NIGHTWARE CLINICAL INFORMATION

NightWare Description and Indication

NightWare is a digital therapeutic system that temporarily reduces sleep disturbance related to nightmares. NightWare provides customized medical treatment for dysfunctional nightmares and is the only FDA-cleared treatment for this disorder.

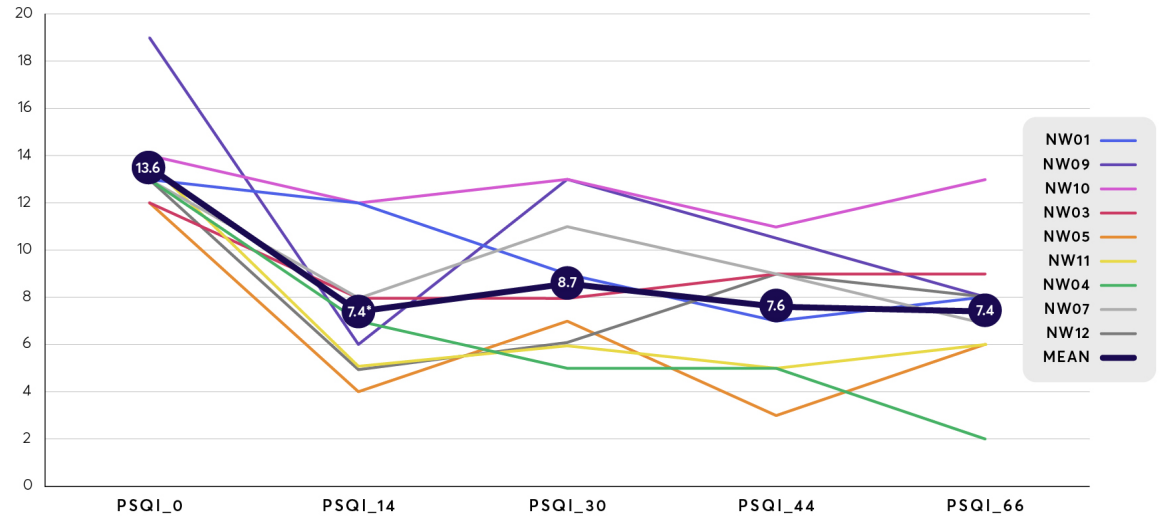
The NightWare digital therapeutic is indicated to provide vibrotactile feedback on an Apple Watch based on an analysis of heart rate and motion during sleep for the temporary reduction of sleep disturbance related to nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). It is intended for home use.

NightWare Clinical Validity

In a single-arm open-label pilot study of NightWare in 9 subjects[1] to explore the effects of NightWare on sleep quality, there was a large effect size of a 6-point improvement in the Pittsburgh Sleep Quality Index (PSQI), a well-validated measure of sleep quality [Figure A].[2, 3] The Patient Health Questionnaire 9 (PHQ-9), a standard questionnaire to measure the severity of depressive symptoms, demonstrated a 6-point improvement [Figure B]. The large effect size for these measures was considered impressive and suggested tangible improvement in sleep quality for patients with frequent nightmares. Importantly, these improvements in sleep quality and depressive symptoms were quickly realized; the improvements were seen within just two weeks of use. No safety concerns were noted in this trial. Based on these results, a large controlled trial was implemented.

FIGURE A

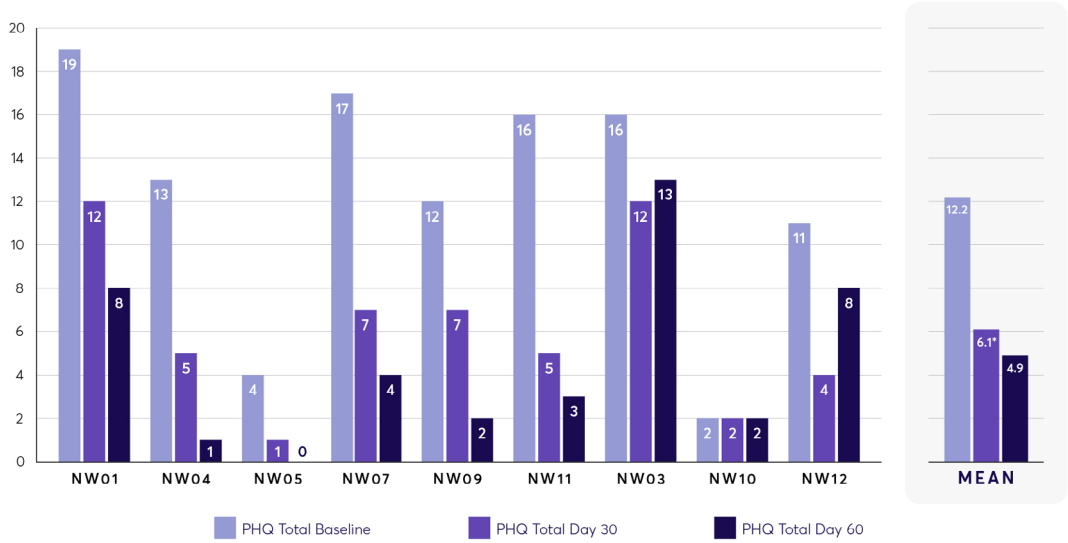
Total PSQI at Biweekly Assessments



*While there was a 3.2 range in the PSQI for NightWare and the Sham was 2.2, there was no statistical significance between the two. The PSQI-A was also not statistically significant.

FIGURE B

Total PHQ-9 at Monthly Assessments



*While there was a 3.2 range in the PSQI for NightWare and the Sham was 2.2, there was no statistical significance between the two. The PSQI-A was also not statistically significant.

Currently, a double-blind, sham-controlled, randomized controlled trial of NightWare is ongoing. This is a 30-day trial with a plan for 180 subjects; currently 70 subjects are enrolled. The inclusion criteria include patients with significant sleep disturbance (a baseline PSQI of 10 or more), repetitive disturbing nightmares, and a PTSD diagnosis. Patients with dream-enacting behavior, DAST-10 score greater than 2 or AUDIT score greater than or equal to 8, and severe depression are excluded. All patients have to be off of prazosin for at least two weeks prior to starting the trial. The primary efficacy measure is a change in the average PSQI score from baseline at the 30-day point in the study. The interim results are shown below. Safety data from this trial shows that NightWare is safe to use. Thus far in the study, there have not been any adverse events attributable to the use of NightWare.

TABLE 1

Mean (SD) Change Between Baseline and Primary Outcome

Visit at 30 Days for Each Outcome Measure by Study Arm.

Baseline Outcome Measure		NightWare (n = 29)	Sham (n = 34)	p-value
PSQI	Pittsburgh Sleep Quality Index	-3.2 (3.7)	-2.2 (2.9)	0.2606
PHQ-9	Patient Health Questionnaire-9	-2 (3.7)	-1 (3.8)	0.2719
PCL	PTSD Checklist	-9.9 (13.4)	-6.5 (9.9)	0.2727
ESS	Epworth Sleepiness Scale	-1.2 (4.1)	-1.2 (3.1)	0.9739
TRNS	Trauma-Related Nightmare Scale	-4.8 (7.3)	-2.7 (4.4)	0.1909
FOS	Functional Outcomes of Sleep Questionnaire	1.4 (2.8)	0.8 (2.3)	0.3683
PSQI-A	Pittsburgh Sleep Quality Index Addendum	-3.3 (4.9)	-1.4 (3.5)	0.0938
VR12	Veterans RAND 12 Item Health Survey	2 (5.8)	1.6 (6.9)	0.8093
Likert	5-point Nightmare Dysfunction Scale	4.5 (4.4)	2.7 (3.8)	0.0910
BMI	Body Mass Index	-0.5 (1.8)	0.7 (3.2)	0.0949
SBP	Systolic blood pressure	4.9 (12.5)	-3.5 (14.7)	0.0410
DBP	Diastolic blood pressure	-1.1 (6)	-2 (7.9)	0.6439

P-values reflect a two-sample t-test.

Like many trials of nightmare treatments, there is a strong placebo effect that is present in this trial thus far. However, based on these interim results, it is expected the primary endpoint will be achieved once the trial is complete. Due to the COVID-19 pandemic, enrollment was put on hold for a period and was resumed in November 2020 to provide further evidence for NightWare. Given the lack of FDA-cleared therapies for nightmare disorder or PTSD-related nightmares, the low safety risks for the use of NightWare, and emerging evidence from the trial interim analysis, the data supported FDA clearance.

Efficacy Results

The primary measure of relative efficacy was the difference in mean PSQI change between NightWare and sham arms. The difference observed between the active and sham groups was 1 point. A secondary measure of efficacy was the change in PSQI-A, which was more than twice that of the sham condition.

As seen in Table 1, the NightWare system was associated with a mean PSQI improvement of 3.2 points, which exceeds the literature-suggested minimal clinically important difference (MCID) of 3 points for the PSQI. The sham system also demonstrated a placebo-associated improvement in the PSQI of 2.2 points, which is less than the literature-reported MCID; however, the difference between NightWare and sham on this measure was not statistically significant at the current N (p=0.26). Figures C–E show the efficacy of both active and sham in the PSQI.

The PSQI-A change was 3.3 points, more than double that of the sham condition (1.4 points). Given that this measure specifically indexes sleep disturbances associated with PTSD, the strength of this dissociation provides evidence that trauma-related nightmares are effectively targeted by the NightWare device.

Mean (SD) change between baseline and visit 2 at 30 days for each outcome measure by study arm. P-values reflect a two-sample t-test.

Baseline Outcome Measure	NightWare (n=29)	Sham (n=34)	p-value
PSQI-A	-3.3 (4.9)	-1.4 (3.5)	0.0938

FIGURE C

PSQI at Baseline (left) and at 30 Day Follow Up (right) for Active Group

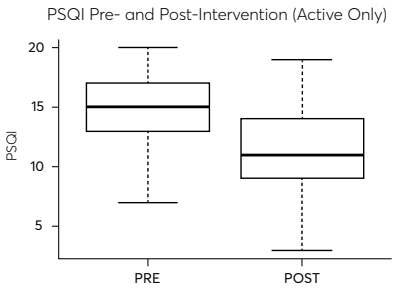


FIGURE D

PSQI at Baseline and 30 Day Follow Up for Active Group (left) and Sham Group (right)

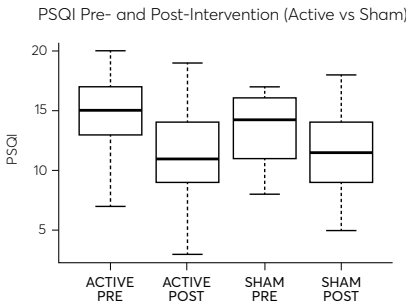
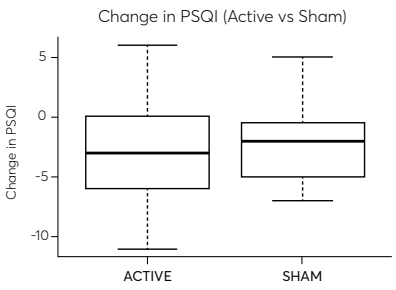


FIGURE E

Global Change in PSQI for Active Users (left) and Sham (right)



1. Data on file.
2. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193–213. doi: 10.1016/0165-1781(89)90047-4. PMID: 2748771.
3. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res. 2002 Sep;53(3):737–40. doi: 10.1016/s0022-3999(02)00330-6. PMID: 12217446.

Important Safety Information

INTENDED USE/INDICATION FOR USE

The NightWare digital therapeutic is indicated to provide vibrotactile feedback on an Apple Watch based on an analysis of heart rate and motion during sleep for the temporary reduction of sleep disturbance related to nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). It is intended for home use.

CONTRAINDICATIONS

If you have acted out your nightmares (i.e. sleepwalking, violence) do not use NightWare and contact your Healthcare Provider.

WARNINGS

- NightWare is not a standalone therapy for PTSD. The device should be used in conjunction with prescribed medications for PTSD and other recommended therapies for PTSD-associated nightmares and nightmare disorder, according to relevant consensus guidelines.
- If daytime sleepiness occurs, contact your Healthcare Provider.
- If you feel drowsy, do not drive or operate heavy machinery. Contact your health care provider.
- If the watch vibration causes awakenings not associated with nightmares, please contact your Healthcare Provider.
- If nightmares persist, worsen, or recur, contact your Healthcare Provider.
- If skin irritation occurs, discontinue use of the watch and contact your Healthcare Provider.
- Your watch may disturb your bedpartner. Try not to expose your bedpartner to the watch at night.
- Do not wear the watch too tightly, it should feel comfortable and snug, not tight on your wrist.
- Wear the watch only when you are planning to go to sleep; do not wear it while reading or watching TV in bed as this may trigger false alerts.
- Use the NightWare watch every night.
- Not intended for use by individuals under age 22.
- The long term safety and effectiveness of the NightWare device has not been established.
- The long term effects of the NightWare device use on the sleep architecture have not been established.

PRECAUTIONS:

- Do not drop or crush the smartphone or watch.
- Be sure to charge the smartphone and watch every day.