

The Effect of Vestibular Stimulation on Transient Insomnia Induced by a Five-Hour Phase Advance of Sleep Time

A comparative, randomized, placebo-controlled trial using the SleepWave Device

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Study objective: To evaluate the efficacy of one hour of continuous vestibular stimulation delivered with the SleepWave device (Philips Respironics, Murrysville, PA, USA) as a means of decreasing Latency to Persistent Sleep (LPS).

Study design: Two-arm, sham-controlled, randomized, double-blind, parallel group.

Setting: Seven standard sleep laboratories in the United States.¹

Participants: A total of 890 normal, healthy people with no sleep problems were consented and screened to acquire 282 completed participants with evaluable polysomnographic (PSG) data.

Measurements and results: A series of variables were compared between the SleepWave (active) and sham treated groups were assessed. Participants were thoroughly screened for eligibility via questionnaires, actigraphy and a 5-nap Multiple Sleep Latency Test (MSLT). Eligible participants (MSLT \geq 14 minutes) underwent an 8-hour PSG study in the laboratory, in which they were randomly assigned to an active or sham treatment with lights out 5 hours prior to their self-reported habitual bedtime (phase advance) to induce transient insomnia. A statistically significant treatment effect of 22.3 minutes ($p=0.0134$) in LPS was observed among evaluable cases for LPS.

Conclusion: These results suggest that the SleepWave device significantly reduces latency to persistent sleep by approximately 22 minutes as compared to the sham treatment in a phase advance model of insomnia.

Abbreviations: PSG (polysomnography), LPS (latency to persistent sleep), SOL (sleep onset latency), MSLT (multiple sleep latency test), TST (total sleep time)

Key words: Insomnia, vestibular stimulation, phase advance model.

Introduction

Insomnia / Transient insomnia

Current therapies for the treatment of insomnia include prescription and non-prescription (OTC) medications, behavioral therapy, and numerous other agents, such as herbal remedies or alcohol. The limitations of prescription and OTC medications include possible dependence, morning-after ‘hangover’ effects, increased risks of falls, associated costs, and limited effectiveness. The primary limitations of cognitive behavioral therapy is that it is not widely available. This approach involves multiple sessions to modify sleep habits, and often includes the avoidance of caffeine, smoking, alcohol, stress and other variables that may impact sleep. Notably, though alcohol initially appears to induce sleep, its use has been found to cause sleep disruption later in the night. Herbal and other remedies have limited scientific evidence demonstrating efficacy or safety. Thus, there is a need for new therapies.

This study was designed to investigate the effects of non-invasive electrical stimulation of the vestibular nerve in healthy adult participants whose sleep pattern was intentionally phase advanced to create a model of transient insomnia. This study design (Phase Advance – Transient Insomnia Model) has been used in pharmaceutical trials early in development in an attempt to assess the benefits on sleep of various medications.²⁻⁴

The vestibular system

The vestibular apparatus is an organ in the inner ear that detects sensations associated with motion/balance. The vestibular nerve is part of Cranial Nerve VIII, the vestibulo-cochlear nerve, enabling afferent and efferent signals to be transmitted to the brain. The vestibular apparatus, in conjunction with visual and proprioceptive inputs, is responsible for maintaining balance.

Vestibular activation during rapid eye movement (REM) sleep has been shown to increase eye movements and affect the architecture of sleep.⁵⁻⁷ Most of these studies induced rocking with a laterally swinging bed producing natural vestibular stimulation.⁸⁻¹⁰ This stimulus is a universally employed means of comforting children and inducing sleep. One study showed a significant decrease in the time to fall asleep on the second night of motion when compared to the first night of motion, as well as nights without motion. Results therefore suggest that stimulating the vestibular nerve may induce relaxation and sleep.

General description of the SleepWave device

The desired action of the SleepWave device is to provide non-invasive vestibular stimulation to aid with falling asleep. This sway or rocking sensation is artificially created by direct electrical stimulation of the vestibular nerve. The stimulation is delivered through two shielded hydrogel electrodes placed over the mastoid processes behind each ear (see Figure 1). Electromechanically, this device is similar to a Cranial Electrical Stimulation, or CES, device. This device is programmed to deliver a peak current from 100 – 1000 micro Amps at a frequency of 0.5 Hertz.

Study methods

The primary objective was to determine if the SleepWave device could reduce the Latency to Persistent Sleep (LPS) – time to fall asleep and stay asleep for 10 minutes (20 consecutive 30-second epochs) – in a model of transient insomnia as measured on full polysomnography (PSG) – using 1 hour of continuous stimulation as compared to a sham treatment.

The secondary objectives were to evaluate the effect of the SleepWave device using the approach described above on other standard PSG sleep variables.

Candidates were screened via a telephone screening script that contained general information on sleep and health. Verbal assent was obtained. Participants who met the initial criteria for participation were scheduled for up to three visits to the sleep laboratory. Following signed consent at the first visit, participants underwent a urine drug screen and a breathalyzer alcohol test to rule out recreational drug use or use of medications known to affect sleep. A urine or serum pregnancy test was performed on females of child-bearing potential.

In addition, at the first visit, participants completed a general medical evaluation that included a general health history, psychiatric history, and sleep history. Participants completed the Epworth Sleepiness Scale to rule out excessive daytime sleepiness (cutoff of 10) and the Insomnia Severity Index to rule out insomnia (score less than 7). Qualifying participants were instructed to complete a daily sleep diary and wear an actigraph device (Actiwatch, MiniMitter; Bend, Oregon) for 3-5 days to monitor sleep / wake behavior. In order to qualify for the second visit, candidates were required to average a 7.5-9 hour sleep opportunity during this period.

At the second visit, those continuing to qualify underwent an MSLT evaluation¹¹⁻¹³ in order to exclude participants with residual sleep debt or pathological hypersomnolence. Participants who had a mean sleep onset latency (SOL) ≥ 14 minutes across 5 naps met this criterion and were randomized to receive either an active or sham SleepWave device. At the end of Visit 2, participants were titrated with the assigned device. For the active device, the therapeutic setting ranged from Level 1 – 10, corresponding to 100 μ A - 1000 μ A. Those in the sham group received a device identical in appearance, but functionally, it provided no therapy. After establishing the proper device setting for comfort and efficacy, the actigraphy device and sleep diaries were again distributed. During the next 7-9 days, participants were required to complete the sleep diary and wear the actigraphy device while having 9 hours sleep opportunity nightly. In order to qualify for Visit 3, participants were required to allow themselves an average of 8.5 - 9.5 hour sleep opportunity the last three nights preceding the visit.

At the third visit, qualifying participants reported to the sleep laboratory and went to bed 5 hours prior to the habitual bedtime they reported on the sleep diary and underwent an 8-hour polysomnography (PSG) sleep study. Participants were set up with their assigned SleepWave device at their titrated setting, and those in the active group received one hour of continuous active therapy that started when the lights were turned off. Thirty minutes after the conclusion of the 8 hour sleep period, participants completed a Post-Sleep Questionnaire regarding their experience with the device and overall sleep satisfaction.

Summary of results

Among the 890 participants who consented, 349 were randomized to receive either active or sham treatment. Among the randomized participants, 57 did not qualify for the study because they did not meet actigraphy criteria. The remaining 292 completed the phase-advance treatment PSG, but 10 PSGs were unevaluable because of technical errors, resulting in a total of 282 evaluable PSGs. Demographic data were balanced between the two treatment groups.

Data analysis

Primary endpoint: Latency to Persistent Sleep (LPS)

A highly statistically significant ($p=0.0121$) site by treatment interaction effect was observed. Subjects at site 6 ($n=40$) exhibited a numerical advantage for the sham treatment while subjects at all other sites showed a numerical advantage for SleepWave. As statistically indicated by this finding, site 6 was excluded from further data analysis.

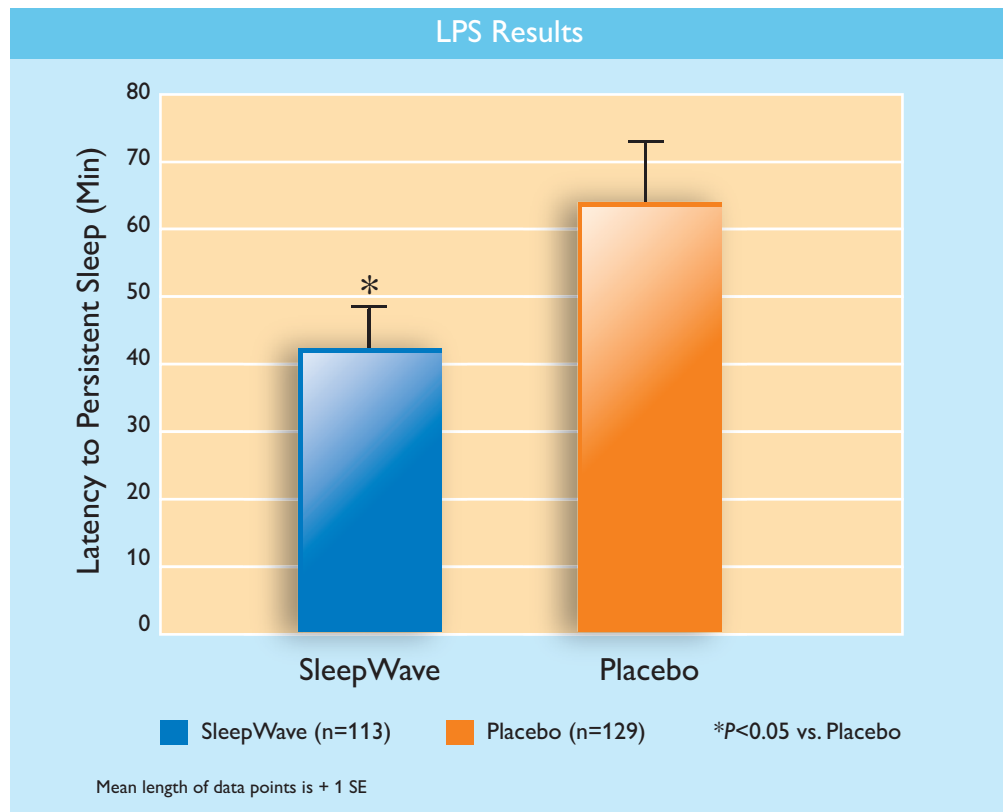


Figure 1

Figure 1 shows the LPS results by actual treatment. The average LPS for sham was 64.9 (\pm SE) versus 42.6 (\pm SE) for active. A statistically significant treatment effect of 22.3 minutes ($p=0.0134$) was observed among evaluable cases for LPS.

Secondary endpoints

Analysis of the secondary endpoints did not demonstrate statistically significant differences between the treatment groups.

Adverse events

Adverse events were captured throughout the study and thoroughly analyzed. It should be noted that there were no reports of any Serious Adverse Events (SAEs) during this trial. Of the 349 randomized participants, 55 (15.8%) reported one or more adverse events. The incidence of reported AEs was 17.3% (30/173) in the sham group and 14.2% (25/176) in the SleepWave group. When this is further subdivided by the events' relation to the study, 53.3% of the AEs reported by the sham participants were reported as having at least some possible relation to the

study, while 68% of the AEs reported by the SleepWave participants were considered to be at least possibly related. The most common AEs reported were skin irritation (1% sham, 3% active), nausea (1% sham, 1% active), and transient headache (2% sham, 4% active).

Conclusion

In this study, the SleepWave device significantly reduced latency to persistent sleep (LPS) by 22.3 minutes ($p=0.0134$) as compared to the sham treatment without any significant adverse events. These results suggest that the SleepWave device may be an effective therapeutic treatment for insomnia.



Figure 2: SleepWave unit

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KB 03/12/10 MCI 4103346