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ORIGINAL RESEARCH

A Real-World Evidence Study on US Patients Demonstrating Safety of High-Frequency Use of the Remote Electrical Neuromodulation (REN) Wearable Device for Migraine Treatment

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ABSTRACT

***Introduction*:** Remote electrical neuromodulation (REN) is an FDA-cleared, nonsignificant-risk, drug-free, prescribed wearable device (Nerivio®) for the acute treatment of migraine and/or every other day for prophylactic treatment in patients aged 8 years and older. Despite established efficacy within labeled use parameters, some patients adopt more frequent treatment regimens, including multiple treatments within a single day, daily use, or both. This study assessed the safety and tolerability of REN when used at frequencies exceeding the labeled indication.

***Methods*:** Real-world observational data from patients with migraine using REN with frequent treatment patterns were collected. Safety assessments evaluated all adverse events (AE) reports, with emphasis on device-related AEs (dAEs), categorized by severity and seriousness per regulatory standards.

***Results*:** A total of 1863 patients with migraine (82.1% female, mean age of 38.8 ± 20.1 years) were eligible: (1) 1654 treated multiple times a day, at least once, (2) 310 treated daily; 101 patients met both patterns. Safety profile was

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favorable, with a total of 17 patients reporting dAEs (0.91% of patients, 0.02% of treatments). Of them, 16 dAEs reported in multiple treatments per day group (0.97% of patients, 0.05% of treatments), and 6 dAEs in daily treatment group (1.94% of patients, 0.01% of treatments) with 5 dAEs overlapping between the groups (reported by patients who met both criteria). dAEs were infrequent, negligible to moderate in severity, and resolved without medical intervention. No serious dAEs were observed, and the majority of patients continued to use REN after reporting the dAE.

***Conclusion*:** REN is a safe and well-tolerated treatment for migraine, even when used more frequently than the labeled indication. These findings support its use in real-world clinical practice, including for patients with severe or highly frequent attacks who may need additional treatments.

***Trial Registration*:** ClinicalTrial.gov NCT07336056.

PLAIN LANGUAGE SUMMARY

Migraine is a disabling disorder that can disrupt daily life. Remote electrical neuromodulation is a wearable device that treats migraine without medication, by sending gentle electrical signals to nerves in the arm, which activate the body's natural pain-control system. The US FDA cleared it for people aged 8 years and older as a nonsignificant-risk device, meaning it poses minimal risk to users. Patients can use the remote electrical neuromodulation either when a migraine starts or every other day to help prevent attacks. Some people use it more often, such as several times a day or every day. This was an observational study that examined whether frequent treatment beyond the indication with remote electrical neuromodulation in real-life setting is safe. Data from 1863 people who used remote electrical neuromodulation often was reviewed, looking at voluntarily reports of adverse events and their severity. Two patterns were studied: several treatments per day (four or more treatments in 1 day), and every day (6–7 treatments per week over a month). The results show that remote electrical neuromodulation is safe, even with frequent use. Fewer than 1% of patients reported mild to moderate treatment-related side effects. No serious side effects occurred, and most patients continued treatment after reporting an adverse event, supporting the remote electrical neuromodulation as a safe option for people with severe or frequent migraine attacks who may require additional treatments.

Keywords: Acute; Drug-free; Migraine; Nerivio; Neuromodulation; Prevention; Remote electrical neuromodulation; REN; Safety

Key Summary Points

Why carry out this study?

Migraine is a common disease and the second most debilitating disease worldwide, and patients with severe or frequent attacks often require multiple treatments per day or daily treatment, creating a critical need for safety data on such frequent use.

The REN wearable (Nerivio®) is an FDA-cleared, drug-free, prescribed device for acute and preventive treatment of migraine in patients aged 8 years and older, which has not been evaluated under frequent use patterns.

This study examined real-world safety of REN when used multiple times a day, daily, or under both frequent use patterns.

What was learned from the study?

Among 1863 patients who performed 79,362 treatments, device-related adverse events (dAEs) were rare (0.91% of patients, 0.02% of treatments), negligible to moderate in severity, and none were serious.

Frequent REN treatment did not increase dAE rate compared to previous clinical trials and real-world evidence studies, supporting its safe application for patients with severe or frequent migraine attacks.

INTRODUCTION

Migraine is a prevalent neurological disorder associated with significant disability and diminished quality of life [1]. While pharmacological interventions remain the mainstay of treatment, concerns regarding medication overuse, adverse effects, and contraindications in certain patient populations have driven interest in non-pharmacological alternatives.

The remote electrical neuromodulation (REN; Nerivio®; Theranica, Netanya, Israel) wearable is a prescription-only, drug-free, non-invasive medical device. It represents an emerging therapeutic approach that leverages conditioned pain modulation (CPM; [2]) to provide acute and preventive migraine relief. It works by sending sub-painful electrical pulses to nociceptive fibers in the skin, triggering pain-control pathways in the brain, enhancing descending pain inhibition by promoting the release of norepinephrine and serotonin. The REN wearable received US Food and Drug Administration (FDA) De Novo clearance in 2019 for acute migraine treatment in adults and has since received expanded clearance for acute and/or preventive use in patients 8 years old and above. The current indication is based on multiple randomized controlled clinical trials (RCTs), open-label studies, and real-world evidence (RWE) studies, demonstrating significant and clinically meaningful benefits for patients in their acute and preventive migraine management compared with placebo and in a clinical practice [3–13]. It provides a valuable treatment option, especially for individuals in whom traditional pharmacological therapies are contraindicated, poorly tolerated, ineffective, or not approved, such as children and pregnant women.

In addition to the efficacy evidence, the REN wearable is considered a nonsignificant risk (NSR) device under US FDA regulations (21 CFR 812.3[m]; [14]). An NSR device is a device that does not meet the criteria for a significant risk (SR) device, which may present a potential serious risk to the health, safety, or welfare of a subject. In line with this classification, the safety of the REN wearable has been well established in multiple clinical studies. Evidence includes RCTs [3, 4, 8] reporting transient, non-systemic device-related adverse event (dAE) rates ranging from 0% to 4.8%, open-label trials [5–7] with dAE rates of 1–2%, and multiple RWE studies [10, 11, 13, 15–19] reporting dAE rates of 0–0.9%, with up to 55,261 patients with migraine per study.

According to the indication, acute treatment with REN should start as early as possible once a migraine attack begins, aiming to achieve relief or freedom from symptoms, with the greatest benefit observed when treatment is initiated within 1 h of attack onset [3, 4, 19]. Preventive treatment is indicated for every other day use to reduce the frequency of migraine attacks [8]. Given that the instruction is to use "as needed", empowering patients to find the best treatment regime that works for them, real-world treatment patterns may deviate from the approved indication. As patients are not limited in the number of treatments they can conduct per day, nor by the number of treatment days per month, some patients who experience frequent and severe headaches and associated symptoms have adopted more frequent treatment regimens, including multiple treatments within a single day, daily use, or a combination of both patterns. The safety profile of REN under such frequent use conditions has not been systematically evaluated.

The objective of this study was to assess the safety and tolerability of the REN wearable device when used at frequencies exceeding the labeled indication, defined as either multiple treatments per day or daily use, using real-world data from patients who were prescribed the device as part of their routine migraine care.

METHODS

Study Design and Settings

This prospective, real-world evidence study evaluated the safety of REN wearable device (Nerivio®) under frequent use patterns. Data

were collected between January 2020 and August 2025 from users across the USA.

Ethical Approval

The study was approved by the WIRB-Copernicus Group Institutional Review Board (WCG IRB; Tracking Number 20260001) and performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Upon registration in the REN mobile application, patients provided informed consent for the collection and research of de-identified research data and submitted demographic information (age and sex).

Participants and Data Collection

Eligible participants included individuals who used the REN wearable to treat migraine attacks in a "frequent use" pattern (see definition below). The application automatically recorded treatment parameters, including date, duration, and intensity. Safety data were collected through an in-app adverse event (AE) tracking system and by documenting AE-related complaints received by the customer support call center. These data were used to evaluate real-world treatment behaviors and safety outcomes, and to characterize the overall safety profile of the REN wearable.

Study Device

The REN wearable device is an FDA-cleared, drug-free, non-invasive prescribed treatment for migraine in patients aged 8 years and older. The device is controlled via a smartphone application, allowing patients to adjust the stimulation intensity to a level that is strong but not painful. Each treatment session lasts 45 min, during which patients can continue their normal daily activities.

Frequent Use Pattern Classification

Frequent use was defined under two treatment patterns which were used to classify patients into two groups:

1. *Multiple treatments per day*: defined as administrating four or more full treatments (45-min sessions) on a single day. All patients meeting this criterion for at least 1 day were included in this group, and all full treatments administered throughout these days were taken into account in the analysis. The threshold of ≥ 4 treatments within a single day was defined to distinguish between patients using REN for both prevention and acute treatment on the same day (typically up to two treatments, which is not considered frequent use), and those exhibiting frequent use beyond this dual-purpose pattern. Patients with three treatments per day were considered closer to the dual-purpose use pattern and more prevalent in the general population; therefore, they were not included in the main analysis to maintain a clear separation between these two treatment patterns. A sensitivity analysis assessed the prevalence of dAEs also in patients treating ≥ 3 treatments within a single day at least once.
2. *Daily treatment*: daily use for 1 month, allowing a few days to be skipped, as is often the case with any daily treatment where patients forget or skip a few days here and there. Therefore, daily treatment was defined as administrating at least one full treatment (45-min session) on 25 or more days within a 28-day period, allowing no more than 10% (3 days) without treatment. For each patient, all possible 28-day windows containing at least 25 treatment days were identified. Consecutive windows were then merged to count the whole period of daily treatment behavior. All full treatments administered during the entire consecutive period were included in the analysis (i.e., there could be more than one treatment per day). This definition of daily use was set to differentiate between patients using REN for preventive treatment

every other day, along with acute treatments as needed throughout a 28-day period (i.e., a few more than 14 treatments in 28 days), and those exhibiting more frequent use beyond this pattern (i.e., nearly daily with more than 25 treatments in 28 days).

These classifications were defined to identify groups of patients with high treatment exposure that is uncommon in the general population of REN users. Patients could be associated with either one of the groups, or both, based on their treatment patterns. The total frequent use group comprised unique patients and treatments from both classifications of frequent use patterns. The analysis included only full treatments (45-min sessions) to address the safety profile of frequent use patterns according to the REN instructions of use. Therefore, sessions less than 45-min were excluded and were not counted as treatments in the multiple treatments per day or daily treatment classifications.

Safety Outcome and Classification of Device-Related Adverse Events

To evaluate the safety profile of the REN wearable under different frequent use patterns, any and all medical reports from patients using the REN wearable are classified by trained medical personnel in accordance with FDA guidelines. Adverse events are classified as serious or non-serious; device-related, procedure-related, or not related; severity level; etc. The proportion of study patients reporting a dAE was assessed (patient-level analysis). Given the large number of treatments conducted by each study participant, the proportion of dAEs per treatments performed was also calculated (treatment-level analysis). Note that while only treatments meeting the frequent use criteria were counted for treatment-level analysis, dAEs were collected from the entire study period and were not limited to the days that met the criteria above. This strict criterion was used because it might have taken patients time to report their AE after it occurred.

Statistical Analysis

The 95% confidence intervals (CIs) of the proportion of patients or treatments with dAEs were calculated with a standard error rate ($\alpha = 0.05$).

RESULTS

A total of 1863 patients (82.1% female, with mean age of 38.8 ± 20.1) were included in the study, as follows:

Multiple treatments per day: Patients ($n = 1654$) who met the criterion for multiple REN treatments per day analysis, were 82.5% female, with mean age of 38.1 years (± 20.2). These patients completed 35,550 full treatments across 7287 days with four treatments or more per day. Overall, this cohort of patients conducted 189,931 full treatments within the time frame

Table 1 Device-related adverse events (dAEs) proportions

	n patients	*n* treatments	Average treatments/patients	*n* dAEs	*n* dAEs/*n* patients	*n* dAEs/*n* patients 95% CI	*n* dAEs/*n* treatments (%)	*n* dAEs/*n* treatments 95% CI
Multiple treatments per day	1654	35,550	21.5	16	0.97%	0.50–1.44%	0.05%	0.02–0.07%
Daily treatment	310	54,372	175.4	6	1.94%	0.40–3.47%	0.01%	0.00–0.02%
Total group	1863	79,362	42.6	17	0.91%	0.48–1.34%	0.02%	0.01–0.03%

dAE device-related adverse event

Table 2 Breakdown of device-related adverse events (dAEs)

		Multiple treatments per day *n* dAE (% dAEs)	Daily treatment *n* dAE (% dAEs)	Total frequent use *n* dAE (% dAEs)
Expected	*n* (%)	11 (0.67%)	4 (1.29%)	12 (0.64%)
Serious	No	0 (0%)	0 (0%)	0 (0%)
Severity	Negligible	2 (0.12%)	0 (0%)	2 (0.11%)
	Minor	8 (0.48%)	2 (0.65%)	8 (0.43%)
	Mild	4 (0.24%)	3 (0.97%)	5 (0.27%)
	Moderate	2 (0.12%)	1 (0.32%)	2 (0.11%)
	Severe	0 (0%)	0 (0%)	0 (0%)
Category	Skin irritation	6 (0.36%)	4 (1.29%)	6 (0.32%)
	Arm pain/soreness	6 (0.36%)	1 (0.32%)	6 (0.32%)
	Tingling	2 (0.12%)	1 (0.32%)	3 (0.16%)
	Burning sensation	1 (0.06%)	0 (0%)	1 (0.05%)
	Muscle spasm	1 (0.06%)	0 (0%)	1 (0.05%)

Number and percentage of dAEs according to their expectancy, seriousness, severity, and category

dAE device-related adverse event

of the study. In this study group, 17 patients (1.03%) reported an AE, from which 16 were classified as device-related (0.97% of patients, 0.05% of treatments; Table 1). Classification of the dAEs defined two events as negligible, eight minor, four mild, and two moderate. N one of them was serious (Table 2). Except for one patient, all patients continued to use the device after reporting the dAE. A sensitivity analysis assessing dAE rates also in patients treating ≥ 3 treatments within a single day was performed on 4824 patients conducting 76,389 treatments across 20,900 days. In this group, 36 patients (0.75%) reported AE, from which 28 were classified as device-related (0.58% of patients, 0.04% of treatments).

Daily treatment: Patients ($n = 310$) who met the criterion for daily REN treatment analysis, were 80.6% female, with mean age of 45.0 years (± 18.2). These patients completed 54,372 full treatments in a daily treatment pattern across 35,567 days. Overall, these patients conducted 120,616 full treatments within the time frame of the study. In this group, 8 patients (2.58%) reported an AE, from which 6 were classified as device-related (1.94% of patients, 0.01% of treatments; Table 1). Classification of the dAEs defined two events as minor, three mild, and one moderate. None of them was serious (Table 2). All patients continued to use the device after reporting the dAE.

Among the total frequent use group of patients who met at least one frequent use classification (n = 1863 patients who completed 79,362 REN treatments meeting frequent use criteria), 17 unique patients reported dAEs (0.91% of patients, 0.02% of treatments; Tables 1 and 2), including 16 meeting the multiple treatments per day criteria, and 6 meeting the daily treatment criteria. Of them, 5 overlapping events performed by 101 patients who met the criteria for both frequent use patterns and therefore counted in both groups.

In this study population, 313 participants (16.8%) were younger than 18 years: 286 in the multiple treatments per day group, 35 in the

daily treatment group, of which 8 met criteria for both frequent use patterns. These youth participants conducted a total of 6372 unique treatments. Of all dAEs reported in the total group, four were in youth (1.28% of patients, 0.06% of treatments). Specifically, three dAEs were reported by patients in the multiple treatments per day group and one was reported by a patient in the daily treatment group.

DISCUSSION

This study presents a comprehensive evaluation of the safety and tolerability of frequent treatments' use of the Nerivio REN wearable device, based on real-world data collected from patients with migraine across the USA. Under both frequent use patterns, multiple times per day and daily use, dAEs were rare and non-serious, highlighting the safety of the REN wearable even when used frequently. Multiple treatments within a single day may reflect a particularly severe migraine attack, which may not be relieved with one or two treatments, or of the recurrence of a migraine attack later on the same day. Daily treatments over a month may indicate a high frequency of migraine attacks, such as in chronic migraine or New Daily Persistent Headache (NDPH).

The reported dAEs were negligible to moderate in severity; none of the events were serious, and all resolved without the need for medical intervention. Reported dAEs primarily involved skin irritation, ranging from mild symptoms such as redness and itching to more pronounced effects such as burning sensation. Additionally, some patients reported nerve-related sensations such as tingling, arm pain/soreness, and muscle spasm. All dAEs were local and not systemic. Importantly, despite these events, all but one patient reporting dAEs continued using the device. Overall, these findings suggest that frequent use of the REN wearable is well tolerated, with manageable dAEs that do not significantly impact treatment adherence.

A recently published RWE study on the REN wearable included a large cohort of 55,261 participants who performed 586,981 treatment sessions [19]. Within this population, 192 patients reported a dAE (0.36% per patient, 0.03% per treatment). This study (referred to as the "large RWE study") provides valuable insight into patient behavior in real-world settings and can serve as a source for evaluating dAE proportions under frequent use patterns. In the large RWE study, the number of treatments varied among patients, with an overall average of 10.6 treatments per patient. In contrast, in the frequent use study groups, the averages were considerably higher: 42.6 in the total frequent use group, with 21.5 treatments per patient in the multiple treatments per day group, and 175.4 in the daily treatment group. These differences reflect the increased REN usage of patients under frequent use patterns. Therefore, when evaluating dAE proportions across frequent use and normal use patterns, it is essential to account not only for the number of patients but also for the number of treatments, which was up to x17 times higher in the current cohort. Expressing dAE proportions relative to the number of treatments provides a more meaningful evaluation across groups: 0.03% dAEs per treatment in the large RWE study, 0.02% in the total frequent use group, 0.05% in the multiple treatments per day group, and 0.01% in the daily treatment group (Table 1). The large cohort size [19] enables reliable estimation of event incidence at the population level (beyond a sample), and formal statistical testing is not methodologically justified for comparing these groups given the substantial imbalance in cohort sizes. Therefore, 95% CIs can be used for descriptive comparison between the cohorts. The 95% CI of the frequent use groups indicate that the 0.03% dAE rate per treatment observed in the large RWE cohort falls within or slightly above the range of these subgroups (Table 1). The observation that the large RWE dAE rate lies above the current study's CI indicates that dAE rates in the present cohort were lower than those observed in the large RWE study. In addition, REN wearable RCT studies showed dAE rates of 2.36% at patient level and 0.29% at treatment level (254 participants performing 2052 treatments, with 6 participants reporting dAEs, combined across studies [4, 8]). Consistent with the large RWE comparison, treatment level dAE rate in the

RCTs fall within or above the 95% CI observed in the frequent users' real-world setting. Overall, dAE proportions across all three study groups, at both the patient and treatment levels, were very low, with the treatment level dAE rates during frequent use patterns not exceeding those observed in the large RWE and RCTs.

Both the nature and rate of dAEs observed in this study are in line with those reported in previous clinical trials and RWE studies of REN, suggesting that frequent use of REN does not impact the characteristics or seriousness of dAEs, nor lead to increased prevalence of dAEs. Most events were anticipated and in accordance with the safety specifications outlined in the user manual, reinforcing the predictability and manageability of the REN's safety profile. As a precaution, patients are recommended to switch arms and wait 30 min between successive treatments, to minimize local dAEs and to allow time for acute efficacy to mature.

While these findings support the safety of the device during frequent use patterns, certain limitations should be acknowledged. First, as the study was conducted in a real-world setting, AE reporting relied on patients voluntarily contacting the customer support center, introducing a risk of underreporting and selection bias. It is therefore possible that some patients who experienced dAEs may have discontinued use without reporting their experience, potentially contributed to underestimation of dAE rates. Nevertheless, the absence of serious or severe dAEs, along with the continued use of the device by almost all reporting patients, suggests that the majority of dAEs were anticipated and did not interfere with treatment adherence. Moreover, this limitation is true for any real-world usage, and as mentioned above, the proportion of dAEs across frequent use patterns reported in the current study and among the general population of REN users in previous studies was in the same ranges. Second, the treatment-level approach taken here does not account for repeated measures (treatments) and clustering of treatments per patient. However, by definition, the current cohorts were investigated due to the high number of treatments each patient conducted (i.e., frequent use patterns). It is therefore important to assess not only patient-level risk but also treatment-level risk, to account for the inherent high number of treatments conducted by these patients. Third, the youth subgroup included relatively few patients; therefore findings should be considered exploratory, and further research is needed to better characterize safety under frequent use in this population. Despite the limited sample size, observed dAE rates were broadly similar to those of the overall population and in previous studies of this age group. Last, evaluating treatment efficacy within these frequent use patterns could be valuable. However, the design of the in-app questionnaires used to collect efficacy data limits such analysis. The questionnaires collect baseline and 2-h post-treatment data for each treatment, with a few hours availability window for completing the post-treatment questionnaire. Thus, patients who administer multiple treatments per day may not be able to accurately associate their responses with a specific treatment session. Moreover, the app is not yet designed to collect preventive efficacy data. As a result, assessing treatment efficacy under frequent use conditions is challenging.

CONCLUSIONS

Considering the significant burden and disability associated with severe migraine episodes and with prevalent attacks, it is particularly important to establish the REN wearable device as a safe and well-tolerated treatment under frequent use patterns. The present findings demonstrate that frequent REN use, either multiple times per day or daily use, was associated with very low dAE rates. The rate of dAEs per treatment in a very large RWE cohort and in RCTs were within or above the confidence interval of the current dAEs. These results suggest that REN is a safe and applicable treatment option for patients experiencing more severe migraine manifestations, providing symptom relief without compromising safety.

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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. Reena G. Rastogi: Advisory board for Theranica. Jason A. Santiago: Promotional Speaker for Theranica, Pfizer. Alicia Chang: No Conflict of interest. Eden Mama: Theranica employee. Alit Stark-Inbar: Theranica employee. Alon Ironi: Employee and stockholder at Theranica. Alan R. Towne: Received grant funding from DOD. Klaus Werner: Advisory board for Theranica.

Ethical Approval. The study was approved by the WIRB-Copernicus Group Institutional Review Board (WCG IRB; Tracking Number 20260001) and performed in accordance with the Helsinki Declaration of 1964 and its later amendments. During registration in the REN mobile application, patients provided informed consent for the collection and research of de-identified data and demographic information (age and sex).

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