NIGHTWARE

NightWare Digital Therapeutic Provider Instructions for Use

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Intended Use/Indications 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 posttraumatic stress disorder (PTSD). It is intended for home use.

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Contraindications, Warnings, and Precautions

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. This 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 Healthcare Provider.
- If the watch vibrations cause awakenings not associated with your nightmares, 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 bed-partner. Try not to expose your bed-partner to the watch at night.
- Do not wear the watch too tightly, it should feel comfortable and snug, but 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.

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Device Description

Nightmares affect 2–8% of the general population with the prevalence of comorbid nightmares in those with PTSD being significantly higher at 72%[1]. The negative sequelae of nightmares are myriad including impaired quality of life, sleep deprivation, insomnia, daytime sleepiness, fatigue, and suicidal ideation.[2] Nightmares may also exacerbate underlying psychological distress in people with depression and anxiety, leading to poor occupational and or social functioning.[3]

NightWare digital therapeutic is a smartwatch-based application that senses physiological signals that are consistent with a nightmare utilizing the hardware's heart rate sensor, accelerometer, and gyroscope. These parameters are used to calculate a stress index threshold for each user. "Stress Index" is a device-specific measurement and does not represent a clinically validated measure of stress. When the threshold is exceeded, the smartwatch is programmed to provide vibrotactile stimulation on the patient's wrist to arouse the patient out of the distressed state. In some instances, it will disrupt the distressing state prior to it reaching a severity that would awaken the patient. By interrupting nightmares at the time they occur, sleep quality has been shown to improve using the clinically validated standard to assess sleep quality, the Pittsburgh Sleep Quality Index (PSQI).

Figure 1: iPhone (right) and Apple Watch (left).

The NightWare device includes a software application and the NightWare server. The device uses an Apple Watch and an Apple iPhone® for its platform. Patients need to have a connection to the internet.

In order to receive therapy from the NightWare digital therapeutic system, patients must use the prescribed NightWare Kit containing an iPhone and Apple Watch pre-provisioned by NightWare, Inc. Patients should be instructed that both the iPhone and Apple Watch must be fully charged before going to bed, and have a consistent connection to wireless internet through Wi-Fi in order to transmit data to the NightWare servers.

NightWare is designed to monitor the patient's heart rate and movement throughout the night and occasionally provide interventions through the Apple Watch. The interventions will occur when NightWare detects that the patient has exceeded a calculated stress threshold and will disrupt the nightmare at the time that it is occurring (Figure 2).

NightWare relies on artificial intelligence algorithms to calculate a patient's heart rate and movement and understand what normal and abnormal levels are for the patient during the night. To create this personalized sleep profile, NightWare requires acquisition of several

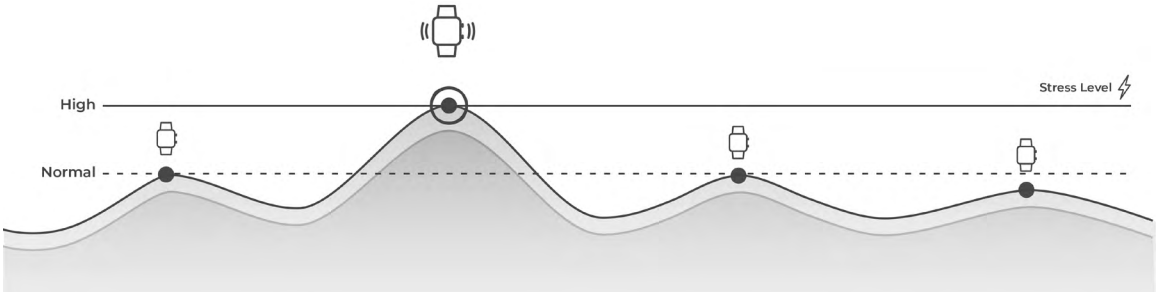

Figure 2: Illustration of an example NightWare interuention.

hours of sleep data prior to the application intervening. The data that NightWare collects from the Apple Watch includes:

- Heart Rate
- Body Movement (Acceleration)
- Body Position (Rotation)

This information is securely sent to the NightWare servers to establish the patient's current stress index thresholds. The stress index threshold will update to accommodate the patient's changing heart rate and movement that naturally occur during consistent use.

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Instructions for Use

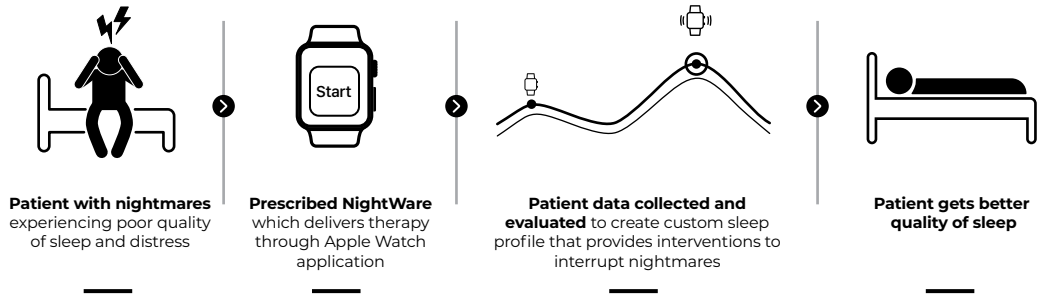

Figure 3: NightWare Prescriber Flow Diagram

When a patient presents with nightmare disorder or is having recurring nightmares from a pre-existing condition such as PTSD, NightWare can be prescribed to help improve the patient's sleep quality. Physicians should inform their patients that:

1. It is recommended the patient wear the Apple Watch loaded with the NightWare application consistently, preferably nightly, for best results.
2. The iPhone and Apple Watch must be fully charged at the beginning of the night prior to using the NightWare digital therapeutic system.
3. The iPhone and the Apple Watch must be connected to wireless internet via Wi-Fi.
4. The first two nights, patients may not experience any vibrotactile interventions (vibrations) on their wrist due to the data collection that the NightWare digital therapeutic system requires during the calibration period.
5. Patients can expect to experience vibrotactile interventions on their wrist that may arouse them from their sleep.
6. Patients may not know whether or not vibrotactile interventions are occurring, but should use the question "Can I remember having a nightmare last night?" as a proxy to elicit if the therapy is working as intended.
7. If daytime sleepiness, nightmare frequency, nightmare intensity, suicidal ideation, or skin irritation on the area where the watch band contacts the skin gets worse, patients should stop using the NightWare digital therapeutic system immediately and consult their doctor for further action.
8. If patients have any questions regarding how to use the NightWare digital therapeutic system, they should consult the User Manual and contact NightWare staff directly at ***833-44-NIGHT, 883-446-4448***.
9. For any questions regarding their personal health, they should contact their doctor.

MINIMUM OPERATING REQUIREMENTS

The NightWare digital therapeutic requires an iPhone 7 or newer, Apple Watch 3 or newer, iOS 13 or newer, WatchOS 6 or newer.

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Clinical Evidence

A.STUDY DESIGN

NightWare's safety and efficacy is supported by a double-blind, sham controlled, randomized clinical trial (NW101002).

NW101002 tested the safety and efficacy of the NightWare digital therapeutic system (NW System) which is to be used for improving the sleep quality in those with nightmare disorder or nightmares associated from conditions such as post-traumatic stress disorder. This system consists of an iPhone, plus an Apple watch, plus the proprietary software application; from

here on referred to as the "Active System". The Active System is contrasted with the Sham NW digital therapeutic system "Sham System", which consists of the same components as the Active System, but the proprietary application never intervenes during the night.

The investigators hypothesize that the Active System will significantly improve sleep quality in subjects with PTSD-related sleep disorders who are suffering from nightmares and poor sleep quality, and that significant improvement will not be observed in the subjects who receive a Sham System.

The study was designed to enroll two hundred forty (240) potential participants, one hundred twenty (120) in each arm, equal to or over the age of 22 years with a diagnosis of PTSD and nightmares. The study is designed to randomly assign participants in a blinded manner to the Active or Sham group. This study conducted at the Minneapolis Veterans Affairs Health Care System.

The primary objective of this trial is to demonstrate that the Active System improves sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in subjects with PTSD, and that this represents a statistically significant improvement over the change seen in subjects receiving the Sham System.

Other outcome measures include:

- Change in ESS at baseline (Day 0) and average ESS at Days 14 and 30 as compared to sham intervention.
- Change in C-SSRS at baseline (Day 0) and average C-SSRS at Days 14 and 30 compared to sham intervention.
- Change in PSQI-A (PSQI Addendum for PTSD-related sleep quality) at baseline (Day 0) and average PSQI-A at Day 30 as compared to sham intervention.
- Change in PCL-5 at baseline (Day 0) and average PCL-5 at Day 30 as compared to sham intervention.
- Change in PHQ-9 at baseline (Day 0) and average PHQ-9 at Day 30 as compared to sham intervention.
- Change in TRNS at baseline (Day 0) and average TRNS at Day 30 as compared to sham intervention.
- Change in FOSQ-10 Quality of Life Measure at baseline (Day 0) and average FOSQ-10 at Day 30 as compared to sham intervention.
- Change in VR-12 at baseline (Day 0) and average VR-12 at Day 30 as compared to sham intervention.
- Change in NW Likert Scale for Sleep Quality at baseline (Day 0) and average Likert Scale at phone Calls 2 and 4 as compared to sham intervention.

B.SAFETY RESULTS

The first subject first visit (FSFV) was 23 July 2019. The final primary outcomes visit included in this summary was conducted 8 April 2020. At the time of this report, 70 participants were enrolled in the trial. Of these, 3 were lost to follow-up, and 4 withdrew before the end of the 30-day

primary study monitoring period. Data are reported from the remaining 63 participants who have complete data from, at minimum, the baseline and primary outcome visits.

The two randomization groups did not significantly differ at baseline on the primary measures used to evaluate safety: Epworth Sleepiness Scale (ESS) and Columbia Suicide Severity Rating Scale (C-SSRS); and effectiveness: Pittsburgh Sleep Quality Index (PSQI); or on the secondary measures of effectiveness related to PTSD (PCL5), depression (PHQ9), quality of life (FOSQ, VR12), and sleep quality (PSQI-A, Likert, TRNS). Measures of physical health (BMI, blood pressure, heart rate) were also similar across groups, though the group randomized to the NightWare condition had significantly higher diastolic blood pressure (Table 1).

Table 1: Baseline summary for each outcome measure by study arm. Reported values are median [min, max]. P-values reflect the Wilcoxon Rank-Sum Test.

Baseline Outcome Measure	***NightWare*** (n = 29)	***Sham*** (n = 34)	***p-value***
PSQI	15 [7,20]	14.2 [8,17]	0.3317
PHQ-9	11 [4,24]	12 [1,25]	0.9889
PCL	47 [23,71]	47.5 [24,72]	0.3735
ESS	11 [1,17]	8.5 [0,17]	0.2083
TRNS	41 [32,60]	42.5 [32,60]	0.7985
FOSQ	11.6 [7,18]	12.6 [7.5,20]	0.0650
PSQI-A	15 [8,24]	16 [6,25]	0.3225
VR12	28 [8,41]	29 [8,42]	0.6388
Likert	10 [3,19]	10.2 [7,15]	0.5944
BMI	30 [23.7,39.6]	28.3 [21.9,44.5]	0.0642
SBP	127 [101,151]	127 [90,180]	0.9822
DBP	84 [62,101]	79 [65,117]	0.0223
HR	72.5 [49,100]	74 [55,103]	1.0000

The two primary measures of safety were increased suicidal ideation, C-SSRS, and increased daytime sleepiness, ESS, between the baseline and primary outcome visits.

C-SSRS

At baseline, 76% of participants reported a lifetime history of suicidal ideation (SI) on the C-SSRS, demonstrating that psychiatric concerns were not uncommon in this sample. However, per protocol, no enrolled participant had experienced SI with intent to act in the prior month or had engaged in suicidal behavior (e.g., preparatory acts, suicide attempts) in the prior 3 months. Lower levels of SI were permitted, and 15 of the 63 participants (24%) reported some level of SI in the previous month at the time of the first visit, including a wish to be dead (N=7), nonspecific thoughts (3), and active

ideation without intent (5). Due to a reported protocol deviation, the C-SSRS SLV was not administered at the primary outcome visit for the first 20 completing participants. Among the 43 participants for whom the C-SSRS SLV was conducted at both visits, 9 reported some level of suicidal ideation (SI) in the month prior to first visit, including a wish to be dead (N=5), nonspecific thoughts (2), and active ideation without intent (2).

At the primary outcome visit, 7 participants reported some level of suicidal ideation (see Table 2). Overall, 33 participants reported no change in SI, 7 reported decreased SI, and 3 reported increased SI. All 3 participants who reported increased SI had a baseline score of 0 (no ideation in prior month), two had a final score of 1 (wish to be dead at some point in prior month), and one had a final score of 4 (active ideation with some intent to act but no plan). Both of the two participants with a final score of 1 reported, at baseline, a lifetime history of active suicidal thoughts, so the transient emergence of thoughts about death would not typically be reason for clinical concern. In contrast, the participant who reported active ideation with some intent at the primary outcome visit was of sufficient concern to warrant a query for additional details, which were documented as part of the C-SSRS at the time of the visit. This subject, who had an acknowledged history of suicidal behavior several years prior to enrolling in the study, reported that the SI occurred transiently, immediately following an intense argument with their romantic partner within 24 hours of the baseline visit. Though this risk was accurately reported per the directions for administration of the C-SSRS SLV, the SI did not persist through the duration of the trial and was not noted to be present at the primary outcome visit. Therefore, given that the device would not yet have been administering interventions as the SI occurred during the calibration period, while this reflects a nontrivial increase in SI during the study period, it is unlikely to be related to study participation or the intervention.

Table 2. Suicidal Ideation

Score	***Description***	***Baseline***		***Completion***	
		Active	***Sham***	***Active***	***Sham***
0	No ideation	16	18	18	18
1	Wish to be dead	2	3	1	4
2	Non-specific active suicidal thoughts	1	1	1	0
3	Active suicidal ideation, no intent to act, no plan	1	1	0	0
4	Active suicidal ideation, some intent to act, no plan	0	0	0	1

ESS

As seen in Table 3, both groups demonstrated a reduction of approximately 1.2 points on the ESS, and the magnitude of reduction did not differ across groups (p=.97). Therefore,

neither the NightWare System nor the Sham System was associated with increased daytime sleepiness.

Table 3: Mean (sd) change between baseline and primary outcome visit 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	-3.2 (3.7)	-2.2 (2.9)	0.2606
PHQ-9	-2 (3.7)	-1 (3.8)	0.2719
PCL	-9.9 (13.4)	-6.5 (9.9)	0.2727
ESS	-1.2 (4.1)	-1.2 (3.1)	0.9739
TRNS	-4.8 (7.3)	-2.7 (4.4)	0.1909
FOS	1.4 (2.8)	0.8 (2.3)	0.3683
PSQI-A	-3.3 (4.9)	-1.4 (3.5)	0.0938
VR12	2 (5.8)	1.6 (6.9)	0.8093
Likert	4.5 (4.4)	2.7 (3.8)	0.0910
BMI	-0.5 (1.8)	0.7 (3.2)	0.0949
SBP	4.9 (12.5)	-3.5 (14.7)	0.0410
DBP	-1.1 (6)	-2 (7.9)	0.6439

C. 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 3, 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 4–6 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.

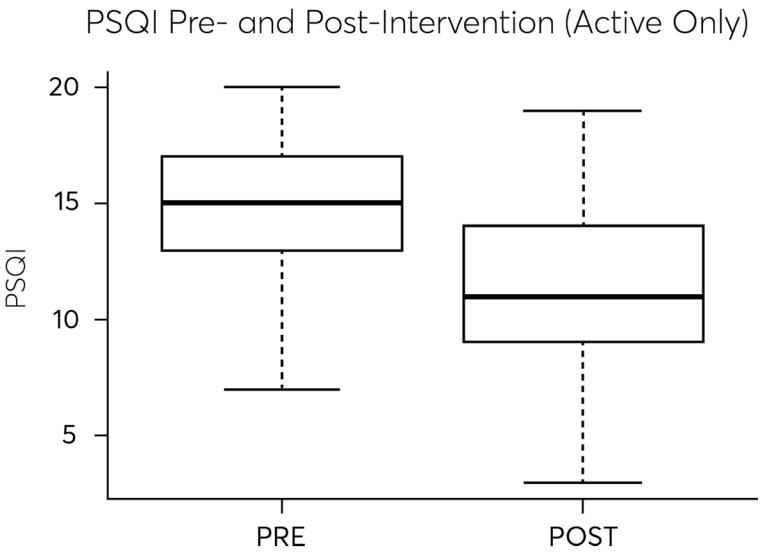

Figure 4: PSQI at baseline (left) and at 30 day follow up (right) for active group.

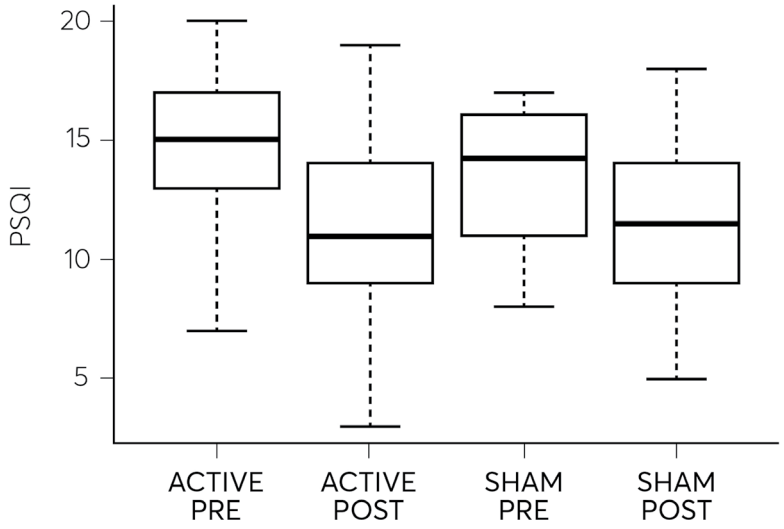

Figure 5: PSQI at baseline and 30 day follow up for active group (left) and sham group (right).

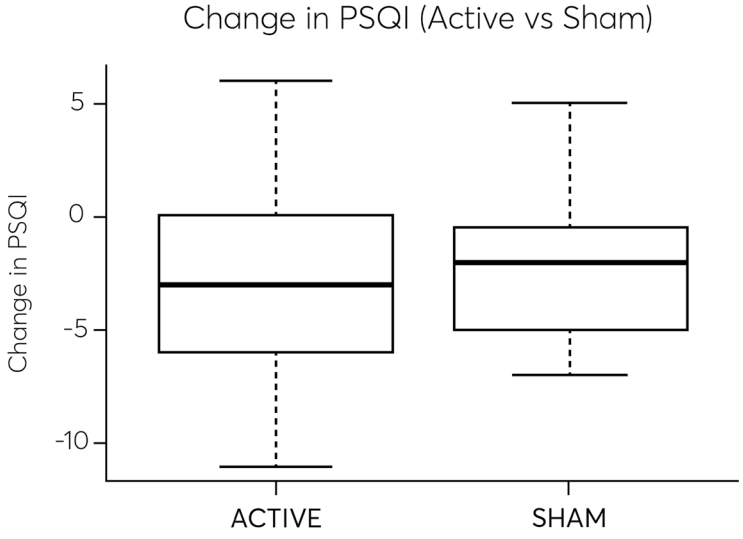

Figure 6: Global change in PSQI for active users (left) and sham (right).

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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

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Contact Us

NightWare, Inc
8900 Excelsior Blvd
Hopkins, MN 55343

Troubleshooting and servicing: If you run into any technical problems with the NightWare Digital Therapeutic System, please contact us.

For technical support contact – ***833-44-NIGHT, 833-446-4448*** or email us at ***support@nightware.com***.

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Symbols Glossary

Symbol	Symbol Title [Reference Number]	Description
	Consult instructions for use [5.4.3][1]	Indicates the need for the user to consult the instructions for use.

1. ISO 15223-1:2016 – Medical devices — Symbols to be used with medical device labels, labeling and information to be supplied.

8

References

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2. Leskin, G. A., Woodward, S. H., Young, H. E., & Sheikh, J. I. (2002). Effects of comorbid diagnoses on sleep disturbance in PTSD. *Journal of Psychiatric Research*, *36*(6), 449-452. doi:10.1016/s0022-3956(02)00025-0.

3. Liu, X., et al. (2019). Nightmares are associated with future suicide attempt and non-suicidal self-injury in adolescents. *The Journal of Clinical Psychiatry, 80*(4). doi:10.4088/jcp.18m12181.

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5. Sheaves, B., Onwumere, J., Keen, N., Stahl, D., & Kuipers, E. (2015). Nightmares in patients with psychosis: the relation with sleep, psychotic, affective, and cognitive symptoms. *The Canadian Journal of Psychiatry, 60*(8), 354-361. doi:10.1177/070674371506000804.

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