

Smith-Magenis Syndrome (SMS) – FDA-Requested Listening Session

August 12, 2020

Objectives of session:

1. Understand patient & caregiver experiences with Smith-Magenis Syndrome (SMS)
2. Understand the burden of sleep disorders for patients diagnosed with SMS
3. Understand the impact of the following on patients' and families' daily life:
 - a. Daytime sleepiness
 - b. Daytime naps
 - c. Duration of nighttime sleep
 - d. Frequency of nighttime awakenings
4. Understand the pharmacological and non-pharmacological strategies that caregivers use (or were prescribed for the patient) to manage sleep disorders in SMS (in the context of no approved therapy available)

Discussions in FDA Listening Sessions are informal and not meant to replace, but rather complement, existing patient engagement opportunities in the Agency. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report summarizes the input provided by patients and those representing patients with SMS at the meeting. To the extent possible, the terms used in this summary to describe specific manifestations of SMS, and the health effects and impacts, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire SMS patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Summary of the discussion by question

1. What has it been like, overall, to care for a patient with SMS? How has your experience caring for a patient with SMS changed with the patient's age/development?
 - All of the caregivers indicated SMS patients experience sleep disturbances and behavioral issues throughout their lives. A majority of caregivers added that although patients' needs may change with development, the level of care remains challenging and complex, requiring constant surveillance.
 - Caregivers described patients' sleep disturbances as lack of sleep, long periods of overnight awakening, falling asleep standing up during the day, having difficulty staying awake during the day, waking up at odd hours overnight, and the inability to remain asleep overnight.
2. Has the patient been diagnosed with other medical, psychological, or neurological conditions besides SMS?
 - All caregivers reported that patients have been diagnosed with other medical, psychological, or neurological conditions. All but one caregiver indicated that patients have received multiple diagnoses.
 - A majority of caregivers indicated that patients had developmental delays, intellectual disabilities, and/or cognitive impairments. In addition to SMS, some patients also received diagnoses of autism, attention deficit hyperactivity disorder (ADHD), obsessive-

compulsive disorder (OCD), pervasive developmental disorders (PDD), and hearing impairment as well as speech and language disabilities.

- One caregiver shared a patient's diagnosis of epilepsy.
3. When thinking about the patient's experiences **during the night** related to sleep disturbances, which are most problematic? For example, taking too long to fall asleep, waking up frequently, having trouble falling back to sleep, problematic activities when awake during the night, etc.
- All of the caregivers identified frequent awakenings during the night as most problematic. Caregivers said patients wake up and are unable to go back to sleep; hence, interrupting the sleep of household members. Caregivers expressed that patients had problematic or disruptive behavior during long periods of being awake overnight.
 - Caregivers described problematic and disruptive behaviors while patients were awake during the night as wandering around the house, inappropriate self-stimulating behavior, escape attempts, noise making such as hand clapping and speaking loudly. Disruptive behaviors while awake overnight also included threats to family members and self-injurious behavior such as head-banging and ripping at skin.
 - Most caregivers indicated that in order to maintain patient's and/or household members' safety, they lock doors and windows, secure refrigerators and cabinets, and hide dangerous or sharp items such as knives.
4. When thinking about how sleep disturbances affect the patient's experiences **during the day**, which experiences are most problematic? For example, feeling sleepy during the day, difficulties completing desired activities due to need for naps, irritable behavior due to poor nighttime sleep, etc.
- Four caregivers specifically cited patients' meltdowns as most problematic during the day. Caregivers added that patients' meltdowns in some cases are exacerbated by lack of sleep or naps and typically occur multiple times a day or even within the hour.
 - One caregiver identified the patient's most troublesome behaviors due to lack of sleep as irritability, exhaustion, poor decision-making, as well as the inability to focus and concentrate. The caregiver shared that the lack of sleep increases number and severity of the patient's seizures.
 - A majority of caregivers shared meltdowns can be triggered by insignificant actions such as hanging up a telephone, turning off bath water or a vacuum, and yawning.
5. When you think about all the sleep disturbances that your child experiences, how much of those disturbances are related to **overnight vs daytime experiences**? Please estimate a percentage as best as possible. For example, 75% night time disturbances & 25% day time disturbances.
- Consensus among all caregivers was that patients' experiences are 80% overnight disturbances and 20% daytime disturbances.

6. Can you tell us what “quality of sleep” means to you and your family? For example, this might mean the length of time your child sleeps, how frequently your child wakes up at night, daytime nap frequency/duration, etc.
- Two caregivers defined “quality of sleep” for the patient as the length of time or duration of sleep without or with fewer awakenings. Caregivers shared their desire for patients to sleep without getting out of bed or roaming the house for hours. Caregivers said they would be able to sleep undisturbed if patients were able to sleep longer.
 - Two caregivers defined “quality of sleep” for their families as the quality and depth of sleep rather than duration. Caregivers indicated that a few hours of deep sleep are more impactful than multiple hours of poor-quality sleep. Caregivers added that prolonged poor-quality sleep does not produce a good day for patients, as compared to even 30 minutes of solid, deep sleep which can improve behavior.
 - One caregiver stated that both length and depth constitute “quality of sleep.” The caregiver mentioned the desire for the patient to experience less awakenings and restorative sleep which helps with the patient’s behaviors and health
7. What has been your experience with medications to treat sleep disturbances in SMS? Which aspects of sleep have been *most improved* by medication therapy, and which aspects have been *least improved*?
- All but one caregiver indicated patients are currently using medications to treat sleep disturbances associated with SMS.
 - All caregivers who are currently using medications to treat sleep disturbances in SMS currently use melatonin. A majority of these caregivers use cannabidiol (CBD) with melatonin to assist patients in falling asleep. Caregivers indicated that although these medications assist patients with going to sleep, they do not help patients stay asleep.
 - A majority of caregivers said they’ve tried several medications many of which were disruptive to patients sleep or had adverse side effects. Antidepressants, antipsychotics, benzodiazepines, clonidine, and blood pressure medications were among the drugs named.
8. If you are not currently using any medications to treat sleep disturbances with SMS, have you used medications or supplements in past? How has that worked for you?
- Caregiver not currently using any medication for patient’s sleep disturbances indicated that melatonin and CBD have been used in past but were both discontinued due to failure to provide consistent effects. The caregiver added that prescription medications have never been used nor is there a plan to do so unless absolutely necessary.

9. What has been your experience using behavioral therapy or behavioral strategies to treat sleep disturbances in SMS? Which aspects of sleep have been *most improved* by behavioral therapy, and which aspects have been *least improved*? Some examples of behavioral strategies might include using a special bed, sealing the windows to light and sound, etc.

- Most caregivers said that patients maintain a strict bedtime routine and good sleep hygiene.
- A majority of caregivers indicated blackout curtains to keep the room as dark as possible, and white noise machines are utilized for SMS patients' sleep. Some caregivers shared that music, books, and shows are played on a tablet or device to help patients sleep.
- Caregivers stated strategies include creating a safe, calm, and secure environment for patients while they sleep. Caregivers discussed their use of monitors, cameras, and alarms to surveil patients. In addition, caregivers shared the use of weighted blankets, safety sleepers, window locks, and alarms on doors. Caregivers expressed removing furniture, televisions, and toys from patients' bedrooms to decrease distractions.
- Caregivers emphasized that behavioral strategies and interventions do not actually *treat* SMS patients' sleep disturbances, but rather are attempts to train their sleep and support a conducive sleep environment.

10. If you could create a treatment (i.e. drug or medication) for sleep disturbances associated with SMS, which experience/behavior would be the *first and most important* symptom you would want to improve or treat?

- All caregivers expressed desire for an SMS treatment to allow patients to sleep for a duration which provides deep, restorative sleep. Caregivers believe restorative sleep at night would improve behaviors. Caregivers expressed concern regarding the impact a lifetime of a lack of sleep will have on patients.
- A caregiver also identified patient's self-injurious behaviors as an important symptom to treat, describing these behaviors as difficult to manage and scary.

11. If you were not able to treat all the sleep disturbances the patient experiences, which aspect(s) would be least problematic to manage if untreated?

- One caregiver indicated that all aspects of sleep disturbances are problematic and important, adding that issues are linked and complex.
- Two caregivers said that the inability to fall asleep is the least problematic. Caregivers highlighted difficulty coping with behaviors like patient's threatening siblings or hitting strangers. Caregivers reiterated desire for restorative sleep.

12. Additional comments:

- Some caregivers emphasized that patients' lack of sleep affect all members of the family. Caregivers believed restorative sleep would impact not only the patient, but all

individuals around the patient. Caregivers added that consistent sleep every night would allow patients to meet the other challenges in their lives.

- Caregivers expressed a desire for a treatment or medication to reduce patient's aggressive behaviors.
- Caregivers said they could be better patients if patients were able to get restorative sleep, adding that the least bit of help would be helpful.

Partner organizations

The National Organization for Rare Disorders (NORD) helped identify and prepare patient community participants.

The Reagan-Udall Foundation for the FDA assisted with producing the summary of this meeting.

NORD and the Foundation were present during the listening session.

FDA divisions represented

- **Office of the Commissioner**, Patient Affairs Staff (*organizer*); Office of Orphan Products Development; Office of Combination Products
- **Center for Biologics Evaluation and Research (CBER)**, Office of the Director
- **Center for Drug Evaluation and Research (CDER)**, Office of Neurology, Division of Psychiatry (*requestor*); Office of New Drugs/Office of Neurology; Office of New Drugs/Office of Neurology/Division of Neurology I; Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Rare Diseases and Medical Genetics (DRDMG); Office of Regulatory Operations (ORO), Division of Regulatory Operations for Neuroscience (DRO-ON); Office of Translational Sciences (OTS), Office of Biostatistics, Division of Biometrics I; Office of Drug Evaluation and Science (ODES), Division of Clinical Outcome Assessment (DCOA)
- **Center for Devices and Radiological Health (CDRH)**, Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships; Office of Product Evaluation and Quality (OPEQ), Office of Health Technology (OHT1), Division of Health Technology - Anesthesia, Respiratory, & ENT Devices; Division of Sleep Disordered Breathing Devices; Office of Science and Engineering Laboratories (OSEL), Division of Biomedical Physics

Patients and caregivers represented

6 caregivers participated in the listening session representing 6 SMS patients.

- Patient ages ranged from 5 to 30 years old.
- Age of onset varied. For example, one patient was diagnosed with SMS at age 17 and another at 10 days old.

Prior to the Listening Session, caregivers shared:

- Problematic aspects of sleep disturbances: Lack of sleep, roaming around home unmonitored, inability to focus, early rising, behavioral issues, and outbursts.
- Management of SMS: Melatonin, CBD, and Clonidine (on occasion).

Financial Interest

Caregivers/Patients did not identify any conflict of interest relevant to this listening session and are not receiving compensation.