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Non-24-Hour Sleep-Wake Disorder is more than missing sleep...

it's a continuous shift in time

Non-24 occurs in both sighted and totally blind persons, but **it is highly common in those who are totally blind—affecting up to 70%**[1,2]

130,000

People who are totally blind with no light perception[3,4]

Up to 95,000

People who are totally blind with Non-24[6]

› Although Non-24 is highly prevalent in this population, awareness of Non-24 is low[5]

Bring this to your next doctor's visit to discuss Non-24-Hour Sleep-Wake Disorder

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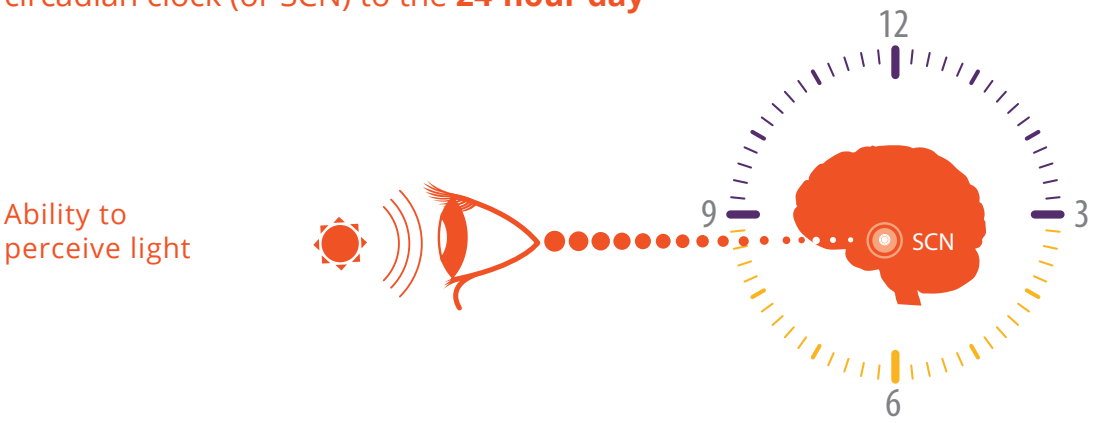
Lack of light perception can lead to Non-24

In sighted individuals: Daily exposure to the light-dark cycle usually synchronizes the circadian clock (or SCN) to the **24-hour day**[7]



In most people who are totally blind: Without light perception, sleep-wake cycles shift, often becoming **desynchronized with the 24-hour day**[7]

SCN, suprachiasmatic nucleus

Inability to perceive light can lead to the desynchronization of the endogenous circadian clock with the 24-hour light-dark cycle[2]

In addition to the totally blind population, other groups of people that may have Non-24 include sighted individuals and those who have suffered a traumatic brain injury (TBI), such as a head concussion.[8,9]

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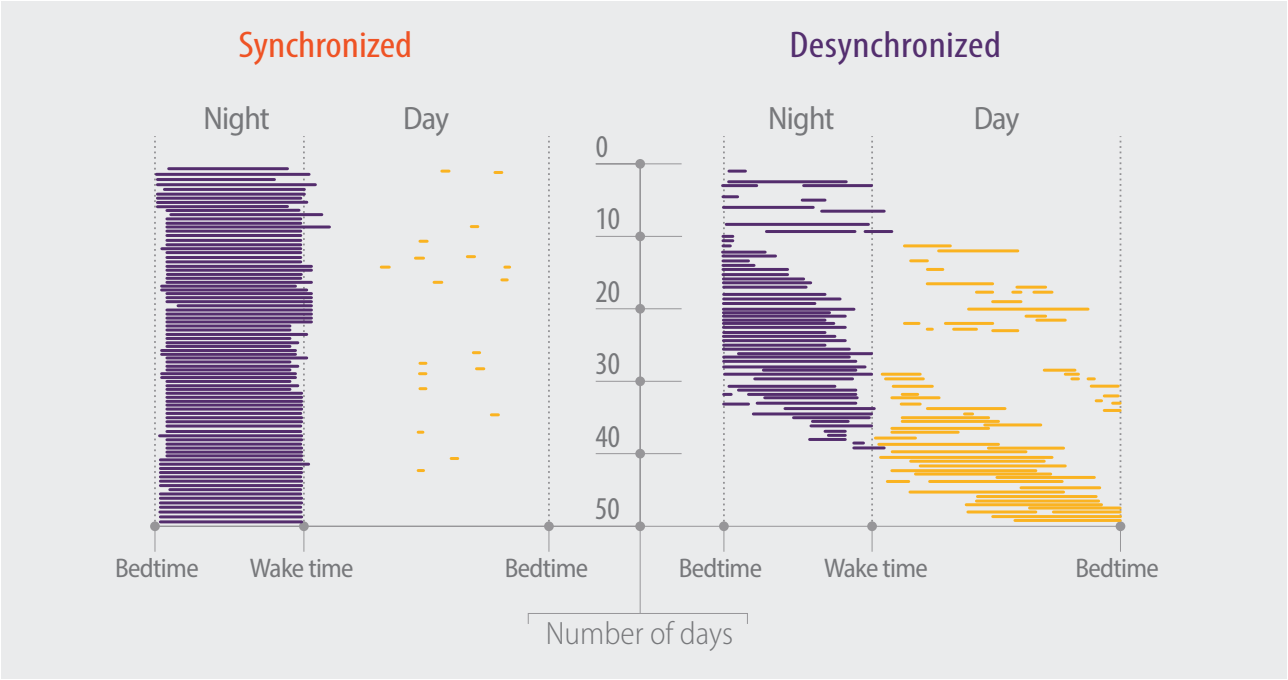
Non-24 is more than amount of sleep — it's a timing issue

Non-24 alters the sleep-wake cycle[2]

24.0 Hour clock › 1 Day cycle

24.5 Hour clock › 48 Day cycle



- In individuals with light perception, wakefulness and sleep are often aligned with the 24-hour day[2,10]
- People with Non-24 experience shifting sleep- wake cycles, marked by a consistent daily drift in sleep and wake times relative to the 24-hour day, broken up by short periods of no symptoms[11]

Because of the **variability in endogenous circadian clocks,** sleep-wake cycles vary from person to person[2]

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Uncovering Non-24

Sleep disturbances may be a sign of something more—here are some questions to ask your patients

- Are you having trouble going to sleep at night and/or staying awake during the day?
- Do you go through periods of good sleep and periods of bad sleep? If so, for how long do these periods last?
- Are sleep-wake problems making it difficult to engage in daily activities and maintain relationships?

Important diagnostic information for Non-24

ICD-10

G47.24
Circadian rhythm sleep disorder, free-running type (Non-24)[12]

DSM-5

Circadian rhythm sleep-wake disorder, Non-24-hour sleep-wake type[11]

A. A persistent or recurrent pattern of sleep disruption that is primarily due to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep-wake schedule required by an individual's physical environment or social or professional schedule.

B. The sleep disruption leads to excessive sleepiness or insomnia, or both.

C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, and other important areas of functioning.

D. Non-24 sleep-wake type has been associated with traumatic brain injury.

ICSD-3

Predisposing and Precipitating Factors
This disorder has also been reported in adults following traumatic brain injury.

It's time to evaluate all of your patients who are experiencing sleep disturbances for Non-24

Bring this to your next doctor's visit to discuss Non-24-Hour Sleep-Wake Disorder

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1. Sack RL, et al. Sleep Med Rev. 2001;5(3):189-206. **2.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **3.** Prevalence of vision impairment. Lighthouse International website. http://li129-107.members.linode.com/research/statistics-on-vision-impairment/prevalence-of-vision-impairment. Accessed January 28, 2016. **4.** Czeisler CA, et al. *N Engl J Med*. 1995;332(1):6-11. **5.** Gallagher A, et al. *Sleep*. 2012;35(suppl): abstract 0608. **6.** Data on file. Vanda Pharmaceuticals Inc. 2014. **7.** Lockley SW, et al. In: Kushida C, ed. *The Encyclopedia of Sleep*. Vol 3. Waltham, MA: Elsevier; 2013:34-40. **8.** Bolvin, Diane B., et al. "Non-24 hour sleep-wake syndrome following a car accident." Neurology 60.11 (2003);1841-1843 **9.** Carter, Kevin A., et.al. "An Unusual Cause of Insomnia Following IED-Induced Traumatic Brain Injury." Journal of Clinical Sleep Medicine, Vol.6, No. 2, 2010) **10.** Dibner C, et al. *Annu Rev Physiol*. 2010;72:517-549. **11.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013. **12.** ICD-10 code lookup. Centers for Medicare & Medicaid Services website. https://www.cms.gov/medicare-coverage-database/staticpages/icd-10-code-lookup. aspx?KeyWord=G47.24. Accessed October 15, 2015.

Important Safety Information

INDICATION

HETLIOZ® (tasimelteon) capsules are indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in adults and nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older. HETLIOZ LQ™ oral suspension is indicated for the treatment of nighttime sleep disturbances in SMS in patients 3 to 15 years of age.

IMPORTANT SAFETY INFORMATION

HETLIOZ® may cause somnolence: After taking HETLIOZ®, patients should limit their activity to preparing for going to bed, because HETLIOZ® can potentially impair the performance of activities requiring complete mental alertness.

The most common adverse reactions (incidence >5% and at least twice as high on HETLIOZ® than on placebo) were headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection. The risk of adverse reactions may be greater in elderly (>65 years) patients than younger patients because exposure to HETLIOZ® is increased by approximately 2-fold compared with younger patients. Adverse reactions were similar in patients treated for Non-24 and patients with SMS treated for nighttime sleep disturbances. Adverse reactions were also similar in pediatric patients (3 years to 15 years) who received HETLIOZ LQ™ oral suspension, and patients ≥16 years of age who received HETLIOZ capsules.

Use of HETLIOZ® should be avoided in combination with fluvoxamine or other strong CYP1A2 inhibitors, because of a potentially large increase in exposure of HETLIOZ®, and a greater risk of adverse reactions. HETLIOZ® should be avoided in combination with rifampin or other CYP3A4 inducers, because of a potentially large decrease in exposure of HETLIOZ®, with reduced efficacy.

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Important Safety Information (Continued)

There are no adequate and well-controlled studies of HETLIOZ® in pregnant women. Based on animal data, HETLIOZ® may cause fetal harm. Caution should be exercised when HETLIOZ® is administered to a nursing woman.

HETLIOZ® has not been studied in patients with severe hepatic impairment and is not recommended in these patients.

The safety and effectiveness of HETLIOZ® for the treatment of Non-24 in pediatric patients have not been established. The safety and effectiveness of HETLIOZ LQ™ oral suspension for the treatment of nighttime sleep disturbances in SMS have been established in pediatric patients 3 years and older.

To report SUSPECTED ADVERSE REACTIONS, contact Vanda Pharmaceuticals Inc. at 1-844-438-5469 or **www.hetlioz.com** or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.

Please see full US Prescribing Information at **www.hetlioz.com**

Consumer Important Safety Information

- You are encouraged to report side effects of prescription drugs to the FDA. To report side effects, contact Vanda Pharmaceuticals Inc. at 1-844-438-5469 or **www.hetlioz.com** or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.
- For more information, ask your healthcare provider or call 1-844-HETLIOZ (1-844-438-5469).
- This information does not take the place of talking with your healthcare provider for medical advice about your condition or treatment.
- Download an accessible PDF or listen to the full **US Prescribing Information**. You can also hear the full US Prescribing Information by calling 1-844-HETLIOZ (1-844-438-5469).

Please see accompanying full Prescribing Information.

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