NEW RESEARCH

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The Effect of Vestibular Stimulation in a Four-Hour Sleep Phase Advance Model of Transient Insomnia

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SCIENTIFIC INVESTIGATIONS

Study Objectives: To determine if vestibular stimulation is an effective therapy for transient insomnia in a sleep phase advance model.

Design: Multi-site, double-blind, randomized, parallel-group, sham-controlled trial

Setting: This study was carried out at 6 sites in the United States.

Participants: 198 healthy normal sleepers.

Interventions: Bilateral electrical stimulation of the vestibular apparatus of the inner ear via electrodes on the skin of the mastoid process at a frequency of 0.5 Hz vs. sham stimulation

Results: We did not find a significant effect of treatment on our primary outcome variable, latency to persistent sleep onset (LPS). However, our planned analysis identified that the mean latency to sleep onset on the multiple sleep latency test was a significant covariate. This led us to carry out post hoc analyses, which showed a significant effect of treatment on LPS in those subjects with a mean MSLT sleep onset latency ≥ 14 minutes.

Conclusions: Vestibular stimulation did not have a therapeutic effect in a model of transient insomnia in the overall population studied. However, this study provides preliminary evidence that vestibular stimulation may shorten sleep onset latency compared with sham therapy in the subset of subjects with mean MSLT sleep onset latency ≥ 14 minutes.

Keywords: Transient insomnia, vestibular stimulation, sleep phase advance

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The majority of individuals with problems sleeping at night have transient sleep difficulty which occurs in the setting of stress, medication/substance effects, a shift in sleep phase, environmental disturbances, or acute medical or psychiatric conditions.[1,2] Recent evidence suggests that the tendency to develop disturbed sleep in response to such events is a "trait-like" characteristic which remains stable over time in individuals across different types of stressors.[2-4] Further, recent studies suggest that this tendency to develop disturbed sleep in response to stressors has a genetic basis.[3,4]

While there have been a number of studies of the pharmacologic management of transient insomnia,[5-7] little data exist supporting the use of non-medication therapies in this setting. Such treatments may be preferable for some patients due to personal preferences, medication side-effects, or long-term cost considerations. Here we explore the utility of vestibular stimulation as a potential therapy for transient insomnia in a sleep phase advance model that has been employed in several prior studies of transient insomnia (simulating eastward travel).[5-7]

We examined vestibular stimulation as a treatment because a series of studies suggest links between the vestibular system and sleep. These include physiological evidence that the vestibular system can affect REM sleep,[8-13] that there is influence of labyrinthine inputs on the pontine reticular formation neurons involved in mediating switching between sleep states,[14,15] and that the medial vestibular nucleus has projections to regions mediating arousal and some aspects of sleep which receive orexinergic inputs from the lateral hypothalamus.[15]

The sensation of rocking, which is created by electrical stimulation of the vestibular system also has the potential to have a therapeutic effect on sleep. Physical rocking is used to induce sleep in infants and has been found to improve sleep in individuals with neuromuscular breathing problems.[16] Sleeping on

BRIEF SUMMARY

Current Knowledge/Study Rationale: The majority of individuals with problems sleeping at night have transient sleep difficulty which occurs in the setting of stress, medication/substance effects, a shift in sleep phase, environmental disturbances, or acute medical or psychiatric conditions. We examined vestibular stimulation in a phase advance model of transient insomnia. based on a series of studies suggesting: 1) links between the vestibular system and sleep; and 2) that the sensation of rocking, which is created by electrical stimulation of the vestibular system, has the potential to promote sleep.

Study Impact: This study provides preliminary evidence that vestibular stimulation may shorten sleep onset latency in a phase advance model of transient insomnia compared with sham therapy in the subset of subjects with mean MSLT sleep onset latency ≥ 14 minutes. Further studies will be needed to determine the potential role of vestibular stimulation in the treatment of transient insomnia.

a lateral swinging bed has been shown to be generally relaxing and to reduce sleep latency significantly, without adversely affecting the sleep of normal subjects.[17]

To assess the potential for a therapeutic effect on sleep latency, we undertook this double-blind, sham–therapy-controlled, randomized study of the effects of nocturnal vestibular electrical stimulation in the treatment of normal sleepers undergoing a 4-h phase advance as a model of transient insomnia.

METHODS

Study Design

This study was a double-blind randomized, sham-controlled study comparing 1 night of 1 hour of continuous vestibular stimulation vs sham stimulation at lights out on polysomnographic (PSG) latency to persistent sleep in a 4-h phase advance protocol in normal sleepers. This study was carried out in accord with the Declaration of Helsinki at 6 sites in the United States. Each site received approval of the protocol by their institutional review board (IRB) or a central IRB, and all subjects gave informed consent prior to participation. Subjects were recruited from clinic populations and local media advertisement.

Subjects were initially screened by the study coordinators and study physicians to determine if they met entry criteria (see below) via history and physical examination. Qualifying subjects underwent 7 days of actigraphy to verify a regular sleep pattern. A standard polysomnography (PSG) to rule out obstructive sleep apnea (OSA) and other sleep disorders was then performed. Those who continued to meet all criteria for participation then completed a 5-nap multiple sleep latency test (MSLT). Those continuing to qualify as determined by a mean SOL ≥ 8 min on MSLT underwent polysomnography (PSG) on 2 consecutive nights. On the first night, subjects went to bed at their usual bedtime and were recorded for 8 h. Following the baseline PSG night, the subject's bedtime was phase advanced 4 h prior to their usual bedtime, and they were randomized to receive either a sham treatment or vestibular stimulation for the first hour of the night. Sham devices were applied and operated exactly like active devices, except they delivered no current. PSG data were collected for 8 h in all subjects on the phase advance night. PSG data were scored according to standard criteria.[18]

Subjects

Entry criteria for this study consisted of: (1) age 21-60 years (inclusive); (2) ability and willingness to provide written informed consent; (3) reported habitual bedtime that varied by no more than 1 hour and fell between 21:00 and 01:00 ≥ 5 nights per week; (4) reported habitual nightly sleep duration of 6.5 to 8.5 h; and (5) confirmation of habitual bedtime and sleep duration by 7–14 days of actigraphic monitoring.

The key exclusion criteria were: (1) participation in a study of investigational or marketed drugs or devices during the 30-day period before the start of the study or during the study; (2) clinically important medical or psychiatric condition; (3) current sleep disorder; (4) positive urine drug screen at any visit prior to randomization; (5) positive alcohol saliva test at any visit prior to randomization; (6) history of current or recent (within past 5 years) alcohol, narcotic, or any other drug abuse or dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, 4th Edition (DSM-IV);[19] (7) working night or rotating shift; (8) travel or planned travel across > 2 time zones within one week prior to randomization; (9) use of any medication that, in the opinion of the investigator, might alter sleep or wakefulness; (10) mean screening MSLT nap latency < 8 min across 5 naps, or a sleep onset REM period on any MSLT nap; (11) sleep efficiency > 94% per screening PSG; (12) apnea/hypopnea index ≥ 10/h, or a periodic limb movement with arousal index ≥ 10/h on the screening PSG; (13) consumption of > 14 alcoholic drinks per week, or recent consumption of > 4 alcoholic drinks in one night; (14) typical consumption > 5 caffeinated beverages per day; (15) smoking > 5 cigarettes per day; (16) pregnancy as determined by serum pregnancy test; or (17) presence of a pacemaker.

Vestibular Stimulation Procedure

Vestibular stimulation was carried out with transcutaneous electrical nerve stimulation (TENS)-type hydrogel electrodes that were positioned over the mastoid process and delivered bilateral stimulation current through the skin to the vestibular apparatus of the inner ear. Electrical stimulation occurred with a peak current from 100–500 μA, at a frequency of 0.5 Hz. Stimulus intensity was determined using a double-blind titration procedure. Subjects randomized to the active treatment were titrated to 1 of 5 electrical stimulus settings between 100 and 500 μA, while subjects randomized to sham treatment were titrated to 1 of 5 sham settings. Neither the individual carrying out the titration nor the subject knew whether the titration was being carried out with an active or sham device. All communication to the subject during the titration was carried out using a script to prevent unblinding. After affixing the stimulus electrodes the following statement was read to the subjects: "At this point I will need you to lie down on this bed and relax, but don't fall asleep at any time throughout this process. Please close your eyes throughout the test. You may open your eyes briefly if you need to. We'll have you lie on your back for a few minutes to get used to the attachments and then we will begin the titration process. We will present the therapy at different settings and ask you questions at the end of each test period. We may go through up to 5 settings in this session. You may or may not feel anything during this process. People who have tried this device previously have indicated various responses. You should not expect to feel abrupt changes as we go from setting-to setting. We are recording peoples' responses to therapy that may or may not have any sensations associated with them. Some therapy treatments are perceivable and others are not. You will experience each setting for approximately 2 minutes. At each step, we will ask you if you feel any sensation that you would consider not comfortable for falling asleep. As long as you are comfortable, we would like to continue with the titration. If at any time you wish to stop the therapy for any reason, please let us know and we will stop."

Titration began with the administration of 2 minutes of stimulation (or sham stimulation) at the lowest level. After completing each stimulation level, subjects were asked: "Please describe any sensations you felt during the last 2 minutes of therapy. If you felt no sensations, please say "No sensations." They were then asked: "are you comfortable enough with the device for falling asleep?" If they answered "yes"

Table 1—Reported sensations for all subjects

Sensations as a Function of Stimulus Level	Sham n/N (%)	Active n/N (%)	p-value
VSOM Setting			
1	0/97 (0.00)	3/101 (2.97)	0.0033*
2	6/97 (6.19)	10/101 (9.90)	
3	3/97 (3.09)	5/101 (4.95)	
4	4/97 (4.12)	17/101 (16.83)	
5	84/97 (86.60)	66/101 (65.35)	
Sensation Type			
***Pins and needles , warmth, itching or burning, tingling or prickling	10/97 (10.31)	35/101 (34.65)	< 0.0001**
***Floating, rocking, dizziness, or comments of sway, boat, ship, shifting from foot to foot, spinning, platform feels uneven or platform moving	10/97 (10.31)	45/101 (44.55)	< 0.0001**

*One-sided χ^2 test; **One-sided Fisher exact test; ***Identified by bubble (list) check-off on CRF or comments

and they were amenable to a trial of an increased stimulus intensity, titration was continued at the next higher stimulation level. The titration procedure ended when: (1) subjects answered "no," in which case the level below the one that made them uncomfortable was used for the treatment night; or (2) the highest level was reached and was comfortable for the subject, in which case the highest level was used for the treatment night. Vestibular stimulation occurred continuously for 1 hour, commencing with lights out on the night of the sleep phase advance.

Subjects reported the following sensations during titration or on treatment nights, including skin sensations—pins and needles, warmth, itching or burning, tingling, or prickling; sway sensations of floating, rocking, and dizzy or comments of sway, wave, boat, ship, shifting from foot to foot, spinning, platform feels uneven, and platform moving. Proportions and titration / therapy settings are indicated in **Table 1**.

Table 2—Baseline variables for all subjects* (ITT)

Variable	Sham Mean (SD) n/N (%)	Active Mean (SD) n/N (%)
	97/198 (48.98)	101/198 (51.01)
Age	33.42 (10.91)	33.99 (10.41)
BMI	24.87 (5.38)	25.65 (4.69)
Actigraphy shortest sleep time	402.29 (47.97)	403.60 (23.25)
Actigraphy longest sleep time	458.29 (53.75)	461.57 (27.69)
Mean sleep onset latency on MSLT	15.50 (3.16)	15.51 (3.61)
	N = 97 n (%)	N = 101 n (%)
Gender (Male)	37 (38.14)	28 (27.72)
Race (Caucasian)	60 (61.86)	65 (64.36)

*None of the variables listed in this table were statisically significant in the active and sham groups.

Measures

The primary outcome measure was polysomnographic latency to persistent sleep (LPS, defined as the time from lights off to the first 20 consecutive epochs of any stage of sleep). This measure was chosen as the primary outcome measure because of its frequent use as the primary objective sleep onset measure in placebo-controlled trials of insomnia therapies.[20-24] Secondary outcome measures included polysomnographic sleep onset latency (SOL, defined as the time from lights off to the first 3 consecutive epochs of any stage of sleep, or one epoch for stage 2–4 sleep), total sleep time (TST), sleep efficiency (SE), and slow wave sleep (SWS) during each quartile of the night; number of awakenings; wake after sleep onset (WASO); minutes in each sleep stage (1, 2, 3-4 NREM, and REM); and subjective ratings of sleep latency, total sleep time, sleep quality, number of awakenings, quality of sleep, and level of alertness upon the morning awakening (i.e., refreshed). Adverse effects were recorded throughout the study and rated as to severity and likelihood of being related to treatment.

Analyses

The data were assessed for normality. LPS was found to be non-normally distributed; as a result, it was logarithmically transformed for analysis. For continuous variables univariate testing was done with the Wilcoxon Rank Sum Test. Multivariate statistical tests were carried out using the mixed models procedure of SAS version 9.1. Thirty-one potential covariates were screened for possible inclusion in the competition for the final model by a method similar to that of Hosmer and Lemeshow for logistic regression.[25] Variables were placed in models one at a time with treatment and the variable by treatment interaction. If the variable or its interaction with treatment had a p-value ≤ 0.02 from this model, the variable (or the variable with its interaction if interaction p-value was < 0.2) was entered into the final model.

The final model was obtained by manual backward elimination, in which at each step, the variable or interaction with the highest p-value was removed from the model, and the model was refit. Under the hierarchical interaction rule, a covariate could not be removed until its interaction with treatment was removed.

In order to further assess the effects of vestibular stimulation on sleep onset, survival analysis was also carried out. This analysis compared the percentage of subjects awake as a function of LPS in the active and sham treatment groups.

The p-value required for statistical significance was 0.0427, to account for 2 interim analyses at one-half and three-quarters of the subjects completed.[26] With the exception of the post hoc analysis, all analyses were carried out with the intent-to-treat (ITT) population.

Table 3—Final multivariate mixed model for LPS (ITT)

Factor	Numerator *df*	Denominator *df*	*F*-statistic	p-value (2-sided)	*t*-statistic	p-value (1-Sided)*
Treatment	1	191	0.36	0.55	0.60	0.27
Base night LPS	1	191	10.15	0.0017		
Mean SOL on MSLT**	1	191	7.99	0.0052		

*Superiority hypotheses are one-sided, and the p-value for the *t*-statistic is the relevant value for the primary and secondary analyses; **Mean SOL cut-off (< 14, ≥ 14)

Table 4—PSG values for baseline and treatment night by treatment (ITT)

	Baseline Night		Treatment Night	
PSG Variable	Sham, Mean (SD)	Active, Mean (SD)	Sham, Mean (SD)	Active, Mean (SD)
LPS*	15.18 (2.53)	13.46 (2.53)	24.05 (2.77)	21.32 (2.41)
REM latency (min)	94.66 (45.03)	88.97 (33.89)	121.94 (81.28)	106.80 (66.90)
REM (min)	85.71 (25.32)	85.83 (22.35)	58.29 (25.24)	62.02 (21.42)
SE (%)	86.26 (7.85)	86.45 (8.83)	74.36 (15.13)	74.52 (13.71)
Time in bed (min)	459.95 (19.32)	462.26 (22.23)	436.87 (65.26)	448.32 (44.53)
SWS (min)	31.38 (26.74)	25.02 (26.93)	31.83 (28.19)	26.09 (25.47)
TIB (min)	478.49 (8.38)	478.54 (14.61)	475.62 (36.63)	480.16 (4.15)
TST (min)	412.71 (37.95)	413.66 (44.30)	355.34 (78.23)	357.82 (65.97)
S1 (min)	32.39 (15.57)	35.45 (18.93)	26.99 (13.71)	28.96 (15.19)
S2 (min)	263.16 (39.22)	267.20 (37.42)	238.22 (57.63)	240.70 (49.74)
S3 (min)	24.96 (18.35)	19.92 (18.30)	24.96 (18.71)	20.96 (17.81)
S4 (min)	6.42 (12.87)	5.10 (12.07)	6.87 (13.10)	5.13 (11.82)
WASO (min)	47.24 (31.63)	48.60 (36.34)	81.53 (64.11)	90.50 (63.25)

*Natural logarithm of LPS used in analysis due to skewness of distribution of LPS; LPS refers to latency to persistent sleep (the time from lights out until 10 min of continuous sleep occurs)

RESULTS

Subjects

One hundred ninety-eight subjects were randomized. This included 101 who received vestibular stimulation and 97 randomized to sham stimulation. The baseline data for these subjects appear in **Table 2**; there were no statistically significantly differences between the groups. Fourteen subjects were excluded from the analysis because of interrupted therapy, not meeting criterion for persistent sleep onset prior to the end of the polysomnogram (PSG) (occurred in one active treatment group subject), or because of an incomplete PSG. In addition, 11 subjects received the wrong therapy; however, in the ITT analyses, data for these subjects were imputed and included in their originally designated group.

Polysomnographic Sleep Effects

Whereas, the test subjects experienced a shorter LPS than did the controls, the group difference was not statistically significant as assessed with the Wilcoxon Rank Sum Test (mean active treatment subjects 33.47 min [SD 42.64]; mean sham subjects: 42.05 min [SD 53.06]). A multivariate analysis employing the mixed models procedure was done with screening for covariates as described above. Among potential covariates, those that qualified for entry into the mixed effects model were: baseline night sleep onset latency ($p < 0.0007$), mean MSLT nap sleep onset latency ($p < 0.0001$), as well as dichotomous variables, defined by whether the mean MSLT nap onset latency exceeded 12 ($p < 0.03$), 13 ($p < 0.02$), 14 ($p < 0.002$), or 15 ($p < 0.0003$) minutes. The direction of these effects were such that shorter baseline sleep onset latency and shorter MSLT nap sleep onset latency were associated with shorter latency to persistent sleep on the night of double-blind treatment. These covariates were allowed to remain in the model if the p-value was ≤ 0.05. The resulting model, including treatment, baseline night LPS, and the dichotomous MSLT mean sleep onset latency variable (defined by a threshold of 14 min), did not indicate a significant overall treatment effect (See **Table 3**). In this regard, it is important to note that the interaction between MSLT and treatment was statistically significant when MSLT was taken as a continuous covariate ($p = 0.02$). When the continuous covariate (MSLT) was dichotomized into sub-groups cut at 14 min, the interaction term was not significant. Thus there is evidence of an interaction with MSLT that is weakened when the data are made categorical. Results for the other polysomnographic variables appear in **Table 4**. No significant differences were found on any of these measures. There was no effect of treatment stimulus level on LPS.

Post hoc Analysis of Significant MSLT Effect

Based on the finding that MSLT sleep onset latency was significantly related to LPS on the treatment night, we carried out an exploratory post hoc analysis in the as-treated population to determine if there was an MSLT-related subgroup effect that

might be useful for providing a further understanding of the data and for guiding future research. We explored whether there was a subgroup of subjects with relatively short MSLT onset latency who fell asleep relatively sooner on the night of double-blind treatment, independently of whether they received active or sham therapy, thereby diminishing the observed overall treatment effect. To explore for this possibility, we once again carried out a multivariate mixed model analysis of LPS in the sham and active groups, but this time included only subjects with a mean MSLT sleep onset latency ≥ 14 min (N = 127; Sham = 68; Active = 59). This was the MSLT nap sleep onset latency threshold associated with the dichotomous variable that qualified for inclusion in our mixed effects model. The results indicate that when the subgroup of subjects with a mean MSLT nap latency < 14 min were excluded, there was a significant effect for those receiving vestibular stimulation to have shorter LPS than sham treated subjects ($t = 1.98$; $p < 0.03$).

Survival Analysis

Survival analysis comparing the percentage of subjects awake as a function of LPS did not identify a significant difference between active and sham treated subjects ($p < 0.08$). However, in the subgroup of subjects with mean MSLT nap latency ≥ 14 min, the survival curves were significantly different ($p < 0.0423$). These survival curves, which appear in **Figure 1**, diverge at an LPS of approximately 30 min. For LPS ≥ 30 min, a greater percentage of active treatment subjects were asleep than sham treated subjects. The analysis of survival curves between the 2 groups showing statistical significance relates to the entire curve, not to just one point. Choosing the median as a convention is often done, but is arbitrary. The deviation in the curves occurs beyond 30 min, and the description is intended to explain where the significant effect occurs.

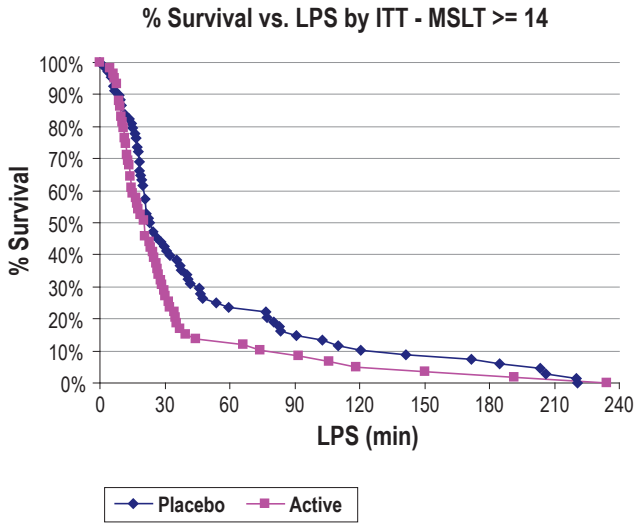
Self-Reported Sleep Measures

There were no significant differences between treatment groups on self-reported global difficulty falling asleep; however, there was a trend for subjects treated with vestibular stimulation to report shorter sleep onset latency on the treatment night (mean 44.2; SD 43.7) vs. sham treated subjects (mean 60.7; SD 65.9) (F 3.3; $p < 0.08$). This difference was not significant in the subset of subjects with MSLT nap latency ≥ 14 min. There was also no evidence for differences between the treatment groups for subjective ratings of total sleep time, sleep quality, waking up at night, global quality of sleep, and level of morning restedness.

Safety

Vestibular stimulation was generally well tolerated. Adverse events occurred in 17 (16.8%) of active treatment subjects vs. 6 (6.2%) of sham-treated subjects. In the active group the most common side-effect of treatment was headache, which occurred in 12 subjects (11.9%); while dizziness, the second most common side-effect, was reported by 3 (3%) subjects. No other adverse effect was reported by more than one subject. Headache was reported by 5 (5%) of sham treatment subjects and was the only adverse effect occurring in more than one individual in this group. Twelve of the 17 adverse events occurring in the active group were rated by the investigator as mild in severity, 4 were felt to be of moderate severity, and one was rated as severe (dizziness/ nausea). In the sham group, 4 of the 6 noted adverse events were rated as mild; the other 2 were rated as moderate in severity. All adverse events resolved spontaneously or with the use of over-the-counter analgesic medication for headache (one in each group). No serious or unanticipated device related effects were reported throughout this study.

Figure 1—Survival (percent awake) as a function of LPS in those with average nap latency ≥ 14 minutes in the intent-to-treat population



DISCUSSION

In this study we did not find a significant effect of treatment with vestibular stimulation over sham therapy on our primary outcome variable, LPS, in the planned analysis. As a result, we must conclude that vestibular stimulation was not an effective treatment in this investigation. The fact that our planned analysis identified that mean MSLT nap sleep onset latency was a significant covariate led us to carry out exploratory post hoc analyses to determine if the lack of a significant overall treatment effect might have been due to the presence of a subgroup of subjects who fell asleep relatively sooner on the treatment night in both treatment groups. We determined that this was indeed the case, in that we found that, among those subjects who were particularly reactive to our experimental phase advance (i.e. those having a baseline MSLT ≥ 14 minutes), vestibular stimulation was significantly more effective than sham treatment for reducing LPS. Thus, post hoc analysis provides a preliminary indication that vestibular stimulation might shorten sleep latency compared with sham stimulation only in the subset of subjects with a baseline MSLT nap latency ≥ 14 minutes.

This analysis also suggests that the MSLT entry criterion used in this study, (average nap sleep onset latency of ≥ 8 min) led to the inclusion of a subgroup of individuals who, contrary to our intent, were able to fall asleep quickly regardless of circadian phase, which outweighed the effects of vestibular stimulation therapy in the 4-hour phase advance model. Whether the use of a threshold of an MSLT nap onset latency ≥ 14 minutes

will serve as the best marker for selecting those who have difficulties falling asleep at an adverse circadian phase or when stressed is unclear. However, it seems logical that individuals with a short sleep onset latency on MSLT are not likely to have difficulty falling asleep. Thus, they would not likely be candidates for the use of a device such as was tested in this protocol. In clinical practice, where the MSLT is generally not performed for patients presenting with insomnia, these data would suggest that vestibular stimulation is most likely to be of utility in the subset of patients who have trouble sleeping throughout the day.

We carried out our post hoc analysis with an MSLT sleep onset latency threshold ≥ 14 minutes because the dichotomous variable using this cutoff met our a priori criterion for inclusion in the planned mixed effects model. However, significant effects were found with dichotomous variables derived from mean MSLT sleep onset latency using cutoffs of 12-15 minutes, and there is no established threshold for identifying individuals who are likely to have difficulties sleeping at an adverse circadian phase or when under stress.

Vestibular stimulation was associated with a trend for shorter self-reported sleep onset latency vs. sham. While the difference between sham and placebo groups was larger for self-reported sleep latency than PSG-defined sleep latency (16 vs 2.7 min), the variability of self-reported sleep latency was substantially greater, resulting in a smaller effect size for self-reported onset latency. In this regard, it is important to note that this study was not powered to detect an effect on self-reported sleep onset. An effect on self-reported sleep onset, however, will be necessary for vestibular stimulation to be of clinical utility. A relatively smaller effect on self-reported sleep onset latency could limit the clinical potential of this therapy. A determination of whether this is the case will require further studies. No effects of treatment on global ratings of difficulty falling asleep or any of the other self-reported measures of sleep were found. These findings are consistent with the absence of a significant overall effect on LPS.

The mechanism of the effect of vestibular stimulation in the subjects with an MSLT sleep onset latency ≥ 14 minutes in this study remains unclear. However, it seems possible that vestibular stimulation might effect sleep via the established physiological connections between the vestibular system and sleep systems.[8-15]

This study provides evidence that vestibular stimulation is associated with an excellent safety profile. The only adverse effects occurring in more than one individual that received vestibular stimulation were headache and dizziness. Though, because these adverse effects occurred more frequently in active than sham subjects, it cannot be ruled out that un-blinding of the active treatment occurred to some degree. In all cases, the adverse effects of vestibular stimulation were transient and only one subject had an adverse event that was rated as severe (dizziness/nausea). No serious or unanticipated device related effects were reported throughout this study.

In summary, vestibular stimulation did not have a major therapeutic effect in a 4-hour phase advance model of transient insomnia in the overall population studied. However, in post hoc analysis we found that vestibular stimulation may shorten sleep onset latency compared with sham therapy in the subset of subjects with mean sleep onset latency ≥ 14 minutes. The need for the development of non-pharmacological treatments for transient insomnia, the preliminary evidence of a therapeutic effect in a subset of the population in a model of transient insomnia, and the excellent safety profile of this intervention support further studies of the potential of vestibular stimulation as a treatment for transient insomnia.

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