

Improving Sleep and Quality of Life after Use of a Haptic Vibrotactile Trigger Technology, Drug-Free, Topical Patch: Results from the HARMONI Study

Paul Doghramji¹, Derek Dietze² and Peter Hurwitz^{3*}

¹Ursinus College, Collegeville, Pennsylvania, USA.

²Metrics for Learning LLC, Queen Creek, Arizona, USA.

³Clarity Science LLC, Narragansett, Rhode Island, USA.

*Correspondence:

Peter Hurwitz, Clarity Science LLC, 750 Boston Neck Road, Suite 11, Narragansett, RI 02882, Tel +1917 757 0521, Fax +1855-891-8303.

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ABSTRACT

Sleep issues are widely prevalent throughout the US and can greatly impact a person's quality of life while imparting a significant personal and societal burden. Evidence supports the importance of sleep health to overall physical health, behavioral health, wellness, and safety. Several diseases have been identified as having a significant association with sleep disorders and sleep duration, including depression, diabetes, obesity, hypertension, and cardiovascular events. Conventional pharmacological treatments for sleep disorders have been associated with dangerous adverse effects. Identifying effective and safe alternative treatment strategies, including those that are non-invasive and non-pharmacologic and that have reduced and limited side effect profiles, will provide options that may be preferable in how clinicians traditionally treat sleep disorders.

There has been research focusing on neuronal pathways and circuits that have been shown to respond to sensory (nociceptive) stimulation. Researchers have shown that these pathways and specific areas of the brain can change in response to external stimuli. Haptic vibrotactile trigger technology (VTT) is designed to target the nociceptive pathways and theorized to disrupt these brain centers. The technology has been incorporated into non-invasive, non-pharmacological topical patches and other routes of delivery.

The purpose of this IRB-approved, minimal risk observational study was to evaluate patients' experiences and/or perceptions and patient response for those who received a haptic vibrotactile trigger technology (VTT) embedded non-pharmacologic, non-invasive, over-the-counter sleep patch (REM Sleep Patch with VTT; Super Patch Company, Srysty Holding Co, Toronto, Canada).

Methods: Baseline, 7- and 14-day data were recorded in one hundred thirteen (113) adult subjects (79 females and 34 males) with a mean age of 53 years who presented with sleep- or insomnia-related issues or associated symptoms. The study evaluated changes in overall sleep quality and insomnia severity scores via validated scales (PSQI (Pittsburgh Sleep Quality Index) and the ISI (Insomnia Severity Index)), changes in the use of prescription and OTC medications, patient satisfaction, and any side effects reported while using the patch. Future analysis will compare the outcomes reported here with control and crossover treatment groups.

Results: The results showed statistically significant decreases in time to fall asleep, an increase in number of hours of sleep, improvement in the quality of sleep, and reduction in global PSQI Score after using the VTT embedded sleep patch. After 14 days, the vast majority of patients reported a reduction of usage of oral medications, that the patch was convenient and easy to use, and preferred the patch over oral and other medications for sleep. Results also showed positive outcomes in Quality of Life (QoL) components with improvements in daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, and mood.

Conclusions: Study results indicate that this non-pharmacologic, non-invasive, haptic vibrotactile trigger technology (VTT) embedded topical patch improves sleep quality, duration, and quality-of-life components and may reduce the use of concurrent medications, including prescribed and other oral medication for adult patients with sleep or insomnia-related symptoms. Results reported suggest that the non-pharmacological topical sleep patch has incredible potential to be added to the current approaches and treatments of noninvasive and nonpharmacological sleep therapies.

Keywords

Haptic vibrotactile trigger technology, Insomnia, Sleep management, PSQI, ISI, REM SLEEP PATCH, VTT.

Introduction

Sleep issues are widely prevalent throughout the US and can greatly impact quality of life and imparts a significant personal and societal burden [1]. It has been estimated that approximately 35 to 40% of the U.S. adult population report having problems with falling asleep or experience daytime sleepiness. These effects can have a significant impact on both morbidity and mortality. There has been a large amount of evidence to support the importance of sleep health to overall physical health, behavioral health, wellness, and safety [2]. Several diseases have been identified as having a significant association with sleep disorders and sleep duration, including depression [3,4], diabetes [5], obesity [6,7], hypertension [8], and cardiovascular events [9,10]. However, the prevalence, burden, and management of sleep disorders are often ignored or overlooked by individuals and society leading to underappreciation and undertreatment, making this a serious health concern [11].

There are currently many treatments that attempt to assist with sleep onset, maintenance, consolidation, or quality. Treating insomnia and other sleep-related disorders typically involves sleep-inducing medication, cognitive therapy, or a combination of both [12]. Depending on the diagnosis, positive-airway pressure (PAP) for patients with sleep-disordered breathing may also be prescribed. Pharmacological approaches, however, have been associated with undesirable and serious side effects, some that can be life-threatening and thus, limiting the effectiveness and desirability of the treatment [12]. Other approaches such as herbal medicine, homeopathy, and dietary supplementation also have been shown to have adverse side effects, limited scientific evidence, and recent studies have indicated that these supplements may not be as helpful as once thought [13]. Due to the common and associated adverse side effects with pharmacological approaches to treat sleep disorders, there is a need to identify alternative, non-invasive, and non-pharmacological approaches for better sleep management.

In recent years, several medical associations have developed guidelines for sleep disorders and recommend treatments that include non-invasive and non-pharmacological therapies as a first line treatment before consideration of other approaches [14]. There has been an effort to minimize the use of pharmacologic treatments as first line therapy in light of their potential adverse effects.

There are known networks of neuronal pathways and circuits along with "neurosignature" patterns of nerve impulses generated by a widely distributed neural network in the brain responding to sensory (nociceptive) stimulation [15-17]. These neurosignature patterns may be triggered by inputs such as tactile sensations. Tactile perception is an innate mechanism for human survival and represents our evolved and adaptive sensorial ability to

apprehend information via haptics – the active touch for object recognition and perception by higher centers of the brain [18,19]. The somatosensory experience is determined by a set of channels and receptors sensitive to thermal, tactile, and mechanical stimuli shown to be critical to survival, balance control, and pain modulation, among other modalities [18-20].

Neuronal signals are measurable by the electroencephalogram (EEG) [17,21,22]. EEG research has shown that haptic vibrotactile trigger technology (VTT) can influence and modulate brain centers and neuronal pathways [23]. In recent years, haptic skin-stimulation technology has been incorporated into several over-the-counter products with different routes of delivery that include patches, apparel (socks), braces, wrist bands, and compression sleeves, among others.

In this pilot HARMONI (Health Assessments: Reviewing, Measuring, and Observing Neuromatrix Interaction) IRB-approved study, we evaluate an over-the-counter, non-invasive, non-drug, sleep-supporting patch (REM Sleep Patch with VTT; Super Patch Company, Srysty Holding Co, Toronto, Canada) that incorporates haptic-vibrotactile trigger technology (VTT). This minimal risk, observational study, evaluated this over-the-counter, non-pharmacological patch that is embedded with proprietary sensory patterns and incorporating VTT. The patch is designed to trigger neural pathways and circuits associated with the sleep cortical networks. This study included patients with sleep or insomnia related symptoms and evaluated their overall perceptions of sleep treatment and associated symptoms with the use of the VTT sleep patch. The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) tools were used to assess patient-reported changes in sleep quality and interference scores, and change in the use of sleep medications at 7- and 14-days following treatment. Data presented here are for patients on active treatment. Future planned analyses will include a control and a crossover group of patients and explore differences between each group.

Methods

Study Design

This study was a prospective, Institutional Review Board-approved Observational Study aimed at evaluating patients' experiences and/or perceptions and patient response for those who have received a haptic vibrotactile trigger technology (VTT) embedded patch (REM Sleep Patch with VTT; Super Patch Company, Srysty Holding Co, Toronto, Canada) or an inactive sleep patch by their clinician. Preliminary study data presented here include only subjects who received active treatment.

Baseline Demographic and Clinical Characteristics of Patients

A total of 113 patients (79 females, 34 males) at 3 US investigator sites were enrolled in the treatment arm of the study and completed the baseline, day 7, and day 14 surveys. Demographic results were similar for gender and age at the baseline survey for all groups of patients. The mean age at baseline was 53 years.

Sleep and Insomnia-related symptoms were evaluated by patient answers to validated sleep and insomnia measurement and symptom scales (e.g., The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI)) as well as additional survey questions regarding patient satisfaction, patient quality of life, and resumption of their normal activities. Evaluation of a Control Group (CG) of patients (given an inactive vehicle patch) and a crossover group of patients (CROSSG) who received the active patch after 14 days of being in the control group, will be included in future analyses.

Patients who met the eligibility criteria and who were treated with the sleep patch comprised the study's treatment group (TG). For the treatment group, patient inclusion criteria were as follows: 1) ages 18 to 85 years, inclusive; 2) ability to provide written informed consent; 3) received the active VTT embedded study patch; and 4) had been diagnosed with sleep or insomnia related symptoms. Patients who had a history of drug use or alcohol abuse, patients who had an implantable pacemaker, defibrillator or other electrical devices, or patients who were pregnant, were ineligible to participate in the study.

Each site provided patients an identification number, and a confidential file containing the informed consent forms and patient identification numbers were kept and maintained in a secured cabinet only accessible to the principal investigator and authorized personnel. Patient survey responses were provided with no identifying patient information.

Patients could withdraw from this study at any time with the assurance of no unfavorable impact on their medical care. All diagnostic tests and treatment decisions were made at the discretion of clinicians, with no tests, treatments, or investigations performed as part of this study. Patients were provided the treatment at no cost and were not compensated for their participation in the study.

The study protocol was approved by ADVARRA institutional review board and was performed in full accordance with the rules of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the principles of the declaration of Helsinki and the international council of Harmonisation/GCP. All patients gave informed and written consent.

Topical Intervention

The active, non-invasive, 2 x 2 inch non-pharmacological patches are embedded with proprietary sensory pattern imprints and incorporate haptic vibrotactile trigger technology (VTT). The active patches contain no drug or energy source. There is an adhesive backing on one side of the active patch. Patients in the treatment group were instructed to place one patch on their forearm before going to bed, remove patch after awakening in the morning, and replace the patch with a new sleep patch each day (See Picture 1). The non-active patches look similar to the active patches but do not incorporate the haptic vibrotactile trigger technology (VTT).



Picture 1:

Study Procedures and Assessments

Following enrollment, patients were asked to complete surveys of the PSQI and ISI at baseline (day 0) and follow-up visits on days 7 and 14 of the study period. The surveys were comprised of questions to address and document sleep length, quality, and impact and level of interference that their sleep- or insomnia-related symptoms have on their quality-of-life components and in their daily lives. Any reported side effects were also documented. Study participants were instructed to wear a patch on their forearm before going to bed and patch placement was the same for the active and non-active treatment arms.

The PSQI is widely used in the field of sleep medicine and is considered an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, in addition to daytime dysfunction [24]. The Insomnia Severity Index (ISI) is a brief instrument that was designed to assess the severity of both nighttime and daytime components of insomnia. It is considered a validated and efficient measure suitable for evaluating sleep quality in a variety of patient and research populations. The seven-item questionnaire asks respondents to rate the nature and symptoms of their sleep problems. Questions relate to subjective qualities of the respondent's sleep, including the severity of symptoms, the respondent's satisfaction with his or her sleep patterns, the degree to which insomnia interferes with daily functioning, how noticeable the respondent feels his or her insomnia is to others, and the overall level of distress created by the sleep problem [25].

Patients were asked to indicate their preference between the patch and any other medications that they had been taking for sleep relief

at the time of the baseline, day 7, and day 14, as well as their satisfaction and ease of use of the patch.

Study End Points

The primary endpoints included changes in patient responses to The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) scores among the treatment group, as well as preference in the use of prescription and OTC medications. We also assessed patient satisfaction with patch treatment and any side effects reported by patients during the trial. Future analysis will compare the non-active control and crossover treatment groups with the outcomes reported here.

Statistical Analysis

For all variables, descriptive statistics were calculated, including frequencies and percent for categorical variables and means with standard deviation (SD) for continuous variables. The maximum sample size available was used for each statistical analysis.

Changes from baseline to day 7, and to day 14, in PSQI and ISI scores were analyzed using the paired *t*-test to identify any statistically significant differences within the treatment group.

Each survey collected responses to questions regarding patient satisfaction and side effects of treatment. Descriptive statistics were used to determine patient satisfaction with the sleep patch within those treated. Descriptive statistics were also used to report any side effects experienced by patients.

A two-tailed alpha was set to 0.05 for all statistical comparisons. SPSS v. 27 was used for all analyses.

Results

Treatment Group

Treatment group paired data were collected and only patients that completed 14 days of treatment were included in the analysis. Over 14 days, the mean Global PSQI score decreased 56% (12.5 to 5.5/21; $p < .001$) and mean ISI Severity score decreased 57% (18.7 to 8.1; $p < .001$). Results also showed positive outcomes in all measured ISI Quality of Life (QoL) components with reductions in daytime fatigue, and improvements in mood, ability to function at work/daily chores, concentration, and memory after use of the sleep patch.

Changes in Time to Fall Asleep and Duration of Sleep

The mean number of minutes that it took a person to fall asleep at baseline was 69.1 (SD 32.5), reducing to 47 minutes (SD 22.7) at day 7, and 36 minutes (SD 23.7) at day 14 while wearing the patch (Table 1). This correlates to study subjects falling asleep almost 50% faster while using the sleep patch. The mean actual number of hours a person slept at baseline, before the introduction of the sleep patch was 5.25 (SD 1.27), increasing to 6.04 hours (SD .94) after 7 days and 6.51 hours (SD .90) after 14 days (Table 2), representing an increase of 25% of sleep duration after 14 days of patch use.

Table 1:

| Statistic | Baseline | Day 7 | Day 14 |
|-----------|------------|------------|------------|
| Mean, SD | 69.1, 32.5 | 47.0, 22.7 | 36.6, 23.7 |
| Median | 60.0 | 45.0 | 30.0 |
| Min | 2.0 | 10.0 | 5.0 |
| Max | 210.0 | 150.0 | 180.0 |

- Each difference is statistically significant at $p < 0.001$
- "How long (in minutes) has it usually taken you to fall asleep each night?"
- N=113 for each of Baseline, Day 7 and Day 14, matched data

Table 2:

| Statistic | Baseline | Day 7 | Day 14 |
|-----------|------------|------------|------------|
| Mean, SD | 5.25, 1.27 | 6.04, 0.94 | 6.51, 0.90 |
| Median | 5.0 | 6.0 | 7.0 |
| Min | 3.0 | 4.0 | 4.0 |
| Max | 8.5 | 8.0 | 8.0 |

- Each difference is statistically significant at $p < 0.001$
- "How many hours of actual sleep did you get at night?"
- N=113 for each of Baseline, Day 7 and Day 14, matched data

Changes in Awakenings during Night

One of the PSQI questions asks the patient "How often have you had trouble sleeping because you wake up in the middle of the night or early morning?" At baseline, over 83% of study participants indicated that they had trouble sleeping at least once or twice a week (41.6%; n=47) or three or more times a week (41.6%; n=47) during the past month. After 7 days of incorporating the sleep patch, only 31% of subjects reported trouble sleeping and waking up either once or twice (n=21) or three or more times (n=14) during the past week, and after 14 days of using the sleep patch, only 22% of subjects reported trouble sleeping due to waking up either once or twice (n=13) or three or more times (n=12) during the past week (Table 3).

Table 3:

| Response | Baseline | Day 7 | Day 14 |
|----------------------------------|-----------|-----------|-----------|
| Not during the past month (week) | 5, 4.4% | 25, 22.1% | 50, 44.2% |
| Less than once a week | 14, 12.4% | 53, 46.9% | 38, 33.6% |
| Once or twice a week | 47, 41.6% | 21, 18.6% | 13, 11.5% |
| Three or more times a week | 47, 41.6% | 14, 12.4% | 12, 10.6% |

- "How often have you had trouble sleeping because you wake up in the middle of the night or early morning?"
- N=113 for each of Baseline, Day 7 and Day 14, matched data, n, %

Almost 70% (n=78) of subjects at Baseline indicated that they had trouble sleeping because they had to use the bathroom during the night at least once and up to three or more times per week. By day 14, after using the patch, only 15% (n=17) of subjects indicated that they had trouble sleeping due to getting up to use the bathroom at night. This is a reduction of 80% (Table 4).

Table 4:

| Response | Baseline | Day 7 | Day 14 |
|----------------------------------|-----------|-----------|-----------|
| Not during the past month (week) | 17, 15.0% | 42, 37.2% | 63, 55.8% |
| Less than once a week | 18, 15.9% | 43, 38.1% | 33, 29.2% |
| Once or twice a week | 43, 38.1% | 21, 18.6% | 12, 10.6% |
| Three or more times a week | 35, 31.0% | 7, 6.2% | 5, 4.4% |

- "How often have you had trouble sleeping because you have to get up to use the bathroom?"
- N=113 for each of Baseline, Day 7 and Day 14, matched data, n, %

Changes in Sleep Quality

At baseline, 78% of patients (n=88) indicated that during the month prior to using the sleep patch, they categorized their quality of sleep as either ‘fairly bad’ (49.6%; n=56) or ‘very bad’ (28.3%; n=22). Only after 7 days of patch use, 7 patients (6%) of patients indicated that their sleep was ‘very bad.’ After 14 days of patch use, this was further reduced to only 5 subjects indicating that their sleep was ‘very bad.’ In comparison, at baseline, only 22% of subjects indicated that they had ‘fairly good’ sleep in the month before patch use. After 14 days of using the active patch, over 80% of patients (n=91) indicated that they had either ‘fairly good’ or ‘very good’ sleep (Figure 1).

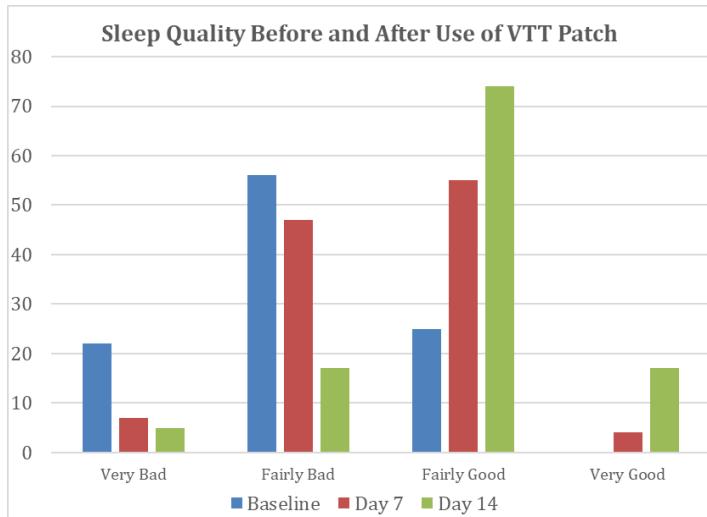


Figure 1: Changes From Baseline to Day 7 and Baseline to Day 14 in the Quality of Overall Sleep.

During the month prior to enrollment, over 56% of patients (n=63) indicated that they took either prescription or over-the-counter (OTC) medications to help them sleep at least once a week, with 57% (n=36) of those patients indicating that they took medications three or more times per week. After 7 days of patch use, only 12 patients (10.6%) indicated that they took medications once or more times per week to help them sleep, an 81% reduction. In addition, after 14 days of patch use, only 10 patients indicated that they took medications to help them sleep at least once a week, a reduction of 85% from baseline. Further, after 14 days of patch use, 80% of patients (n=90) indicated that they did not take any medication during the past week to help them sleep, compared to only 35% (n=40) at baseline.

Use and Preference of the Sleep Patch

Subjects were queried on specific satisfaction rating aspects regarding use of the sleep patch (scale: 0 = N/A, 1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree). At day 14, approximately 90% of patients ‘agreed’ or ‘strongly agreed’ that the patch was “easy to apply” (n=101) and “convenient” (n=100), and approximately 70% of patients ‘agreed’ or ‘strongly agreed’ that they “preferred the patch over pills and other oral medication” (n=76) and “preferred over other sleep-relieving treatments” (n=75).

Safety

Patients reported no serious adverse events while being treated with the sleep patch. There were 5 reports (5/113) of side effects including: lucid dreams (1), insomnia (1), itching (1), sleeplessness (1), and adhesive irritation (1).

Discussion

Here we report results of this HARMONI study, a prospective, non-randomized observational study evaluating the safety and efficacy of the REM Sleep Patch with VTT in patients presenting with sleep or insomnia-related symptoms. This analysis showed reductions in Global PSQI and ISI Severity scores and a preference for the patch over other sleep medications from baseline to day 7, and to day 14.

Over the past several years, research of haptic vibrotactile trigger technology (VTT) indicates that there are changes in EEG patterns for those patients exposed to VTT [23]. In addition, researchers have developed a deeper understanding of the multiple neural networks impacted by VTT and have developed related theories of how different brain regions interact with VTT [15,26,27]. The brain centers targeted by VTT have been shown to be responsive to external stimuli that incorporate the VTT technology and have produced positive outcomes in balance and stability measurements [28,29].

Ronald Melzack first proposed and hypothesized that networks of neurons communicating in “large loops”, or through continuous cyclical processing, connect specific regions of the brain with the PNS during sensory processing [15]. He envisioned 3 distinct looping pathways: 1) a traditional sensory pathway with neural projections routed through the thalamus, 2) one that follows a path through the brainstem and parts of the limbic system, and 3) one associated with pathways that are routed through different Brodmann Areas (BA), particularly the somatosensory cortex. These loops were meant to explain the cognitive, emotional, and motor modalities through which humans experience sensations [15,26].

The EEG mapping of the pain neuromatrix is corroborated with neuroimaging techniques such as functional analysis using magnetic resonance imaging (fMRI) in many experimental paradigms. The sensory patterns within the patches are in close symmetry between known EEG patterns and their role in modulating EEG and neuronal circuits within higher brain centers. [26].

There remains an unmet need for alternative treatment options for patients experiencing sleep-related symptoms and issues. Besides a recommendation of the non-pharmacological approach of Cognitive Behavioral Therapy (CBT) to address patients with sleep disorders, The American Academy of Sleep Medicine (AASM) has noted that non-prescription drugs such as over-the-counter antihistamine sleeping aids and herbal/nutritional agents were not recommended due to lack of demonstrated efficacy as well as safety concerns [14]. Many individuals experiencing sleep-related issues and symptoms use medications or substances (e.g. over-the-counter sleep aids or alcohol) which have not

been demonstrated to be effective in managing insomnia and sleep-related issues and/or have significant potential for harm. For clinicians, there remains a large gap of understanding for the estimated 3.5% to 7% of individuals receiving prescription medication for sleep disturbance [30-32] and about the proper usage of these agents. Risks and benefits must be weighed for each of currently prescribed medications for sleep issues, including those with diphenhydramine, doxylamine, melatonin, valerian or chamomile as the active ingredients. Potential life-threatening adverse effects, including links to increased heart risk, have been shown with current treatment approaches including those classified as sedative hypnotics [33]. They are much stronger than OTC options and have been linked to serious side effects including dizziness, nausea, hallucinations, depression and more [33]. There is also a concern that the use of various medications prescribed for sleep is especially concerning in older or elderly individuals as they may be at a higher risk for confusion, dizziness and falls [34]. The rate of use of sleep medications is high in elderly people due to an increase in sleep disorders with aging [35,36]. Careful selection of treatment for sleep disorders and related symptoms are needed and novel, non-pharmacologic and non-invasive therapies fulfill an unmet need for additional safe and effective treatment strategies and options for patients [34].

Limitations

This was a nonrandomized, observational study based on a sample of patients attending diverse clinical settings for the treatment of sleep- or insomnia-related symptoms who consented to participate in this study. This analysis reported on a group of 113 patients who were treated with the VTT embedded study patch.

The data of those patients who did not complete the follow up surveys after baseline, or patients who indicated that they did not use the patch after the baseline visit were removed from evaluation. Due to patients having different sleep symptoms and differences in how they report their sleep patterns and quality, overall generalization and consistency of results may be impacted due to the differences in sleep issues, the amount of time the patient utilized the patch, and subjective self-reporting by the patient. We have attempted to accurately evaluate and provide the most detailed reporting of the data while considering these limitations. Inclusion of control group and crossover group data in future analyses will assist in confirming the validity of these results due to the nonrandomized nature of this clinical trial.

Conclusion

Study results indicate that this non-pharmacologic, non-invasive, haptic vibrotactile trigger technology (VTT) embedded topical patch improves sleep quality, sleep duration, and quality-of-life components and may reduce the use of concurrent medications, including prescribed and other oral medication for adult patients with sleep or insomnia-related symptoms. Results reported suggest that the non-pharmacological topical sleep patch with VTT has incredible potential to be added to the current approaches and treatments of non-invasive and non-pharmacological sleep

therapies with minimal side effects. Further evaluation, including data from control and crossover groups are forthcoming and should support the use of this OTC sleep patch as a first-line non-pharmacological treatment option as part of a multimodal treatment approach.

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Disclosure

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