Non-24 Sleep Wake Disorder: presentation and management

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2. I have the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients:

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<th>Type of Potential Conflict</th>
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Objectives

1) Know when to suspect Non-24 Sleep Wake Disorder (N24SWD)
2) Review ICSD-3 diagnostic criteria for N24SWD
3) Be familiar with AASM practice guidelines of N24SWD
4) Discuss use of tasimelteon
Case: Initial presentation

CC: 25 year old male, difficulty falling and staying asleep

HPI:
• Estimated BT between midnight and 3 am, SOL up to 3 hours, several night-time awakenings, WT of around 10 am. Naps 2 to 3 times a week, at random times of the day.
• Spent his days at home playing video games and watching television, and did not go outside the house much
• Loud snoring, witnessed apneas, non-refreshing sleep and excessive daytime sleepiness (ESS 7)

PMH: Asperger’s disease, ADHD

Medications: sertraline

PE: overweight male with BMI of 32 and a crowded oral airway with a Friedman class 3
Case: initial work-up

- Asked to keep sleep logs (actigraphy not readily available)
- PSG: SE 53%, SOL 180 minutes (LO 10:10 pm), severe OSA (AHI 43) with excessive central apneas (CAI 10.3)
- Titration: CPAP 8 cm water effective
Case: 1 month follow up

• Using CPAP every night
• More energy and more motivation
• Estimated BT 10 pm, SOL 20 minutes, WT 7-11 am, no naps
• CPAP download: CPAP use of 100%, average use of 9 hrs 15 minutes, residual AHI not available
• He was not able to keep sleep logs
• Detailed download...
Initial follow up CPAP download
N24SWD: ICD-3 diagnosis

Criteria A-D must be met
A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity.
B. Symptoms persist over the course of at least three months.
C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
N24SWD

• Previously called Free-Running Type
• Occurs when the hypothalamic circadian pacemaker fails to entrain (synchronize) to the 24-hour day
  – As a result, individuals can suffer from periodic nighttime insomnia and daytime somnolence as the circadian rhythms of sleep propensity and alertness drift in and out of synchrony with the 24-hour day
  – Daily delay depends on endogenous circadian period, may range from less than 30 minutes to more than 1 hour
• Most individuals with N24SWD are totally blind, due to non-functional photosensitive retinal ganglion cells resulting in an absence of photoperiod information being transmitted through the retinohypothalamic pathway.
  – It is estimated to be present in 50% of blind individuals
Pathophysiology

• The intrinsic period of human circadian pacemaker is usually longer than 24 hrs
• Requires daily input from the environment to maintain synchrony to the 24-hour day
  – Light-dark cycle is the most important zeitgeber in humans
Melanopsin-containing retinal ganglion cells are the major circadian photoreceptors and communicate the presence of light to the SCN via the RHT.

SCN - suprachiasmatic nucleus
RHT - retinohypothalamic tract
N24SWD: sighted individuals

- Reported in sighted individuals with a history of intellectual disability, autism spectrum disorder, dementia, or delayed sleep-wake disorder with decreased light and social exposure or who have undergone chronotherapy.
  - Pathophysiology among sighted individuals is unknown, may be due to excessively long circadian period or inappropriate exposure to light
- Attempts to regulate sleep and wake times may involve the use of alcohol, sedative hypnotics and stimulants
- Depressive symptoms and mood disorders can be common
There is no evidence to support the use of:
- prescribed sleep-wake scheduling
- timed physical activity or exercise
- strategic avoidance of light (as monotherapy)
- use of sleep-promoting medications
- wakefulness-promoting medications

There is insufficient evidence to support the use of:
- light therapy
- melatonin among sighted patients
- oral vitamin B12
- combination treatments

The Task Force suggests that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults.
Strategically timed melatonin for the treatment of N24SWD in blind adults

- Only 3 studies met inclusion criteria for the present analysis and the level of evidence from these small trials was LOW.
- Doses ranged between 0.5–10.0 mg, and were administered either 1 hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days.
- Patient preference would be expected to favor the use of easily obtained and inexpensive melatonin that requires once daily dosing.
- No serious adverse reactions to melatonin have been described to date, and therefore the benefits of use appear to outweigh any potential harms.
- A majority of well-informed patients and caregivers would therefore accept this treatment option versus no treatment.
Case: initial management

• CPAP download showed progressive delay in bedtime

1. Prescribed sleep-wake scheduling:
   – Scheduled BT of 10 pm, WT 7 am with an alarm clock
   – Avoid naps, stay active during the day

2. Light therapy: seek bright light upon awakening

3. Melatonin 1-3 mg at 5 pm
Case: 6-month follow up with use of timed light and melatonin (after 4 visits reviewing recommendations)
Case: 9-month follow up with timed light and melatonin, states BT is 1-4 am, WT noon to 3 pm, melatonin 5 mg 1 hour before bedtime
Case: 18 month follow up: not able to maintain a regular schedule
Case: further management

• Not able to maintain a consistent bedtime
• Depends on others for transportation, stays at home on most days
• Still doing well with CPAP
• Tasimelteon ordered
  – Initially denied, appeal was approved
tasimelteon (Hetlioz)

• FDA approved for treatment of N24SWD in blind patients with N24SWD
• Has been shown to improve sleep onset and maintenance in blind patients with N24SWD
• Selective agonist at melatonin MT1 receptors (associated with sleep induction) and MT2 receptors (associated with circadian rhythm regulation)
• Dosing: 20 mg at night
• Side effects: headache, abnormal dreams, elevated LFTs, URI, UTI
• Monitoring: no routine tests recommended
• Restricted distribution though a centralized pharmacy
Case: follow up taking tasimelteon
Case follow up

• Continues to take tasimelteon 20 mg every night at 10 pm
• BT 11 pm, SOL 30-60 minutes, FNA once up to 2 hrs, WT 10-11 am
• Side effects: vivid dreams initially
• No residual sleepiness
• Stable on tasimelteon for 3 yrs now
  – Was stopped once for 2 weeks but progressive delay in bedtime returned
Take away points

• Suspect N24SWD when patients present with intermittent insomnia and excessive sleepiness, alternating with normal periods
• Occurs when the hypothalamic circadian pacemaker fails to entrain to the 24-hour day, leading to a progressive delay in sleep
• Seen in 50% of blind patients, may also be seen in sighted individuals
• AASM practice parameters: use melatonin in blind individuals
• tasimelteon is FDA approved in blind individuals and seems to be effective
References


• Morgenthaler TI; Lee-Chiong T; Alessi C; Friedman L; et al. Standards of Practice Committee of the AASM. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. *Sleep* 2007;30:1445-1459.

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