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Measurement of sleep in SMS: a case example

Valentina Mantua, M.D., PhD.
Division of Psychiatry

ISCTM 18th Annual Meeting
23-25 February 2022
Grand Hyatt, Washington DC

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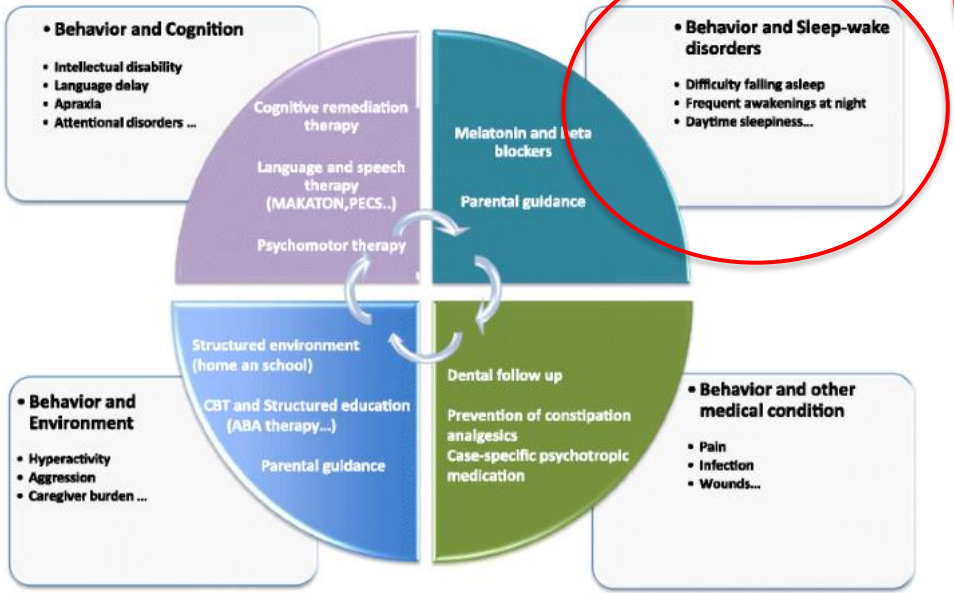
- Views expressed in this presentation are those of the speakers and do not necessarily represent an official FDA position

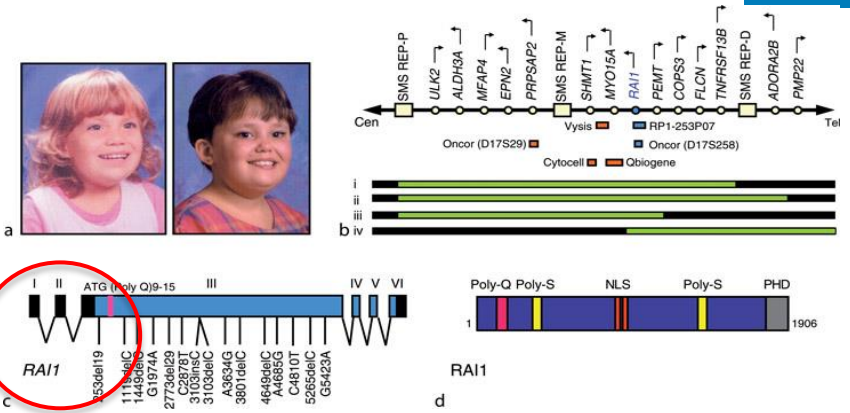
Case example:

- Tasimelteon was approved for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in 2020
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214517Orig1s000MultidisciplineR.pdf

Population: Smith Magenis Syndrome (SMS)

- Rare genetic disorder
- Sleep disturbances in SMS have a biological etiology
- An inversion of typical melatonin secretion is a hallmark of SMS, with elevated melatonin levels during daylight hours and lower levels during the night.





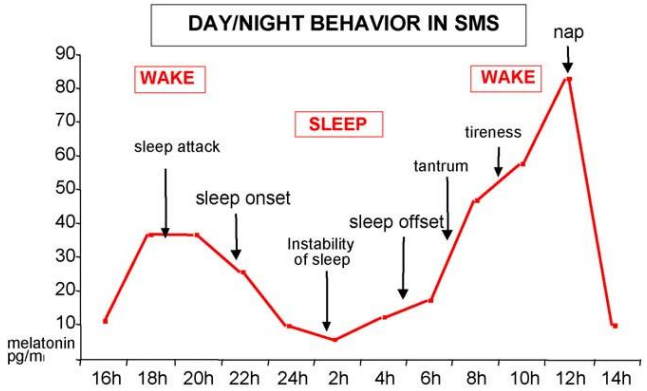
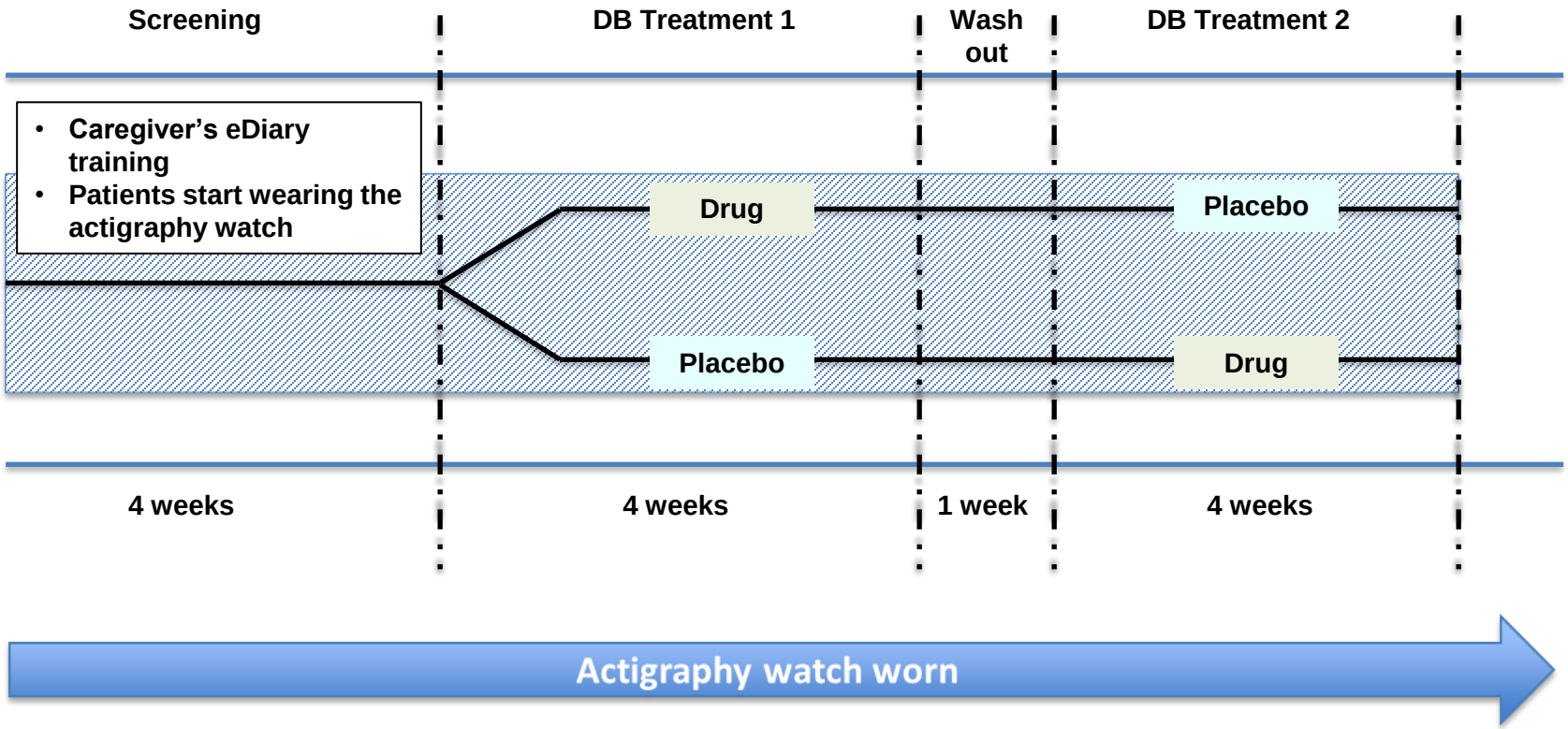


Fig. 2. Sleep–wake patterns correlated with melatonin secretion in SMS.

Challenges of measuring sleep in SMS

- Polysomnography may be unfeasible or uncomfortable and even disturb sleep particularly in individuals with behavioral problems associated with intellectual disabilities
- Questionnaires and sleep diaries are rated by parents/caregivers; however their reliability depends on how well raters are instructed and on each individual's reliability for measuring nighttime awakenings
- Digital health technologies (e.g., wearable sensors) have been considered as potential tools for measuring sleep parameters in patients who cannot tolerate polysomnography.

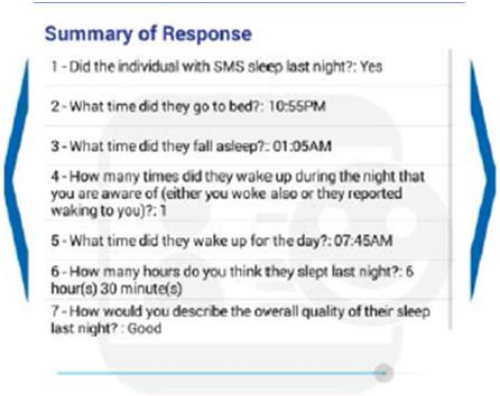
Clinical Study in SMS



Study Endpoints

Primary: e-Diary Post-Sleep Questionnaire (PSQ)

- Daily Diary Sleep Quality of Sleep was rated as follows: 5 = excellent; 4 = good; 3 = average; 2 = fair; 1 = poor.
- Daily Diary Total Sleep Time was rated in minutes and compared across placebo and treatment periods for each participant.



Secondary: Actiwatch (accelerometer plus light sensor)

- Total nighttime sleep (duration in minutes)
- Latency to persistent sleep (duration in minutes)
- Number of nighttime awakenings (count)
- Length of nighttime awakenings (duration in minutes)

Patient Listening Session

Participants

- 6 parents of patients with SMS
- Age of patients ranged from 5 to 30 years old
- 3 males, 3 female patients
- All currently experiencing sleep disturbances

Key messages

- Frequent awakenings the most problematic aspect of sleep disturbances during nighttime particularly because of safety risks
- Daytime naps can be beneficial for some, burdensome for others
- The burden of sleep disturbances is attributable to the nighttime experience for 80% vs 20% to the daytime experience
- Caregivers unanimously defined an improvement in “quality of sleep” as an increased duration of continuous (non interrupted) nighttime sleep (deep and restorative sleep)

Actiwatch: verification and validation*

- A paper by Kushida et al. (2001) was used in support of the validation of the **algorithm** that translated data (motion) into the **clinical event of interest** (sleep) and further into the **clinical trial endpoints** (total sleep time, number of awakenings).
- The data from the published study refer to a population of **healthy subjects**.
- The algorithm performance metrics can be described as follows:
  - **sensitivity** is the probability that the actigraphy algorithm scores an epoch as sleep when PSG scores it as sleep,
  - **specificity** is the probability that the algorithm scores an epoch as awake when PSG scores as awake
  - **accuracy** is the probability of correctly scoring any epoch over the total number of epochs scored.
- The algorithm used a "medium" threshold which increased sensitivity at the cost of specificity, due to the greater activity count threshold required for wake.
- The algorithm could detect sleep at each minute epoch with **sensitivity of 0.96, specificity of 0.38**, and **accuracy of 0.77,** when compared with PSG

*https://www.fda.gov/media/155022/download

Regulatory considerations

- We compared subjects' actigraphy time course traces with the associated caregiver diaries. We found that the correlations varied substantially between subjects, which would be consistent with the challenges in accurately documenting sleep/wake times by diary, particularly for overnight awakenings. Many patients also had periodic nighttime activity spikes on the actigraphy tracings that looked different from daytime wake periods, and the clinical meaningfulness of this was unclear.

- Assuming that SMS influences the amount of activity during both wake and sleep, the algorithm should have been validated in the SMS population.

- Even if the performance metrics from the published adult study could be bridged to patients with SMS, the low specificity could be an issue.

- High accuracy in wake detection required not only a high sensitivity, but a high specificity to differentiate wake from sleep

- In our case example, **the actigraphy data could not be used to support regulatory decision making** on the effectiveness of the investigational drug in the treatment of sleep disturbances in SMS.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Selection of outcomes for sleep assessment

1. Population of interest
   - What are the characteristics of sleep disturbances in the population under study?
   - E.g.: MDD ≠ IDs
2. Clinical outcome
   - What is the clinical event or characteristic related to sleep that you want to measure in your chosen population?
   - E.g.: Sleep architecture (REM stages) ≠ sleep parameters (TST)
3. Clinical relevance
   - Are sleep disturbances important for the patient?
4. Selection of tool/instrument
   - What is the best tool/instrument to measure sleep in your clinical population?
   - E.g.: Feasibility of PSG, usability of actigraphy, reliability of diaries
5. Selection of endpoint
   - Is your tool fit-for–purpose to be used as an outcome in a clinical investigation?