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ORIGINAL RESEARCH

One-Year Consistent Safety, Utilization, and Efficacy Assessment of Remote Electrical Neuromodulation (REN) for Migraine Treatment

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ABSTRACT

Introduction: Migraine is a chronic neurological disorder causing severe pain and disability in more than a billion people worldwide. Ideal treatment should provide long-term efficacy with minimal side effects. Previous studies indicate that remote electrical neuromodulation (REN) is an efficacious and safe treatment option for the acute treatment of migraine in clinical practice. This study examined long-term safety, utilization, and efficacy of REN during 12 consecutive usage months.

Methods: Data from patients with migraine across the USA using REN to treat their migraine attacks were electronically collected from the Nerivio® device. All patients who used REN during 12 consecutive months were included, and data were compared across months. Safety was assessed by the number and type of adverse events. Utilization was measured by the number of monthly treatments. Efficacy was evaluated as consistent change in headache pain intensity, functional disability, and disappearance of associated symptoms from baseline to 2 h post treatment.

Results: Data were analyzed from 409 people living with migraine who treated with REN for 12 consecutive months, performing a total of 39,531 treatments. The incidence of device-related adverse events (dAEs) was 1.96% (8/409), including two negligible (0.49%), five mild (1.22%), one moderate (0.24%), and no severe events. All patients continued treatment with REN despite dAEs. One-year average monthly utilization was 8.05 treatments (SD 1.15). Month-to-month utilization did not change during 12 months of consecutive use [$F(4.895, 1997.204) = 2.014, p = 0.075$, repeated-measures ANOVA]. One-year average efficacy showed 74.1% of users reported consistent 2-h pain relief, and 26.0% reported consistent pain freedom. Month-to-month pain relief and pain freedom

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did not change during 12 months of consecutive use [$F(11, 1069) = 0.55$, $p = 0.873$ and $F(11, 1295) = 0.69$, $p = 0.750$ respectively; generalized linear mixed model analysis].
Conclusion: REN is a safe and well-tolerated acute migraine treatment, with stable efficacy and utilization over 1 year, making it an advantageous non-drug option for the long-term management of this chronic disease.
Trial Registration Number: NCT05760638.

PLAIN LANGUAGE SUMMARY

Migraine is a chronic disease leading to decades of significant disability, thus requiring safe, effective, and tolerable treatment for years. Remote electrical neuromodulation (REN) is a smartphone-controlled wearable device (Nerivio®) indicated for the acute and/or preventive treatment of migraine in patients 12 years of age or older. It is a prescribed, self-administered device for use at the onset of migraine headache or aura for acute treatment, or every-other-day for preventive treatment. Treatments are automatically registered in the REN app and database, and users can prospectively report subjective migraine indicators and response to the treatment in the REN app, at treatment onset and again 2 h later. This study analyzed data from people who used REN for the acute treatment of their migraine attacks at least once per month, for at least 12 consecutive months. Data from 409 patients who met the study criteria and performed a total of 39,531 treatments was analyzed. Safety was measured by the incidence of device-related adverse events, which was 1.96%. Severe device-related adverse events were not reported, and all patients continued treating after the events. Efficacy over the year showed that 74.1% of the patients reported consistent pain relief, and 26.0% reported consistent pain freedom. Average monthly utilization over the year was 8.05 treatments. Month-to-month pain relief, pain freedom, and utilization did not differ between 12 months of consecutive use. These results show that REN is a safe and well-tolerated treatment, with stable efficacy and utilization over at least 1 year, making it an advantageous non-drug option for the long-term management of migraine.

Keywords: Migraine; Long-term; Non-pharmacological; Remote electrical neuromodulation; REN; Safety; Utilization; Efficacy; Prospective; Real-world evidence

Key Summary Points

Migraine is a chronic disease, causing significant disability, thus requiring effective, safe, and tolerable treatment for long durations.

Remote electrical neuromodulation (REN) is a smartphone-controlled wearable device (Nerivio®) FDA-cleared for the acute and/or preventive treatment of migraine in patients 12 years of age or older.

The study assessed 1-year safety, utilization, and efficacy of REN from patients with migraine treated with REN for at least 12 consecutive months, at least once per month.

Data from 409 patients with migraine who performed 39,531 REN treatments showed a high safety and tolerability profile with a very low incidence of device-related adverse events (1.96%); all not severe and not serious, and that patients continued using the device after their device-related adverse events.

One-year efficacy and usability were stable over 12 treatment months, with 74.1% of patients reporting consistent pain relief, 26.0% reporting consistent pain freedom, and average monthly utilization of 8.05 treatments per month.

The study shows REN is a safe and well-tolerated treatment, with stable efficacy and utilization over at least 1 year, making it an advantageous pill-free and needle-free option for the long-term management of migraine.

INTRODUCTION

Migraine is a highly prevalent chronic neurological condition, characterized by attacks of headache and associated symptoms including photophobia, phonophobia, nausea, and/or vomiting [1, 2]. A recent epidemiological study suggests that approximately 21% of women and 11% of men in the USA currently suffer from migraine headaches, affecting about 40 million people in the USA, including 5 million children and adolescents [3]. More than 4 million emergency department visits [2], 50,000 inpatient hospitalizations [4], and 4.3 million office visits [3] are attributable to migraine each year in the USA. Migraine experiences vary substantially by person, with costs and burden of illness concentrated in patients with the most frequent and intense attacks (high-frequency episodic and chronic migraine).

Migraine affects individuals from their childhood or youth, through their most productive adult years, until around retirement age or even beyond, causing significant disruptions in daily activities and work performance [5]. While various pharmacological treatments are available in the USA, many patients struggle with adherence as a result of intolerance of side effects, lack of efficacy, risk of chronification, and/or high cost [6–10].

The American Headache Society (AHS) consensus statement suggests over-the-counter drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and a few families of prescribed drugs including generic oral triptans as first-line acute treatments of migraine [11]. However, these current first-line acute treatments do not provide a sustainable solution for many patients with migraine for several reasons. First, they are not universally effective in managing headache and associated symptoms. About 30–50% of patients prescribed triptans have insufficient response [12, 13]. Second, first-line treatments can have intolerable adverse effects [14]. Third, these medications are not appropriate for all patients with migraine because of contraindications from other diseases or medications [15]. Fourth, triptans, some NSAIDs, and other acute medications may cause chronification of migraine and/or medication overuse headaches (MOH) [16, 17], which results in more frequent headaches and may result in the need for detoxification from the overused medications [18]. Therefore, their usage is limited and patients may require additional acute treatments [19]. Fifth, some patients prefer not to take medications [20]. Sixth, not all treatments are approved or desirable for children and adolescents [21] and other sensitive populations (e.g., pregnancy) (see references in [22, 23]). On the basis of these factors, many patients struggle with adherence to pharmacological acute migraine treatments, and up to 60% of triptan users discontinue treatment within the first year of usage [24]. Insufficient adherence to treatment also increases the risk for disease complications [25]. Given the chronic nature of migraine over many years of patients' lives, there is a pressing need for tolerable, safe, and effective treatments that can be used for long durations (years) to help individuals regain daily function and relief from pain.

Remote electrical neuromodulation (REN) is a smartphone-controlled wearable technology, US Food and Drug Administration (FDA)-cleared for the acute and/or preventive treatment of migraine in patients 12 years of age or older. By stimulating arm nociceptive receptors, the device turns on an endogenous pain mechanism called conditioned pain modulation (CPM), which initiates a global pain inhibition process generated by the brainstem.

REN was shown in numerous studies to be a safe and effective treatment for the acute treatment of migraine in adults with episodic migraine [26–28] or chronic migraine [29, 30], and in adolescents [31]. Recently, its safety, efficacy, and cost-effectiveness were shown in preventing migraine [32, 33]. Moreover, previous real-world studies show that when using REN many adult patients with migraine [34, 35] and adolescent patients with migraine [22] reported a reduction in their utilization of acute medications.

REN presents several potential advantages as a treatment option for the acute treatment of migraine compared to pharmacological treatment. It is a non-invasive, targeted treatment. Unlike pharmacological treatments, REN does

not have any systemic side effects and has a very low risk of adverse events. Additionally, REN can be customized to meet the individual needs of each patient by personally modifying treatment intensity and has no risk of drug–drug interactions or abuse. REN can be used either as a standalone treatment or in combination with other treatments according to patients' needs. These factors highlight the potential benefits of REN as a safe and effective treatment option for acute treatment of migraine.

Given the chronic nature of migraine disease and that most patients with migraine require long-term treatment over years, the evaluation of treatments over an extended period of time is crucial. This study aims to examine REN's long-term safety, efficacy, and usage. The hypothesis is that REN provides a safe, efficacious, and stable treatment over 1 year of consecutive use.

METHODS

REN (Nerivio®) Device

A prescribed, self-administered device for use at the onset of migraine headache or aura for acute treatment, or every other day for preventive treatment. It is FDA-cleared for the acute and/or preventive treatment of migraine in patients 12 years of age or older. It is a wearable, smartphone-controlled, non-pharmacological device, applied to the upper arm. During each 45-min treatment, patients set treatment intensity via the app to a degree that is well-felt, but not painful [26].

Study Design and Participants

This real-world evidence analysis (clinicaltrials.gov NCT05760638) investigated long-term tolerability, adherence, and effectiveness of REN for the acute treatment of migraine during 12 consecutive months of use. The study followed the Helsinki Declaration of 1964 and its later amendments. Data was collected from real-world users of the Health Insurance Portability and Accountability Act (HIPPA)-secured Nerivio app®. At app signup, patients signed on the terms of using their data, acknowledging that their personal information is provided willingly, and that they agree that their anonymous (deidentified) data may be collected, analyzed, and possibly published for research. Treatments are automatically registered in the Nerivio® database (including time of treatment, treatment duration, treatment intensity). At the beginning of each treatment, and again 2 h after that, users can voluntarily answer a few quick questions about their migraine manifestation and therapies they are using. Thus, an additional ethics approval was not required for the analysis of this type of data. All study participants are real-world users of the REN device, who are patients with migraine, diagnosed by a US health care provider, and prescribed the REN device by a US health care provider according to the FDA-clearance of the device. Data collection resembles that described in previous RWE studies of REN [11, 22, 34].

Inclusion Criteria

Users were included in the study if they had at least 12 consecutive calendar months of treatments with REN, with at least one use per month. Treatments had to be at least 30 min long to be included in the study.

Real-world data from all patients in the USA who treated their migraine attacks with REN between October 1, 2019 and August 31, 2022 and met the inclusion were included in the study.

Outcome Measures

Primary Outcome

Incidence of device-related adverse events (AEs). All AEs registered during the study's period were assessed: number of AEs; number of device-related AEs (dAEs); proportion of severe, moderate, and mild dAEs; percentage of serious vs. not serious dAEs.

Secondary Outcomes

Utilization Consistency of monthly usage of Nerivio device was recorded during 12 calendar months. Consistent usage indicates both adherence and overall satisfaction. The number

of Nerivio treatments per month was calculated for each participant, for each of the 12 consecutive months of treatment (the exact month varied between users). The date of the first treatment in the first consecutive month of use varied between patients on the basis of the day in which they began treatment and therefore was corrected by multiplying the actual number of treatments a patient conducted in that month by the average date of the first treatment.

Efficacy Common migraine efficacy endpoints were used as secondary outcomes and were calculated from all treatments in which patients provided prospective information both at the beginning of treatment and at 2 h post treatment initiation about (1) intensity of their headache, (2) their functional disability, and (3) associated migraine symptoms. A 0–3 intensity scale (3 = severe, 2 = moderate, 1 = mild, 0 = none) was used for headache intensity and functional disability. The presence of an associated symptom at the beginning of treatment (photophobia, phonophobia, nausea/vomiting) and its corresponding disappearance (and the disappearance of at least one of the associated symptoms) was further measured. Only treatments during which patients reported no use of abortive medications were included in this analysis. Therefore, the number of evaluable treatments with reported data per outcome could vary across outcomes (and is smaller than the actual number of treatments conducted).

The percent of patients achieving treatment response in half or more of their treatments per month was calculated: (1) for headache pain: repetitive pain relief (reduction from headache intensity of 3 or 2 at treatment initiation to headache intensity of 1 or 0 at post 2 h), and repetitive pain freedom (disappearance of any intensity of headache pain, i.e., from intensity of 3, 2, or 1 at treatment initiation to 0 pain at post 2 h); (2) for functional disability: repetitive improvement in function (in attacks where functional limitation was reported at baseline, improvement of at least one level of disability from 3, 2, or 1 at post 2 h), and repetitive return to normal function (in attacks where functional limitation was reported at treatment initiation and no functional disability was reported 2 h later); (3) disappearance of each associated symptom and disappearance of at least one associated symptom.

Data Analysis

Statistical analysis was conducted in IBM SPSS Statistics 20. To compare the effect of treatment month on utilization, repeated-measures analysis of variance (ANOVA) was used, with Greenhouse–Geisser correction since the sphericity assumption was violated. Generalized linear mixed model (GLMM) was used to compare the effect of treatment month on efficacy rate outcomes. The Akaike information criterion (AIC) was used to assist with selecting the appropriate statistical model. The probability distribution was binomial and the link function was probit for all efficacy measures.

All tests were two-tailed with significance level of $p < 0.05$.

RESULTS

Four hundred and nine patients with migraine met the inclusion criteria and were included in the analysis. The average age of patients was 45.8 ± 15.9 years (mean ± SD), and 84.6% were female, 13.7% male, and 1.7% undefined.

Safety

The 409 patients reported nine AEs during the study period (2.20%). Eight of these were dAEs (1.96%; 8/409), including two (0.49%) negligible, five (1.22%) mild, one moderate (0.24%), and no severe. Most common dAEs were local paresthesia or skin sensitivity in the stimulation area. Reports of dAEs distributed over the year, with single reports during the first, fourth, fifth, sixth, seventh, eighth, tenth, and twelfth months of consecutive treatment. All patients continued treatment with REN despite their dAEs.

Utilization

During the study period, users performed a total of 39,531 treatments, with a monthly average of 8.05 ± 1.15 (mean ± SD) treatments per patient. Figure 1 shows the average month-to-month number of treatments over users. A repeated-measures ANOVA determined that the month-to-month number of treatments conducted by patients did not differ significantly between 12 months of consecutive treatment [$F(4.9, 1997.2) = 2.0$, $p = 0.075$].

Efficacy

One-year average annual consistent efficacy in at least 50% of all treatments per patient was achieved by 74.1% (180/243) of patients for pain relief, by 26.0% (67/258) for pain freedom, by 70.2% (177/252) for functional disability relief, and by 33.7% (85/252) for functional disability freedom. Moreover, regarding associated symptoms, average annual consistent efficacy in at least 50% of all treatments per patient was achieved by 43.2% (95/220) of patients for photophobia, by 52.7%% (107/203) of patients for phonophobia, by 70.8% (121/171) of patients for nausea/vomiting, and by 73.5% (180/245) of patients for at least one associated symptom.

Comparing consistent efficacy across 12 consecutive treatment months showed no significant difference in any of the efficacy outcomes (Fig. 2 and Table S1): month-to-month

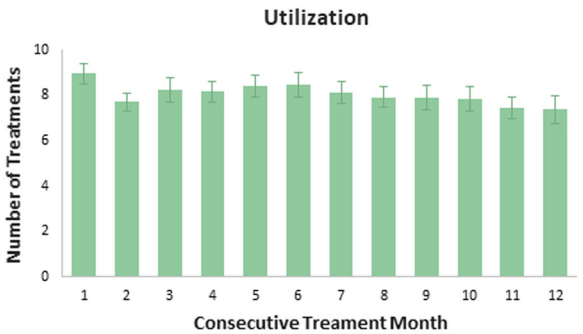

Fig. 1 Month-to-month 1-year utilization. Monthly average number of REN treatments over 12 months over patients ($n = 409$). Error bars represent standard error (SE)

values did not differ significantly during 12 months of consecutive use for pain relief [$F(11, 1069) = 0.55$, $p = 0.873$]; pain freedom [$F(11, 1295) = 0.69$, $p = 0.750$]; disability relief [$F(11, 1202) = 0.860$, $p = 0.580$]; functional disability freedom [$F(11, 1202) = 0.77$, $p = 0.672$]; as well as disappearance of associated symptoms (Fig. 3 and Table S2): photophobia [$F(11, 996) = 0.56$, $p = 0.863$]; phonophobia [$F(11, 819) = 0.27$, $p = 0.991$]; nausea/vomiting [$F(11, 608) = 0.66$, $p = 0.779$]; and for at least one associated symptom [$F(11, 1119) = 0.86$, $p = 0.582$].

DISCUSSION

The real-world evidence presented in this study shows that remote electrical neuromodulation (REN) is safe, effective, and has a high level of patient adherence and tolerance for the treatment of migraine over the long-term course of 12 months of consecutive use, confirming the stated study hypothesis.

First, this study shows that REN is a safe long-term treatment option, having a low incidence of device-related adverse events (1.96%) and no severe dAEs. The most common side effects were local paresthesia or skin sensitivity in the area of the device, without any systemic events. All of the patients who reported dAEs continued treating with REN after their reports, and the dAEs were distributed over the year indicating that even in the case of dAEs, the users found the treatment tolerable, with treatment benefits overcoming the discomfort from the dAEs.

Second, patient compliance with REN therapy remained consistent over 1 year, with a substantial number of patients utilizing the device throughout a year. While inclusion criteria required consecutive treatment over 12 months, there was no selection criterion on the actual number of treatments per month beyond the constraint of at least one treatment per month for each of the 12 consecutive months. Maintaining a stable level of treatment utilization and thus adhering to treatment over time is a complicated issue in migraine, for both acute treatment and preventive treatment.

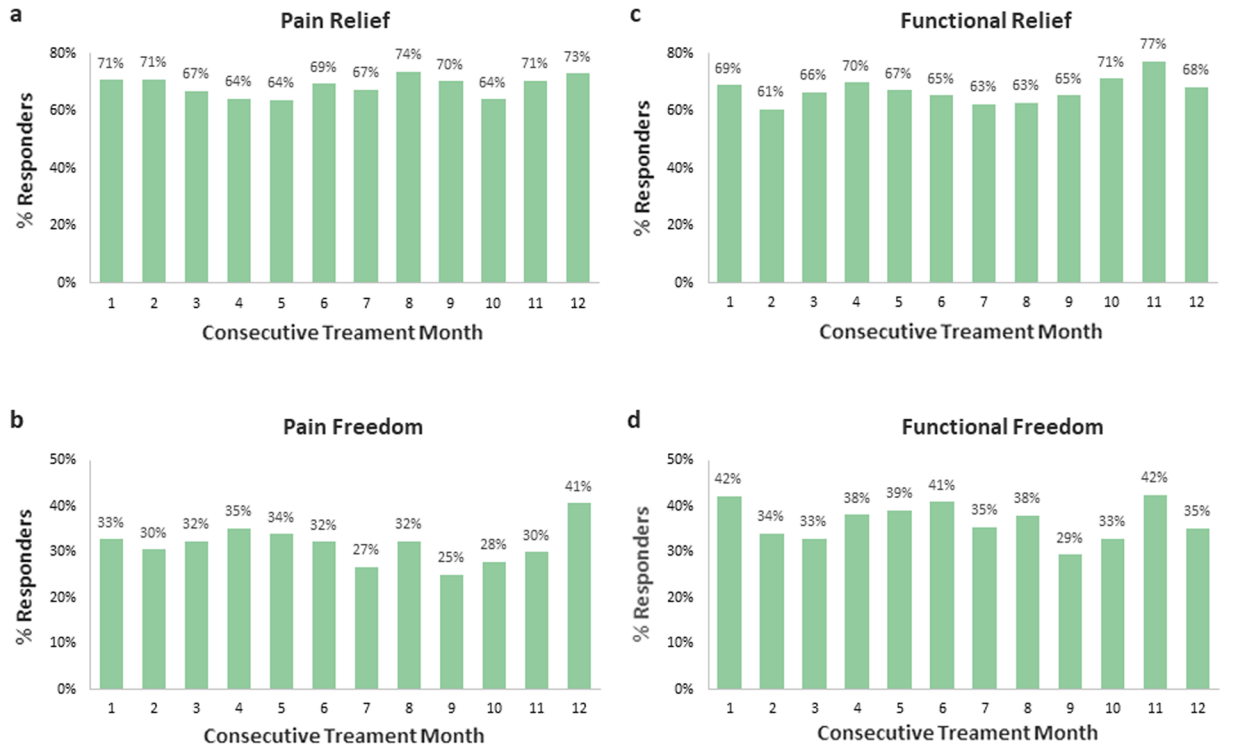

Fig. 2 Month-to-month 1-year efficacy. Monthly percent responders for four efficacy measures per month: **a** pain relief, **b** pain freedom, **c** functional relief, **d** functional freedom

Third, REN was effective in providing long-term benefits for the majority of patients over 1 year, in all efficacy endpoints measured. Nearly two-thirds of patients experienced consistent efficacy in at least 50% of their treatment, including reduction in pain 2 h following REN treatments (74.1%), functional disability relief (70.2%), and disappearance of least one associated symptom (73.5%) over the course of a year. The most common associated symptom is photophobia, reported by 46 to 114 patients per month over 12 months, while the least common associated symptom is nausea/vomiting, reported by 29–78 patients per month. While nausea/vomiting is less common, it is the associated symptom most benefiting from REN treatment with an annual average of 70.8% reporting its disappearance at 2 h post treatment, followed by phonophobia (52.7%), and photophobia (43.2%).

Moreover, 26.0% of the patients achieved consistent pain freedom during REN treatments and 33.7% achieved functional disability freedom. These results are clinically meaningful, given that pain, associated symptoms, and functional disability are key factors in the overall burden of migraine and significantly impact patients' quality of life and ability to function [36].

Commonly used migraine medications for the acute treatment of migraines include NSAIDs and triptans. The latter constitute the most common first-line physician-prescribed acute treatment for migraine, yet up to 60% of users abandon their triptan treatment within the first year of usage [24], due to lack of adherence caused by intolerability to AEs and/or lack of efficacy [37]. On the other hand, those who do continue using triptans frequently and for long time periods are at risk for medication overuse headache (MOH) and migraine chronification [9, 16]. Widespread adverse effects of triptans include nausea, vomiting, dizziness, somnolence, and chest tightness [38, 39]. Long-term use of NSAIDs can lead to gastrointestinal bleeding [40], renal dysfunction, and

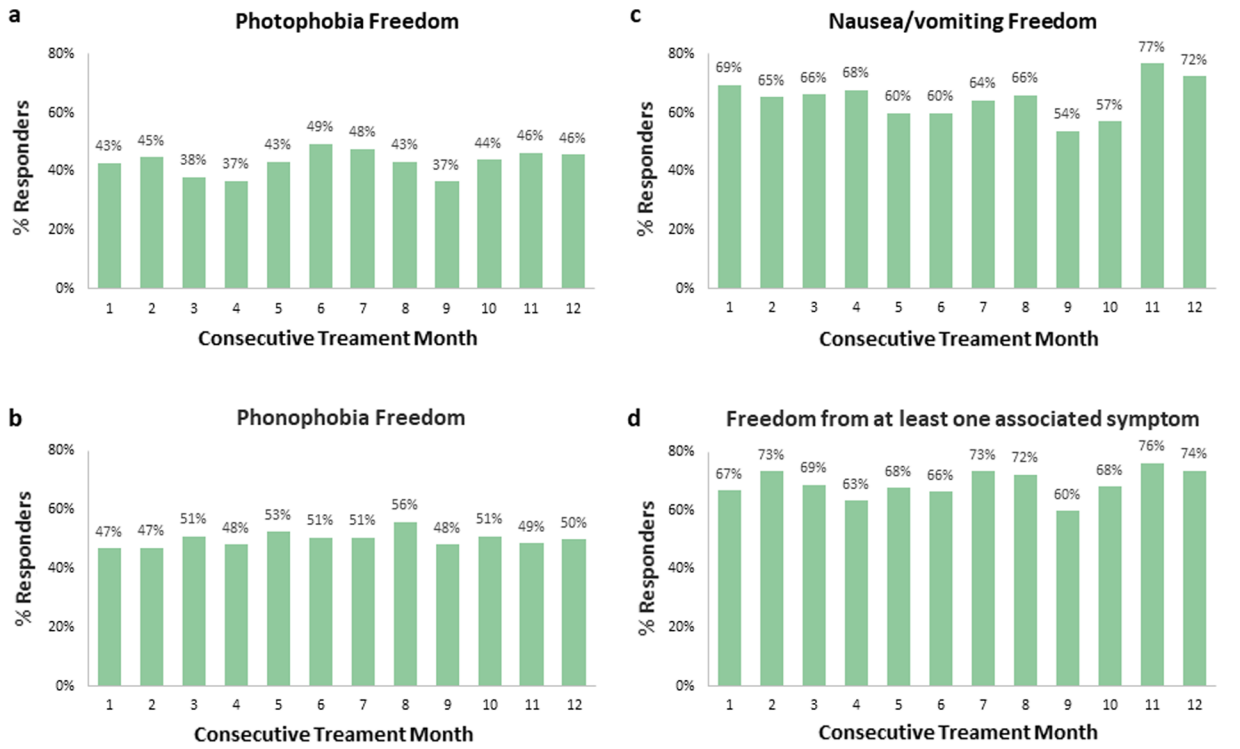

Fig. 3 Month-to-month 1-year efficacy of associated symptoms. Monthly percent responders for the disappearance of associated symptoms per month: **a** photophobia, **b** phonophobia, **c** nausea/vomiting, **d** at least one of the associated symptoms

cardiovascular events. In the past, opioids were sometimes used for the acute treatment of migraines, but their long-term use is generally discouraged because of the risk of dependence and addiction [41]. Other reported adverse effects of opioids include nausea, vomiting, constipation, respiratory depression, and overdose leading to death.

Open-label post-marketing surveillance studies on long-term effects of treatment with new migraine drugs are recently emerging, reporting treatment-emergent adverse events (TEAEs). TEAEs from 12-month treatment with lasmiditan [42, 43] include dizziness, paresthesia, fatigue, nausea, vertigo, somnolence, and asthenia (ranging between 5.8% and 35.7% of patients, and 0.8% and 9.5% of attacks). Most TEAEs were mild or moderate in severity, with 0.9% of participants experiencing serious TEAE. Nearly a third of the study participants did not complete the open-label extension, mostly because of study withdrawal, lack of efficacy, and adverse events. While the authors report no new safety concerns during this long-term study, patients are not allowed to drive for 8 h after lasmiditan dosing based on previous trials [44], and the results from this 1-year study add to the existing safety concerns and intolerability associated with lasmiditan (dizziness, somnolence and paresthesia, and rare cases of serotonin syndrome [45, 46]).

The long-term safety, tolerability, and efficacy of small-molecule antagonists of calcitonin gene-related peptide (CGRP) receptor called gepants were assessed in open-label studies of 52 weeks in adults with migraine. Both rimegepant 75 mg every other day for preventive treatment of migraine plus as-needed for acute treatment of migraine in adults [43], and once-daily orally administered atogepant 60 mg [47] were associated with consistent reductions in monthly migraine days (MMDs). However, TEAEs were not rare during the 52 weeks of treatments, including upper respiratory tract

infection, nasopharyngitis, and back pain (4.3–7.1% of patients) from rimegepant, and upper respiratory tract infection, constipation, nausea, and urinary tract infection from atogepant (6.3–10.3% of patients). Serious TEAEs were reported in 4.4% for atogepant. Discontinuation rate due to AEs/TEAEs was 2.8% and 5.7% for rimegepant and atogepant, respectively [43, 48].

Evidence for long-term effects of monthly injectable monoclonal antibody preventive medications (mAbs) targeting CGRP are also emerging. Spontaneous adverse events reported to the US FDA Event Reporting System (FAERS) included disproportionate reporting of significant alopecia signals, with 3.26% cases of alopecia [49–51].

Participants in the current study performed an average of 8.05 ± 0.44 (mean $\pm$ SD) REN treatments per month, suggesting they should be offered migraine prevention treatment, as per the consensus statement of the American Headache Society (AHS) in 2021 [13]. The long-term evidence presented here on REN from 12 consecutive months should therefore be interpreted in light of, and compared to, evidence from other treatments for the acute and/or preventive treatment of migraine, according to the current indication of the Nerivio® REN device.

While this is the first study to assess long-term treatments with REN, there are some study limitations that should be acknowledged. First, the users included in this analysis constitute a subset of all REN device users. As in any sub-analysis, there is a concern for selection bias. In this case, users who did not treat consecutively for 1 year were not included in the study. We therefore excluded users who did treat for at least 1 year; however, they did not treat in each and every calendar month of the year. Such a scenario could result from either infrequent attacks or from using a combination of treatments (having a "migraine toolbox") and deciding which treatment(s) to use for each attack. Some users excluded from this analysis are also those who discontinued treating with REN, and therefore did not meet the 12 consecutive treatment months criterion. Discontinuation of REN could result from lack of efficacy for some patients. Pain relief from various acute migraine treatments is around 60%, and despite REN being on the higher end with 66.7% of the patients reporting pain relief in the pivotal REN randomized controlled study of acute treatment of migraine, by Yarnitsky et al. [28], there is no one treatment that works for all patients with migraine. However, our only selection criterion was at least one treatment per month, for 12 consecutive months, without any additional constraint on the number of monthly treatments, safety, or efficacy.

Second, the current study did not incorporate additional outcomes such as standardized migraine questionnaires to measure the effects of REN on patients' quality-of-life, which could show a wider effect than focusing mainly on measures of effectivity. However, since this is a real-world evidence study and not a clinical trial, there is a limit to the number of questions patients can be asked and expected to answer on a regular basis via a commercial app (i.e., every treatment). Standardized migraine questionnaires can be embedded in the app and users may be prompted to answer them periodically to explore associations of REN long-term use with quality of life and with psychiatric comorbidities in future studies.

Third, although 1-year consecutive use is considered a long period to track patients, studies looking at longer durations could benefit the medical and patient communities. This is true for all types and families of migraine treatments, pharmacological and devices alike. However, REN has the benefit that usability information regarding each and every treatment performed is automatically registered into the Nerivio® app and database, even without the need for patients to actively record this data, making it more accurate than information from patient or pharmacy-reported drug usage. Having validated data provides a strong benefit, and future studies can be conducted to track patients over even longer time periods.

CONCLUSION

This study demonstrates a combination of persistent efficacy, excellent safety profile, and

consistent tolerability of REN over 12 months. Together with solid utilization and adherence over a long period of time, especially with the recent indication expansion to dual use (acute and preventive), this data makes REN a valuable comprehensive treatment option for people suffering from migraine, particularly for adolescents and adult patients who fail on medications or need to minimize or even avoid use of drugs because of comorbidities.

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Author Contributions. Study conceptualization and design: Alit Stark-Inbar, Alon Ironi. Data analysis and interpretation: Alit Stark-Inbar, Maya Weinstein, Alon Ironi. Manuscript drafting: Alit Stark-Inbar, Maya Weinstein. Manuscript revision for intellectual content: Alon Ironi, Andrea Synowiec, Alexander Mauskop. Final approval of the completed manuscript: All authors.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Alit Stark-Inbar and Alon Ironi are employees of and hold stock options in Theranica Bio-Electronics Ltd.; Maya Weinstein and Andrea Synowiec have consulted for Theranica Bio-Electronics Ltd.; Alexander Mauskop has nothing to disclose.

Ethical approval. The study followed the Helsinki Declaration of 1964 and its later amendments. Data was collected from real-world users of the HIPPA-secured Nerivio app®. At app signup, patients signed on the terms of using their data, acknowledging that their personal information is provided willingly, and that they agree that their anonymous (deidentified) data may be collected, analyzed, and possibly published for research. Treatments are automatically registered in the Nerivio® database (including time of treatment, treatment duration, treatment intensity). At the beginning of each treatment, and again 2 h after that, users can voluntarily answer a few quick questions about their migraine manifestation and therapies they are using. Thus, an additional ethics approval was not required for the analysis of this type of data.

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