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RESEARCH SUBMISSION

Three years of remote electrical neuromodulation (REN) acute treatment for migraine shows consistent effectiveness and no tachyphylaxis phenomenon

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Abstract

Objective: The current study aimed to evaluate the remote electrical neuromodulation (REN) wearable device over 3 years, assessing the potential for tachyphylaxis, consistent effectiveness, overall utilization patterns, and safety.

Background: Migraine is a highly prevalent chronic neurological disease, especially during peak years of productivity, requiring ongoing management to prevent and reduce its disability. Traditional treatments often face challenges with long-term adherence due to waning efficacy, side effects, and medication interactions. REN offers a nonpharmacological approach for acute and preventive migraine treatment.

Methods: This prospective real-world cohort study analyzed data from 224 patients with migraine in the United States who consistently treated their migraine attacks with the REN wearable device for 3 years between December 2019 and September 2024. The primary endpoint was defined as lack of tachyphylaxis, aka an increase of no more than 2.5 intensity units on a scale of 100 units between 2 consecutive years, representing a nonclinically meaningful change in treatment intensity over 3 years. Secondary endpoints were consistent effectiveness in at least 50% of treatments and consistent utilization, compared over 3 years. The safety outcome assessed the proportion of users with device-related adverse events (dAEs) and the severity and seriousness of the dAEs.

Results: Over 3 years, there was no clinically meaningful change in treatment intensity, and the average (± standard deviation, SD) change between 2 consecutive years was no more than 2.5 intensity units (1.8 ± 5.5 between years 1 and 2, and 1.4 ± 5.3 between years 2 and 3; $p = 0.120$, McNemar test for two related dichotomous variables), indicating no tachyphylaxis. Effectiveness endpoints remained consistent

Abbreviations: CPM, conditioned pain modulation; dAEs, device-related adverse events; HIPAA, health insurance portability and accountability act; MOH, medication overuse headache; REN, remote electrical neuromodulation; RWE, real-world evidence.

over 3 years of treated attacks (generalized linear mixed model of repeated measures categorical data) with no significant differences over the 3 years: 72.1%–76.8% of users reporting pain relief ($p = 0.846$), 26.8%–28.7% pain freedom ($p = 0.966$), 65.3%–70.8% functional disability relief ($p = 0.749$), 31.4%–38.9% functional disability freedom ($p = 0.680$), 29.0%–37.0% freedom from photophobia ($p = 0.590$), 37.9%–49.4% freedom from phonophobia ($p = 0.534$), and 57.1%–66.7% freedom from nausea/vomiting ($p = 0.753$). Monthly utilization was consistent, ranging between 8.0 and 8.8 treatments per month, suggesting sustained adherence to therapy ($p = 0.337$, generalized linear model of repeated measures). Only two (0.9%) expected, nonserious dAEs were reported (mild or moderate localized skin reactions), neither leading to treatment discontinuation.

Conclusion: This study demonstrates the long-term safety, consistent utilization, and acute treatment effectiveness, with no tachyphylaxis, in patients with migraine consistently treating with REN for 3 years. This suggests that REN offers an effective, well-tolerated, safe, and sustainable long-term treatment option for individuals with migraine.

Plain Language Summary

Individuals with migraine often struggle to find long-term relief due to medication side effects or reduced effectiveness over time. This study assessed the characteristics of acute treatment of migraine with the remote electrical neuromodulation (REN) wearable device over 3 years of consistent use. The results showed that REN provided consistent relief without the need for a dosage increase over time, and that patients continued using the device regularly over 3 years; thus, the study suggests that REN may be an effective, safe, and sustainable long-term treatment option for migraine.

KEYWORDS
drug-free, long-term, migraine, remote electrical neuromodulation, tachyphylaxis

INTRODUCTION

Migraine is a highly prevalent, chronic, neurological disease, affecting up to 15% of the global population.[1,2] It is characterized by debilitating headaches and associated symptoms that can significantly impair an individual's quality of life, productivity, and social functioning over decades.[3] Migraine usually emerges during adolescence or early adulthood, spanning over an individual's most productive adult years, and even persisting into senior years.[3] As such, migraine requires ongoing management throughout a significant portion of a person's life.

Current migraine treatments, including both acute and preventive options, can be effective for many patients; however, medications are often accompanied by considerable adverse events, drug–drug interactions, and demanding dosing and administration schedules, leading to low adherence.[4–7] Considering the protracted nature of the disease, the potential for disease progression when untreated, and the risk of medication-overuse headache (MOH), there is a pressing need for sustainable long-term treatments.[8–10] Ideally, long-term interventions should provide consistent relief while avoiding adverse events and MOH, in parallel with preserving quality of life. Another major concern associated with long-term migraine management is the potential for tachyphylaxis, the phenomenon in which a treatment's efficacy diminishes over time, requiring either a higher dosage or a change in medication. Relatively few studies have evaluated the long-term (over 3 years or more) effects and dosage stability of migraine medications.[4,11–13] These showed that therapies can become less effective over time, leading to dose escalation or poor adherence, ultimately followed by a switch to alternative treatments.[4,11] Other studies have indicated that patients frequently may require numerous preventive and acute medication changes over time, potentially due to waning efficacy.[13]

Remote electrical neuromodulation (REN) is a noninvasive, drug-free, prescribed therapy that has emerged as a long-term treatment option for migraine. REN is US Food and Drug Administration (FDA)–cleared for acute and preventive migraine treatment in patients aged 8 years and older. REN delivers low-intensity electrical stimulation to specific peripheral nerves, leveraging conditioned pain modulation (CPM) to decrease the pain signals of migraine.[14,15] Prior clinical trials and real-world evidence (RWE) studies underscore REN safety

and efficacy across diverse populations.[16–20] A previous study suggested robust long-term effectiveness and safety[21] over 1 year of REN treatment, yet multi-year data have yet to be analyzed. The current study aimed to evaluate REN usage over a longer period, assessing the potential for tachyphylaxis, consistent effectiveness, utilization patterns, and safety over 3 years of acute treatment by retrospectively analyzing prospective user data. The primary hypothesis being tested in this study is that long-term consistent use of the REN wearable device for acute migraine treatment does not result in tachyphylaxis, such that there is no clinically meaningful change in stimulation intensity (treatment dosage), defined as an increase of no more than 2.5 units between any 2 consecutive years, to obtain a consistent level of effectiveness of outcomes (pain relief, pain freedom, functional disability relief, and functional disability freedom at 2 h) across years 1–3.

METHODS

Study design and ethics

The study was a prospective, RWE cohort study of long-term users of the REN wearable device across the United States. The study was reviewed by WCG IRB (WIRB-Copernicus Group, Puyallup, WA, USA; approval number 20245084), which found that it meets the requirements for a waiver of consent under 21 CFR 50.22. The data were collected between December 2019 and September 2024 in accordance with Good Clinical Practice and the Declaration of Helsinki guidelines. The study was registered with ClinicalTrials.gov (NCT06738056). On Clinicaltrial.gov, the primary endpoint was revised from initially being safety focused device-related adverse events (dAEs) to efficacy focused (lack of tachyphylaxis) to better align with the study's main research question. Data analyses were provided by the study sponsor, Theranica (Netanya, Israel).

Participants

Inclusion criteria: (1) patients with migraine aged 12 years and older who were prescribed the REN wearable device as part of their routine treatment, (2) began treating with the REN wearable device between December 2019 and September 2021, and (3) used the REN device for acute or acute and preventive treatment at least once a month over at least 9 months per year for 3 consecutive years. No statistical power calculation was conducted prior to the study. The sample size was based on the available data. Of the 17,967 patients with migraine who began treating with REN during the abovementioned period, all REN users who met the three criteria were included in the study cohort and analyzed (see Figure 1). Users who did not meet at least one criterion were excluded from the analysis.

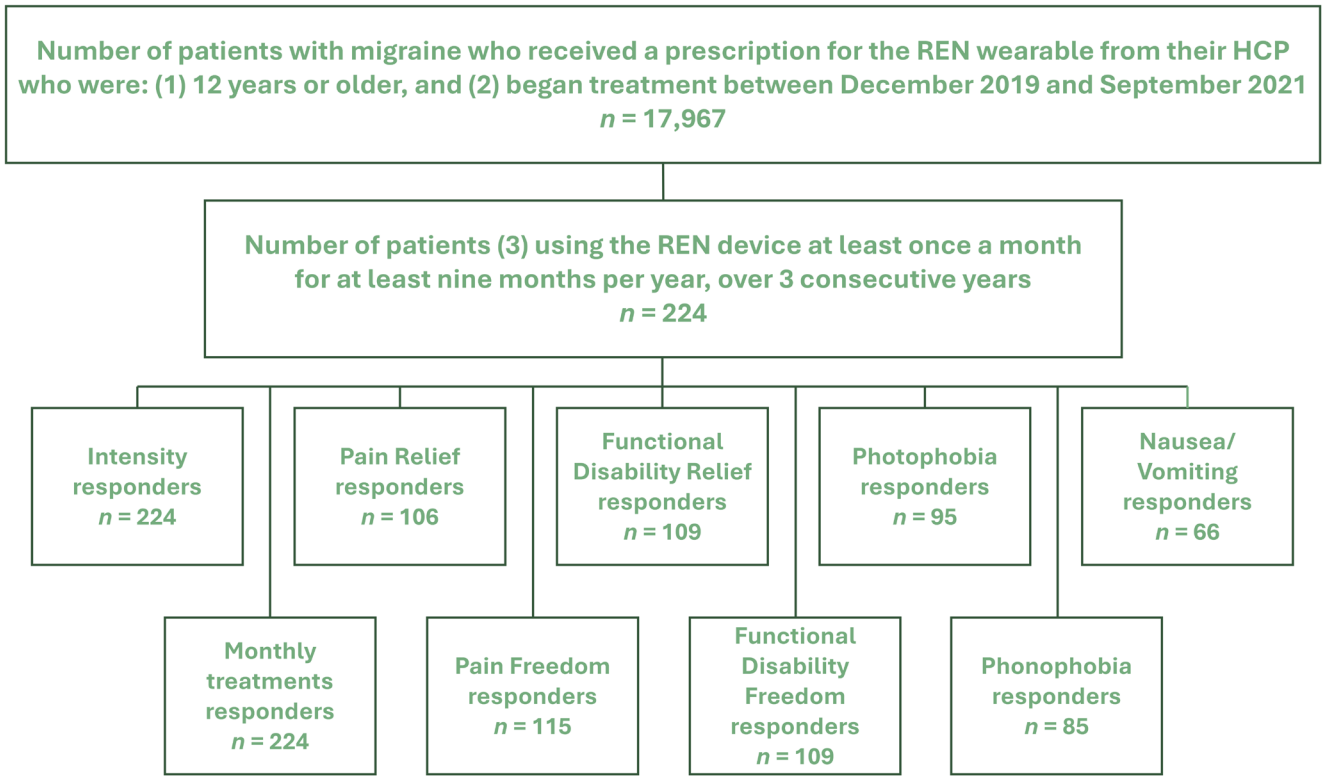

FIGURE 1 Participant flow chart. The number of patients who met the three inclusion criteria are presented in a disposition chart. Effectiveness endpoints were calculated from patients with available data at both baseline and 2 h posttreatment, which resulted in varying patient counts across endpoints. For each endpoint, the number of unique patients who were classified as responders in at least 1 of the 3 years is presented. HCP, healthcare providers; REN, remote electrical neuromodulation.

Study device

The REN wearable device (Nerivio, by Theranica) is a wireless, drug-free, noninvasive stimulation device placed on the upper arm for the treatment of migraine. It has received clearance from the FDA for both acute and preventive management of migraine in individuals aged 8 years and older. The device stimulates small nerves in the skin using a tailored electrical signal, triggering CPM, a natural, endogenous pain control mechanism.[14] Patients control each 45-min treatment session using the device's companion mobile application on their smartphone and can go about their daily activities throughout the session. Patients are instructed to adjust the treatment intensity over a scale of 0–100 units via the application to a level that is strong yet nonpainful; this level is equivalent to treatment dosage.

Data collection

This study retrospectively analyzed prospective data collected using the REN mobile application. During the sign-up process, patients agreed to the terms of use, consenting to the collection of deidentified data for research purposes. Moreover, patients agreed to provide personal information (age, sex) to be securely stored on a Health Insurance Portability and Accountability Act (HIPAA)–compliant REN server. Treatment variables, including timing, length, and intensity were automatically logged into the REN server. Additionally, at the start of each REN treatment, users were prompted to voluntarily report characteristics of their migraine attack, and again 2 h after acute treatments, they were re-prompted to voluntarily report attack characteristics and treatment outcomes through in-app questionnaires. The collected data included headache pain intensity, presence of associated symptoms, functional impairment, and any additional therapies used concomitantly (see Data S1).

Outcome measures

The outcome measures focused on acute treatments conducted over 3 consecutive years (36 months). For each user, outcome measures were calculated annually. The first 3 full months of treatment in the first year were considered an adaptation period and were excluded from the analyses.

Primary endpoint

Lack of tachyphylaxis

The primary endpoint, lack of tachyphylaxis, was defined as clinically nonmeaningful change in treatment intensity, quantified as an increase of no more than 2.5 intensity units between any 2 consecutive years (and a total increase of no more than 5 intensity units across the 3-year period). This metric was selected based on years of experience with the REN wearable device. The average treatment intensity was calculated annually for each user to assess the difference between average treatment intensity of 2 consecutive years for each pair of consecutive years. These differences were then transformed into categorical dichotomous variables, indicating whether the change was ≤2.5 (classified as 1) or >2.5 (classified as 0) intensity units. Treatment intensity is equivalent to drug dosage, and as such an increase in treatment intensity over time would reflect tachyphylaxis (an increase in the dosage needed to achieve effectiveness).

Post hoc subanalyses of the primary endpoint

Three post hoc sub analyses on the primary endpoint of lack of tachyphylaxis were performed: (1) checking if there was a difference in the change in treatment intensity between the subgroup of participants who also participated in the earlier study, looking at 1-year continuous REN treatment, versus participants who did not participate in that earlier study; (2) checking if there was a difference in the change in treatment intensity between subgroups of two treatment patterns types, preventive treatment pattern. which is 12 or more treatments in a month, versus acute treatment pattern, which is less than 12 treatments a month; and (3) sensitivity analysis accounting for all 12 months in the first treatment year versus the main analysis conducted in this study considering the first 3 treatment months as an adaptation period.

Secondary endpoints

Long-term consistent effectiveness

Pain and functional disability were rated on a 4-point scale: severe, moderate, mild, or none. Associated symptoms, including photophobia (light sensitivity), phonophobia (sound sensitivity), and nausea/vomiting were reported as either being present or absent. All were reported voluntarily at the start of treatment (baseline), and at 2 h posttreatment when pain was reported at treatment onset (i.e., reflecting acute care of a migraine attack). *Evaluable* treatments for effectiveness analyses were those in which pain, functional disability, or an associated symptom presence were reported at baseline, and reported at 2 h posttreatment, in addition to REN being used as a standalone therapy (no report of medication usage). Patients were considered *consistent responders* if they showed an improvement from baseline to 2 h posttreatment in the respective reports in at least 50% of their treatments for each endpoint. *Consistent effectiveness* is the proportion of consistent responders for each effectiveness endpoint per year, which was compared over the 3 years.

Seven consistent effectiveness endpoints were assessed:

1. Pain relief: reduction in pain intensity from moderate or severe (baseline score of 2 or 3) to mild or no pain (score of 1 or 0) at 2 h posttreatment.

2. Pain freedom: reduction in pain intensity from mild, moderate, or severe (baseline score of 1, 2, or 3) to no pain (score of 0) at 2 h posttreatment.
3. Functional disability relief: reduction in functional disability by at least 1 point from baseline at 2 h posttreatment.
4. Functional disability freedom: reduction in functional disability from mild, moderate, or severe (baseline score of 1, 2, or 3) to no disability (score of 0) at 2 h posttreatment.

5–7. Freedom from an associated symptom (photophobia, phonophobia, nausea and/or vomiting): absence of the associated symptom at 2 h posttreatment for treatments when the symptom was present at baseline.

Long-term utilization (adherence)

The average number of monthly treatments per year was calculated per user and compared over the 3 years.

Safety and tolerability

An adverse events (AEs) reporting system was used in the app as well as via the customer support call center. AEs were escalated to the medical team for further care and classification. All AEs reported during the study period were analyzed. The proportion of users with a report of an AE was analyzed and characterized with respect to device-relatedness (dAE), severity, and seriousness.

Statistical analysis

Descriptive statistics were used to summarize demographic data and treatment outcomes including average, standard deviation (SD), minimum and maximum values, and 95% confidence intervals. The McNemar test, a nonparametric test for two related dichotomous variables, was used to test the change in intensity levels between following years using the chi-square distribution. Post hoc analyses of the primary endpoint compared subgroups (patients who participated in the previous 1-year study vs. those who did not; and participants who treated in a prevention-like pattern vs. those who did not; using McNemar tests), and a sensitivity analysis (taking all 12 months of the first treatment year vs. considering the first 3 treatment months as an adaptation period) using *t*-tests on the difference between pairs of consecutive years.

Generalized linear mixed model (GLMM) was used to compare categorical data of effectiveness rate outcomes over 3 years (the fixed effect), and the assumed structure covariance was diagonal. The GLMM did not include random effect, and the coefficient was set to zero because it was redundant. 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 effectiveness measures. Trend over time for continuous data of average monthly treatments was measured by a GLM repeated measures analysis, including tests for multivariate trends and within-subjects contrasts. Except for three post hoc analyses of the primary endpoint, all tests were preplanned. A two-tailed significance level of $p < 0.05$ was used. In line with common practice in RWE studies, missing data were handled using a complete case approach; no imputation or extrapolation was performed. Analyses were therefore restricted to available data. Data extraction and management were performed using Structured Query Language (SQL) in BigQuery, and statistical analyses were conducted using SPSS version 29.0 (IBM Corp., Armonk, NY, USA).

RESULTS

All patients who met the inclusion criteria of treating monthly for 3 consecutive years were included in the analysis ($n = 224$). These individuals were 43.8 ± 16.2 (mean ± SD) years of age, 85.7% female, and they performed a total of 64,717 treatments throughout the study period. On average, a user performed 288.9 ± 271.7 (mean ± SD) treatments over the 3-year period. Participants treated with the REN wearable for an average of 11.0–11.3 months per year. See Tables 1 and 2.

Primary endpoint: lack of tachyphylaxis

Over 3 years, there was no clinically meaningful change in treatment intensity with an increase of no more than 2.5 intensity units on a scale of 100 units between each pair of 2 consecutive years (1.8 ± 5.5 between years 1 and 2, and 1.4 ± 5.3 between years 2 and 3; $p = 0.120$, McNemar test for two related dichotomous variables),

TABLE 1 Participant and clinical characteristics.

	N (Percent) or Mean (SD)
Age	
All	43.8 (±16.2)
≤17	15 (6.7%)
18–35	60 (26.8%)
36–55	101 (45.1%)
≥56	48 (21.4%)
Sex	
Female	192 (85.7%)
Treatments	
Total number of treatments conducted	64,717
Average number of REN treatments/month	8.03 (±7.55)
Average number of active treatment months	33.5 (±2.25)

Abbreviations: REN, remote electrical neuromodulation; SD, standard deviation.

TABLE 2 Treatment intensity and utilization over 3 years.

	Year 1			Year 2			Year 3		
	Mean (±SD)	Min Max	95% CI	Mean (±SD)	Min Max	95% CI	Mean (±SD)	Min Max	95% CI
Treatment intensity	35.0 (±16.2)	10.6–97.6	32.8–37.1	36.8 (±17.0)	12.2–99.0	34.6–39.1	38.2 (±18.3)	12.4–99.0	35.8–40.6
Monthly treatments	8.0 (±7.9)	1.1–78.3	6.95–9.04	8.5 (±8.6)	1.6–79.6	7.35–9.62	8.8 (±9.9)	1.4–115.8	7.45–10.04
Yearly treatment months	11.3 (±1.0)	9–12	11.1–11.4	11.2 (±1.0)	9–12	11.1–11.4	11.0 (±1.1)	9–12	10.8–11.1

Note: Year-to-year treatment intensity values, number of monthly treatments and number of treatment months, with no significant change over time.
Abbreviations: CI, confidence interval; Min Max, minimum–maximum; SD, standard deviation.

suggesting no occurrence of tachyphylaxis. Average treatment intensity increased by a total of 3.2 units from the first to the third treatment year (35.0 ± 16.2; 36.8 ± 17.0; 38.2 ± 18.3; for years 1, 2, and 3, respectively; see Table 2 and Figure 2).

Post hoc subanalyses of the primary endpoint

Three post hoc subanalyses of the primary endpoint of lack of tachyphylaxis were performed. First, we looked at the overlap with the previous 1-year study (Synowiec et al.).[21] Of the 224 participants in the current study, 142 (63.4%) participated also in the 1-year study. McNemar tests compared the proportion of participants who increased the treatment intensity by ≤2.5 units between each pair of consecutive years in each of the two subgroups. In both McNemar tests, we found no statistically significant difference between the change for each pair of years ($p = 0.557$ for patients who were not included in the 1-year study, and $p = 0.174$ for patients who were also included in the 1-year study).

Second, we looked at the subgroup of patients with a prevention-like treatment pattern (≥12 treatments per month). Of the 224 participants in the current study, 39 (17.4%) followed a prevention-like treatment pattern. McNemar tests compared the proportion of participants who increased the treatment intensity by ≤2.5 units between each pair of consecutive years in each of the two subgroups. In both McNemar tests, we found no statistically significant difference between the change for each pair of years ($p = 0.549$ for patients who followed a prevention-like treatment pattern, and $p = 0.193$ for patients who treated with an acute-like treatment pattern).

Third, we conducted a sensitivity analysis of the primary endpoint, taking all 12 months of the first year, as opposed to treating the first 3 months as an adaptation period and excluding them from analysis. The average (mean ± SD) difference between first 2 years was larger when accounting for all 12 months of the first year (2.54 ± 5.78) than when excluding the first 3 months of treatment as an adaptation period (1.84 ± 5.53). When including all 12 months of the first year, the difference between pairs of years was significant ($p = 0.004$), whereas when treating the first 3 months of treatment as an adaptation period, the difference was not significant ($p = 0.210$), justifying this decision.

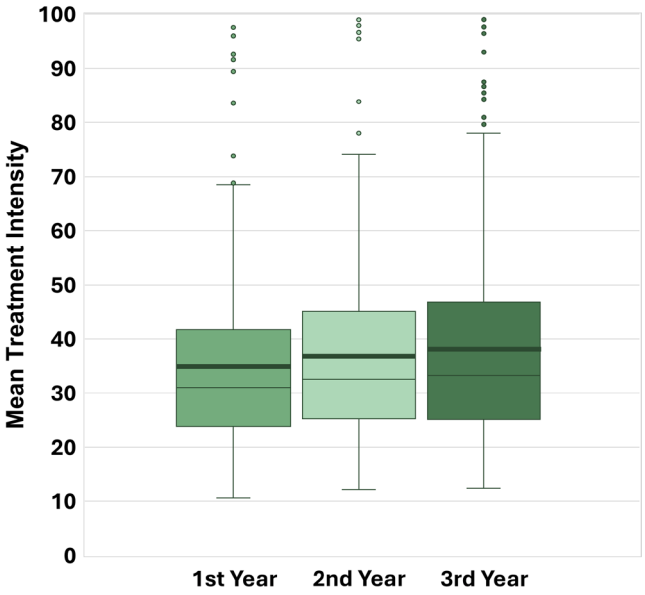

FIGURE 2 Distribution of average treatment intensity across patients over 3 years. Treatment intensity ranges from 0 to 100. There was no clinically meaningful change in average treatment intensity between consecutive years. The boxplot graph shows the following information: bold line: mean, thin line: median, box: IQR spanning from Q1 (25th percentile) to Q3 (75th percentile), whiskers: range of "typical" data (1.5 × IQR), outliers: data points beyond the whiskers. The figure contains all data points. IQR, interquartile range; Q, quartile.

Secondary endpoints

Long-term consistent effectiveness

Year-to-year clinical effectiveness did not change across the 3 years in any of the seven post–2 h effectiveness outcomes as determined by a GLMM test for each outcome, suggesting stable effectiveness over years of treatment. Over the 3 years, pain releif was reported by 72.1%–76.8% of users ($F_{(2,205)} = 0.167$, $p = 0.846$), pain freedom by 26.8%–28.7% of users ($F_{(2,228)} = 0.034$, $p = 0.966$), functional disability relief by 65.3%–70.8% of users ($F_{(2,216)} = 0.290$, $p = 0.749$), and functional disability freedom was reported by 31.4%–38.9%

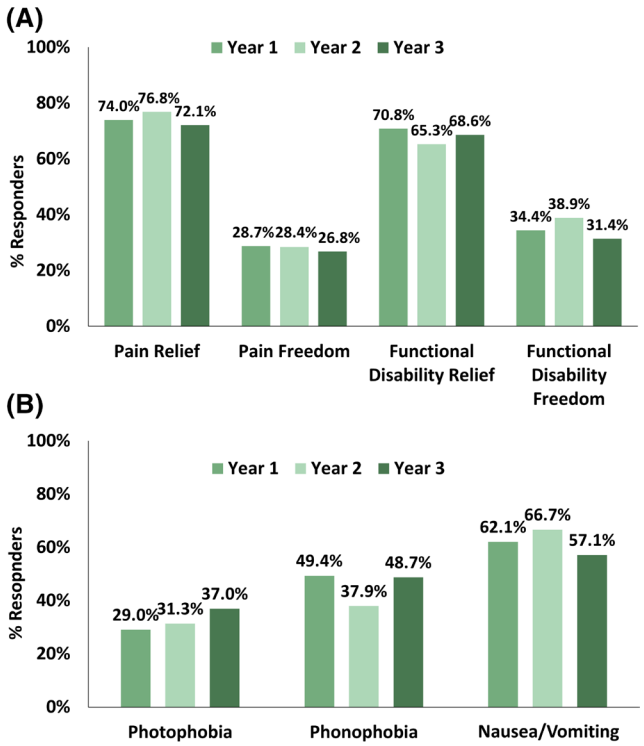

FIGURE 3 Effectiveness endpoints over 3 years. Year-to-year consistent effectiveness of (A) pain and disability relief and freedom, and (B) freedom from associated symptoms, represented as the percentage of responders from evaluable treatments. Effectiveness endpoints of pain relief, pain freedom, functional disability relief, functional disability freedom, and freedom from photophobia, phonophobia, and nausea/vomiting, remained stable with no significant change over the course of 3 years.

of users ($F_{(2,216)}=0.386$, $p=0.680$) (see Figure 3A). Freedom from associated symptoms was reported by the following percentages of users: 29.0%–37.0% ($F_{(2,180)}=0.530$, $p=0.590$) for photophobia, 37.9%–49.4% ($F_{(2,157)}=0.630$, $p=0.534$) for phonophobia, and 57.1%–66.7% ($F_{(2,113)}=0.284$, $p=0.753$) for nausea (see Figure 3B). Annual averages are presented in Table 3 and Figure 3.

Long-term utilization (adherence)

The average number of treatments per month remained consistent over time, with a 3-year monthly average ranging between 8.0 and 8.8, and no statistically significant differences from year to year as determined by a GLM repeated measures analysis ($F_{(2,446)}=1.090$, $p=0.337$; see Table 2 and Figure 4).

Safety and tolerability

Only two (0.9%) adverse events were reported, each by a different user. Both were expected, nonserious, dAEs, reported by one participant at month 12 (mild redness on the arm) and by the other participant at month 36 (moderate skin rash on the arm) of treatment. In both cases, these participants continued treatment after reporting the dAE and even after the termination of the study.

DISCUSSION

This prospective RWE cohort study followed 224 patients living with migraine who used the REN wearable device consistently for 3 consecutive years. Results suggest that the REN wearable is an effective and safe long-term acute treatment for migraine.

First, this study's findings suggest the absence of tachyphylaxis; users did not require higher device intensities (reflecting REN dosage) to treat their attacks over 3 years. Contrary to scenarios in which patients with migraine escalate medication doses to maintain efficacy or need to switch medications due to the loss of effectiveness over time,[11] the stable average intensity observed here provides clinically meaningful evidence, suggesting that therapeutic effect of REN can be maintained without dose adjustments.

Second, monthly utilization remained consistent over 3 years, indicating that users neither substantially increased treatments (e.g., to compensate for waning effectiveness) nor decreased usage (e.g., due to dissatisfaction, inefficacy, adverse events, or poor tolerability). Whereas inclusion criteria required consecutive monthly treatment over 3 years, there was no selection criterion on the actual number of treatments per month. Stable treatment utilization and long-term adherence are hard to achieve in migraine management.[13,22] It is reported that only about 50% of patients with migraine adhere to their triptan medication as prescribed.[5] Longitudinal studies of migraine treatments used for 3 or more years are very scarce.[7] The consistent usage patterns found in the current study suggest the REN wearable device is a feasible long-term treatment to which patients may adhere for years beyond the initial months of adaptation.

In addition to stable dose and utilization, acute effectiveness endpoints reflecting relief or freedom from pain and functional disability, as well as freedom from associated symptoms, did not differ significantly from year to year over 3 years. The percentage of users reporting consistent effectiveness per endpoint aligns with previous REN studies, including the pivotal randomized controlled trial (RCT),[16] and short-term real-world studies.[18,20,23] Moreover, this study extends the 1-year study on the effectiveness of REN,[21] which showed consistent 2 h pain relief in 74.1% and 2 h pain freedom of 26.0% of participants, to 3 years. These results not only show that REN effectiveness is stable over years but also it is similar to other acute treatments for migraine reported in the literature. For example, a systematic review and network meta-analysis of 133 RCTs shows that 2 h pain relief reported in triptan clinical studies ranged between 42% and 76% of patients, and 2 h pain freedom was 18%–50%.[24] Efficacy of gepants in RCTs was in similar ranges with 2 h pain relief reported by 58.1%–59.3% of patients using rimegepant[25,26] and 62.7% of patients using ubrogepant,[27] and 2 h pain freedom of 19.6%–21.2% and 21.8%, respectively. The current findings are particularly significant given the protracted nature of migraine,

TABLE 3 Effectiveness outcomes over 3 years.

	Year 1		Year 2		Year 3	
	% Responders (95% CI)	*n/N*	% Responders (95% CI)	*n/N*	% Responders (95% CI)	*n/N*
Pain relief	74.0% 64.0–82.4	(71/96)	76.8% 65.1–86.1	(53/69)	72.1% 56.3–84.7	(31/43)
Pain freedom	28.7% 20.1–38.6	(29/101)	28.4% 18.5–40.0	(21/74)	26.8% 15.8–40.3	(15/56)
Functional disability relief	70.8% 60.7–79.7	(68/96)	65.3% 53.1–76.1	(47/72)	68.6% 54.1–80.9	(35/51)
Functional disability freedom	34.4% 25.0–44.8	(33/96)	38.9% 27.6–51.1	(28/72)	31.4% 19.1–45.9	(16/51)
Photophobia freedom	29.0% 20.1–39.4	(27/93)	31.3% 20.6–43.8	(21/67)	37.0% 23.2–52.4	(17/46)
Phonophobia freedom	49.4% 37.9–60.8	(39/79)	37.9% 25.5–51.6	(22/58)	48.7% 32.4–65.2	(19/39)
Nausea/vomiting freedom	62.1% 48.4–74.5	(36/58)	66.7% 50.4–80.4	(28/42)	57.1% 37.2–75.5	(16/28)

Note: Year-to-year effectiveness measures (of all seven effectiveness endpoints) with no significant change over time.
Abbreviations: CI, confidence interval; n, responders; N, evaluable treatments.

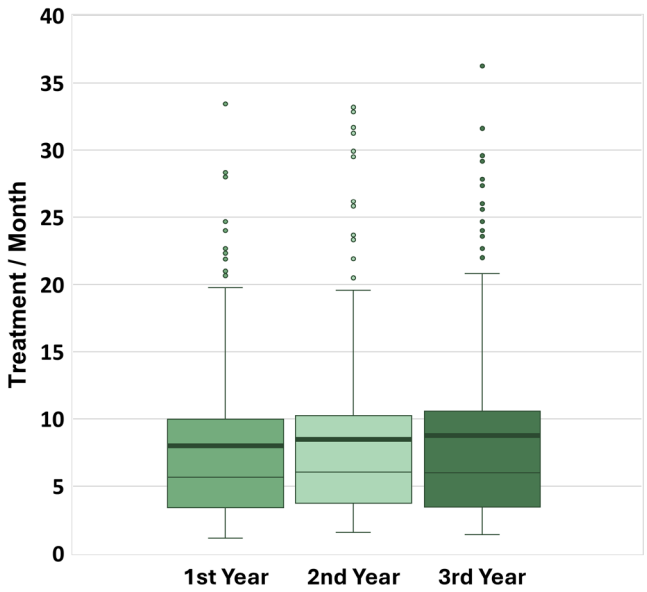

FIGURE 4 Distribution of average number of monthly treatments across patients over 3 years. Average number of monthly treatments remained consistent over time, with no statistically significant differences from year to year. The boxplot graph shows the following information: bold line: mean, thin line: median, box: IQR spanning from Q1 (25th percentile) to Q3 (75th percentile), whiskers: range of "typical" data (1.5 × IQR), and outliers: data points beyond the whiskers. For visualization purposes, five outlier data points were removed from the figure: Two patients from first year, two patients from second year, and one patient from third year (ranging from 43 to 116 in the number of monthly treatments). IQR, interquartile range; Q, quartile.

which can require management throughout much of an individual's life.[3] Traditional medication-based approaches can be effective initially, but as previously stated, adherence often diminishes because of side effects, interactions, and waning efficacy. By contrast, the present results suggest that the benefits from acute therapy do not appear to degrade among users of REN over an extended timeline, as indicated by stable dose, utilization, and effectiveness.

Only two dAEs of localized skin reactions, one mild and one moderate, were recorded. Neither event prompted discontinuation of treatment, and in both cases the users continued REN beyond the scope of the study. These outcomes reinforce earlier studies' findings of the favorable safety profile of REN[18,23] and further show that it is a sustainable long-term solution. Whereas pharmacological options may show increased side effects over time, leading to low adherence,[4,6] REN showed consistent safety and tolerability throughout the 3 years. Given the long-term nature of migraine management, a consistently low adverse event rate is clinically important for ensuring ongoing patient adherence.

Limitations

Whereas this study provides valuable insights into the long-term effectiveness and safety of acute treatment using REN, limitations must be acknowledged. First, the study population consisted of individuals who chose to continue using REN for 3 years, introducing a potential selection bias. The high exclusion rate (98.8%) indicates that only a small fraction of REN users maintained consistent long-term usage. Users who found the device ineffective or had difficulty adhering to the treatment protocol may have discontinued use before the 3-year mark. This could lead to a highly selected population with favorable treatment response as well as an overestimation of the device's effectiveness and utilization in the overall migraine population. However, discontinuation rates of prescribed migraine medications are known to be high. A recent 3-year claims-based cohort study of

prescribed migraine medications in the United States shows that only 14.3% continued using the initially prescribed acute treatment they received for 3 years; of those, only 5.1% continued using only that initial treatment.[28] However, the inclusion criteria in that study were much less rigorous than in the current study because patients were included if they had at least one claim over 6 months, without requesting actual treatment verification, and without requiring month-by-month usage. Moreover, the selection process used in the current study also allows us to specifically examine the long-term effects of acute treatment using REN in a population that has demonstrated sustained engagement with the therapy, providing valuable insights into its potential for long-term management. Furthermore, the stable utilization over the 3 years, which was not an inclusion criterion, suggests that REN is well tolerated and perceived as beneficial, which is an important consideration for long-term adherence.

Second, reporting in this study was voluntary, meaning that effectiveness endpoints were subject to reporting bias from those users who chose to report over the 3 years. Whereas patient-reported outcomes provide crucial information about the real-world impact of migraine treatments on patients' lives, including pain and functional improvement, the voluntary nature of reporting may not accurately reflect the experiences of all users. That said, the consistent reporting of positive outcomes over 3 years by a substantial portion of the participants (between 40% and 45%) strengthens the validity of these findings, which are similar to previous short-term efficacy reports of REN treatment. This suggests a sustained benefit of REN therapy for those actively engaged with the reporting process.

Finally, the focus of this study was the acute treatment of migraine attacks with REN, even though the device is also indicated for migraine prevention. Data on the effectiveness of preventive treatment over 3 years is not available yet. With that, at an average of 8.4 treatments per month, it can be inferred that our long-term users had a substantial burden of migraine, and the use of REN may have contributed to reducing disease severity by treating a large proportion of acute attacks effectively.

CONCLUSIONS

This study's analysis of data collected from REN users who treated consistently for 3 years as part of their clinical regimen in a real-world setting enhances the generalizability of previous findings, showing long-term stable effectiveness, safety, and utilization, with no evidence of tachyphylaxis in these patients.

AUTHOR CONTRIBUTIONS

Stephanie J. Nahas: Data curation; supervision; writing – review and editing. **Marius Birlea:** Data curation; validation; writing – review and editing. **Alit Stark-Inbar:** Conceptualization; data curation; formal analysis; methodology; writing – original draft. **Sharon Shmuely:** Data curation; formal analysis; methodology; writing – original draft. **Eden Mama:** Formal analysis; writing – original draft. **Alon Ironi:** Conceptualization; funding acquisition; writing – review and editing. **William B. Young:** Data curation; writing – review and editing. **Alan M. Rapoport:** Methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Stephanie J. Nahas: Advisor for AbbVie, Amneal, Axsome, Eli Lilly, Lundbeck, Pfizer, and Tonix. **Marius Birlea**: Ad hoc advisor for AbbVie. **Alit Stark-Inbar**: Theranica employee. **Sharon Shmuely**: Theranica employee. **Eden Mama**: Theranica employee. **Alon Ironi**: Employee and stockholder at Theranica. **Alan M. Rapoport**: Advisor for AbbVie, Axsome, Doctor Reddy's, Satsuma; Speakers Bureau of AbbVie, Doctor Reddy's and Teva Pharmaceutical Industries. **William B. Young** declares no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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