may include amitriptyline, topiramate, or propranolol. Non-pharmacologic interventions may include behavioral interventions and lifestyle changes focused on the avoidance of known migraine triggers.

*Outcomes*
The general outcomes of interest are: symptoms, functional outcomes, quality of life, and treatment-related morbidity. Specific important health outcomes include reduction of future attack frequency, severity, and duration, improved responsiveness to acute treatments, improved function and reduced disability, and prevention of progression of episodic migraine to chronic migraine. In adolescent and pediatric populations, functional disability can also be captured as changes in missed days of school.

Follow-up over several days to months is needed to monitor for preventive treatment effects.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Use of REN for the prevention of migraine has been assessed in 1 double-blind, multicenter RCT by Tepper et al. (2023), comparing an active REN device (Nerivio) used every other day with a sham device in adult patients with at least a 6-month history of headaches that meet the International Classification of Headache Disorders, third edition (ICHD-3) and 6 to 24 headache days per 28-day period in the past 3 months. (32) Included participants either did not use preventive medicine or were on a stable dose of a single migraine preventive medication during the 2 months before enrollment and throughout the study. Prior to initiation of REN, all patients participated in a 4-week baseline phase, where they were instructed to continue their regular medications when needed, and document daily reports, regardless of if they had a headache that day or not, to rate symptoms using a 4-point scale. Symptoms that were collected included pain, functional disability, presence or absence of nausea and/or vomiting, photophobia, and phonophobia, and acute medication usage.

To be eligible for the intervention phase, individuals had to have had 6 to 24 headache days during the 28-day baseline period, with at least 4 headache days fulfilling ICHD-3 criteria for

migraine, and had at least 80% compliance on completing their daily record of symptoms. The intervention phase was 8 weeks long and included participants were randomized 1:1 to active REN or sham REN. The active and sham devices were visually identical, so staff and participants were blinded to their randomized group. Participants were directed to complete a full 45-minute treatment with REN every other day and to complete a daily diary. If acute treatment was needed, participants were instructed to use their usual acute treatments. The primary outcome was the mean change in number of migraine days per month in the 4-week baseline phase compared to the last 4 weeks of treatment phase (weeks 9 through 12). Overall, patients treated with the active REN device had statistically significantly fewer migraine days during the intervention period compared to baseline compared to those treated with sham. This was also demonstrated in subanalyses based on episodic or chronic migraines. Of the participants, 40.8% used a preventive medication in combination with REN. Half of the medication users were on first-line preventive medications (e.g., amitriptyline, topiramate), while the other half were on second line agents (e.g., anti-calcitonin gene-related peptide monoclonal antibodies, onabotulinumtoxin A, gepants). There were 2 non-device-related serious adverse events, both in the REN arm. There was a single device-related adverse event in the sham group and no device-related adverse events in the active group. There were no differences in quality of life questionnaires or Headache Impact Tests, a tool used to capture the impact of headache on functional health and well-being, between groups at any time period. These results are limited by the 8-week duration, shorter than the recommended 12-week duration by the International Headache Society guidelines for neuromodulation devices and lack of medical history reporting previous preventive medications used by participants. Tables 8 and 9 describe the key characteristics and results of the RCT. No significant difference between REN and sham groups was noted for mean change in the Headache Impact Test Short Form (HIT-6) or Migraine Specific Quality of Life Questionnaire - Function Domain (MSQ). Tables 10 and 11 describe notable limitations.

**Table 8. Summary of Key RCT Characteristics**

| **Study** | **Countries** | **Sites** | **Dates** | **Participants** | **Interventions** | |
|---|---|---|---|---|---|---|
| | | | | | *Active* | *Comparator* |
| Tepper et al. (2023) (32) | United States | 15 | 2021-2022 | Adults (18 to 75 years) with ICHD-3 migraine at least 4 days/month in baseline period with no preventive medication use or stable medication use 2 months prior to enrollment; 85% female, mean age of 41.7 years; and ratio of episodic to chronic patients was 47.6%: 52.4%. | n=128 (ITT); 95 (mITT) Active REN device, use every other day | n=120 (ITT); 84 (mITT) Sham REN device |

ICHD: International Classification of Headache Disorders; ITT: intention to treat; mITT: modified intention to treat; RCT: randomized controlled trial; REN: remote electrical neuromodulation.

**Table 9. Summary of Key RCT Results**

| Study | Overall mean change in migraine days/month[1] | Mean change in migraine days/month: Episodic subgroup[1] | Mean change in migraine days/month: Chronic subgroup[1] | Mean change in moderate/ severe headache days | Mean change in number of headache days | Percentage of patients achieving at least 50% reduction from baseline in headache days |
|---|---|---|---|---|---|---|
| **Tepper et al. (2023) (32)** | | | | | | |
| n | n=95 active REN; n=84 sham REN | n=45 active REN; n=42 sham REN | n=50 active REN; n=42 sham REN | n=95 active REN; n=84 sham REN | n=95 active REN; n=84 sham REN | n=95 active REN; n=84 sham REN |
| Active REN | -4.0±4.0 | -3.2±3.4 | -4.7±4.4 | -3.8±3.9 | -4.5±4.1 | 26.3% |
| Sham REN | -1.3±4.0 | -1.0±3.6 | -1.6±4.4 | -2.2±3.6 | -1.8±4.6 | 11.9% |
| Difference versus sham (95% CI); p value | -2.7 (-3.9 to -1.5); <.001 | 2.3 (NR); .003 | 3.0 (NR); .001 | -1.6 (-2.7 to -0.5); .005 | -2.7 (-3.9 to -1.5); <.001 | NR; NR; .015 |

CI: confidence interval; NR: not reported; RCT: randomized controlled trial; REN: remote electrical neuromodulation.

[1] Change in migraine days from baseline (weeks 1 through 4) compared to last 4 weeks (weeks 9 through 12)

**Table 10. Study Relevance Limitations**

| Study | Tepper et al. (2023) (32) |
|---|---|
| **Population[a]** | 1, 2. Intended use population is unclear (e.g., treatment naive, those with contraindications to medication, or those who have failed pharmacologic treatment); time since migraine diagnosis and details about current migraine management regimen not reported |
| **Intervention[b]** | 1. A clinically relevant device intensity threshold has not been established |
| **Comparator[c]** | 2. Comparison versus specific pharmacologic preventive treatments with established efficacy would be preferred if attempting to establish first-line use |
| **Outcomes[d]** | |
| **Duration of Follow-up[e]** | 3. 8-week duration is less than the recommended 12-week duration by IHS guidelines for neuromodulation devices |

IHS: International Headache Society.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 11. Study Design and Conduct Limitations**

| **Study** | Tepper et al. (2023) (32) |
|---|---|
| **Allocation[a]** | |
| **Blinding[b]** | |
| **Selective Reporting[c]** | |
| **Data Completeness[d]** | 2. LOCF imputation methodology for full ITT set not prespecified and generally does not meet MCAR assumptions; worst case sensitivity analysis not reported; 28% of data missing in mITT analysis |
| **Power[e]** | |
| **Statistical[f]** | |

ITT: intention to treat; LOCF: last observation carried forward; MCAR: missing completely at random; mITT: modified ITT.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

## Nonrandomized Studies

Prospective, real-world data collected and analyzed by the manufacturer on the use of Nerivio in adolescents was summarized in the FDA approval packet for the indication of Nerivio in migraine prevention in adolescents and adults. (13) The data were collected from adolescents who used the device for acute migraine treatment, but use was equivalent to the suggested preventive use (10 times per month or higher). Prospective data were collected through the Nerivio app between January 2021 and November 2022. Eligible adolescent patients used Nerivio on at least 10 days in their first 28-day month of using the device, and used the device on at least 3 days in each of the 2 subsequent months. The goal of analysis was to assess the mean reduction in migraine headache days from the first month of use to the second and third month of use. In total, 61 patients (mean age, 15.7±1.3 years, 87% female) were eligible for analysis. Investigators found significant month-to-month reduction in migraine headache days from 15 days (standard error [SE], 0.6) in month 1, to 10.6 days (SE, 0.8) in month 2 ($p<.0001$), and 8.7 days (SE, 0.7) in month 3 ($p<.0001$), demonstrating substantial reduction from baseline during months 2 and 3 of device use. This data is limited by a lack of comparator and no description of medications or alternative interventions patients were additionally using.

A prospective, real-world evidence analysis investigated whether the use of Nerivio in adolescents who have frequently utilized the REN wearable device had reduced mean monthly migraine treatment days (MMTD) compared to baseline. (33) Patients (N=83) were 15.9 ± 1.3 years of age (mean±SD) and were evaluated for a 3 month period. There was a statistically significant monthly reduction in MMTD (a reduction of 3.6 [±4.8] MMTD) from the first month to the second month of consecutive use ($p<.001$). In the third month of treatment, there was a further reduction of 1.6 (±4.1) MMTD ($p<.001$), for a cumulative total reduction of 5.2 (±4.8) MMTD throughout the first 3 months of consecutive treatment.

The FDA 510(k) summary for the expanded approval of preventive use of Nerivio in pediatric patients (ages 8-11) was based on a retrospective real-world analysis of 293 children, aged 6-11. (14) Preventive use of the device was assumed by analyzing patients whose frequency of use in month one was suggestive of preventative treatments. No specific data on proportion of patients in whom preventive use was assumed or efficacy outcomes in the assumed preventive use population were reported in the 510(k) summary. Well-defined, controlled studies are required to confirm benefit in this population.

Section Summary: Prevention of Migraine

Evidence from a small RCT found REN with the Nerivio device was more effective than a sham device for decreasing migraine days per month, regardless of episodic or chronic subgroup, when used every other day for 8 weeks. Patients treated with the Nerivio device were also more likely than those treated with sham to have reduced moderate to severe headache days, reduced headache days in general, and at least a 50% reduction from their baseline in overall headache days. Approximately half of patients included in this study were also taking preventive pharmacologic therapy. There were no differences in quality of life or functional health patient-reported outcomes between groups at any time point. Prospective, observational data in 2 real world evidence studies using the device for acute treatment of migraine demonstrated a significant reduction in migraine headache days from baseline to

months 2 and 3 with device use in adolescent patients. Based on the existing evidence, it is unclear how Nerivio would fit into the current migraine prevention pathway, although it could provide benefit for those who do not receive adequate benefit from pharmacologic first- or second-line therapies, or who may have a contraindication to pharmacologic therapies. Study limitations include a high-degree of missing data and choice of imputation method. Controlled data in pediatric populations is lacking.

**Summary of Evidence**

For individuals with acute migraine due to episodic or chronic migraine who receive remote electrical neuromodulation (REN), the evidence includes 2 randomized controlled trials (RCTs) and nonrandomized, uncontrolled studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Use of an active REN device resulted in more patients with improved pain and symptoms at 2-hour follow-up compared with a sham device based on 2 RCTs (N=212) with numerous relevance limitations. Based on the existing evidence, it is unclear how Nerivio would fit into the current acute migraine management pathway. No significant between-group difference in functional disability or quality of life was noted in a post-hoc analysis of the pivotal RCT. Additionally, controlled studies in adolescent and pediatric populations are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For adult individuals who may benefit from preventive migraine therapy, including those with frequent or long-lasting episodic or chronic migraines, migraine attacks that diminish quality of life or cause significant disability despite acute treatment, contraindications to or failure of acute therapies, and risk of medication overuse headache, who receive REN, the evidence includes 1 RCT and 1 prospective, observational study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Use of an active REN device resulted in more adults with decreased migraine days per month, regardless of episodic or chronic subtype, when used every other day for 8 weeks compared with a sham device based on 1 RCT (N=248). Prospective, observational data in 2 real world evidence studies using the device for acute treatment of migraine demonstrated a significant reduction in migraine headache days from baseline to months 2 and 3 with device use in adolescent patients. Based on the existing evidence, it is unclear how Nerivio would fit into the current migraine prevention pathway, although it could provide benefit for those who do not receive adequate benefit from pharmacologic first- or second-line therapies, or who may have a contraindication to pharmacologic therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For adolescent individuals who may benefit from preventive migraine therapy who receive REN, the evidence includes data from the summary submitted in the FDA approval packet and 1 RWE analysis. The data in the FDA summary were collected from adolescents who used the device for acute migraine treatment, but use was equivalent to the suggested preventive use (10 times per month or higher). There was substantial reduction from baseline during months 2 and 3 of device use. This data is limited by a lack of comparator and no description of medications or alternative interventions patients were additionally using. A prospective, real-world evidence

analysis investigated the use of Nerivio in adolescents over a 3 month period. There was a statistically significant monthly reduction in mean monthly migraine treatment days. Well-defined, controlled studies are required to confirm benefit in this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For children who may benefit from preventive migraine therapy who receive REN, the evidence includes the FDA summary for the expanded approval of preventive use of Nerivio in pediatric patients (ages 8-11) based on a retrospective real-world analysis. Preventive use of the device was assumed by analyzing patients whose frequency of use in month one was suggestive of preventive treatments. No specific data on proportion of patients in whom preventive use was assumed or efficacy outcomes in the assumed preventive use population were reported. Well-defined, controlled studies are required to confirm benefit in this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**2025 Clinical Input**

Clinical input was sought to help determine whether the use of remote electrical neuromodulation (i.e., Nerivio) for the listed populations would provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice:

- Individuals who are 12 years and older with episodic or chronic migraine, with or without aura, who are treated for acute migraine or migraine prophylaxis
- Individuals who are 8-11 years old with episodic or chronic migraine, with or without aura, who are treated for acute migraine or migraine prophylaxis

Clinical input supports this use provides a clinically meaningful benefit, with the majority of respondents supportive that its use is consistent with generally accepted medical practice. Respondents noted that all patients with migraine may benefit from a nonpharmacologic option for either stand-alone or adjunctive use, particularly among those who have failed other options, who have contraindications or an intolerance to alternatives, who are at risk for or have a history of medication overuse headache, or who are at risk of drug-drug interactions. While some clinicians trial acute treatment with REN first, failure in the abortive setting does not preclude success with preventive use. Additionally, clinicians support first-line use of REN for acute or preventive treatment, particularly in adolescent and pediatric populations where there are limited alternatives with evidence of efficacy or suitable side effect profiles. Respondents emphasize that the discreet nature of the REN device is ideal for use by children and adolescents in the school setting.

**Practice Guidelines and Position Statements**

American Academy of Neurology/American Headache Society

A 2012 joint guideline by the American Academy of Neurology (AAN) and the American Headache Society (AHS) on pharmacologic treatment for episodic migraine prevention in adults was published prior to the approval of Nerivio in the U.S. and did not address the use of remote electrical neuromodulation (REN) or other nonpharmacologic treatments. (7) Similarly, 2019

joint guidelines issued by AAN and AHS on the treatment of acute migraine (34) and prevention of migraine (8) in children and adolescents did not address the use of REN or other nonpharmacologic treatments.

**American Headache Society**

In 2021, AHS issued guidance on the integration of new migraine treatments, including REN, into clinical practice. (4) The AHS addressed the use of neuromodulatory devices as a group that included electrical trigeminal nerve stimulation, noninvasive vagus nerve stimulation, single-pulse transcranial magnetic stimulation, and REN; no guidance specific to REN use was issued.

The AHS determined that initiation of a neuromodulatory device is appropriate when all of the following criteria are met:

- Prescribed/recommended by a licensed clinician
- Patient is at least 18 years of age (*the guidance noted that 3 devices, including REN, are approved for use in patients age 12 to 17 years*)
- Diagnosis of International Classification of Headache Disorders (ICHD)-3 migraine with aura, migraine without aura, or chronic migraine
- Either of the following:
    - Contraindications to or inability to tolerate triptans
    - Inadequate response to 2 or more oral triptans, as determined by EITHER of the following:
        - Validated acute treatment patient-reported outcome questionnaire (Migraine Treatment Optimization Questionnaire, Patient Perception of Migraine Questionnaire-Revised, Functional Impairment Scale, Patient Global Impression of Change)
        - Clinician attestation.

**Department of Veterans Affairs/ Department of Defense**

The U.S. Department of Veterans Affairs/Department of Defense (VA/DoD) 2023 guidelines for the management of headache state that "there is insufficient evidence to recommend for or against any form of neuromodulation for the treatment and/or prevention of migraine"; examples of neuromodulation treatments mentioned include remote electrical neurostimulation. (35)

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing trials that might influence this policy are listed in Table 12.

**Table 12. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT05940870[a] | A Prospective, Open-label, Post-marketing Observation Study Assessing the Safety and Efficacy of Nerivio for Migraine Prevention in Real-world Environment | 250 | Aug 2024 (completed) |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | None |
| **HCPCS Codes** | A4540, [Deleted 1/2024: K1023] |

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
|---|---|
| **Date** | **Description of Change** |
| 12/15/2025 | Document updated. The following change was made to Coverage: Moved from experimental, investigational and/or unproven to a conditionally medically necessary coverage position for remote electrical neuromodulation for prevention of migraine. Added reference 14, 19, and 29-31. |
| 01/01/2025 | Document updated with literature review. Coverage unchanged. Added references 28 and 30. |
| 05/15/2024 | Document updated with literature review. The following change was made to Coverage: Added prevention of migraine to the experimental, investigational and/or unproven statement. References 6-8, 13 and 27 added; others updated. |
| 02/15/2023 | New medical document originating from medical policy MED201.040 Transcutaneous electrical Stimulation (TENS) and Transcutaneous Electrical Modulation Pain Reprocessing (TMPR). Remote electrical neuromodulation for acute migraine is considered experimental, investigational and/or unproven. |