Underrecognized Sleep Disorders Across Rare Diseases: Real-world Insights From a Patient and Caregiver Summit

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Abstract

**Background:** Disorders of sleep-wake stability have a negative impact on patient and caregiver quality of life. There is evidence that sleep disorders and their sequelae may be an underrecognized burden for people living with rare diseases. Given that the sleep-wake cycle is regulated via the hypothalamus, people with neurological disorders may be particularly affected. To collect real-world insights into the impact of sleep disturbances and excessive daytime sleepiness (EDS) on people with rare disorders, Harmony Biosciences organized a Summit on Sleep Disruption. The attendees were from seven patient advocacy groups, each representing a rare neurological disorder reporting sleep disturbances, specifically EDS: Angelman syndrome, idiopathic hypersomnia, Kleine-Levin syndrome, myotonic dystrophy, narcolepsy, Prader-Willi syndrome, and Smith-Magenis syndrome. One person represented COMBINEDBrain, a patient advocacy consortium representing 25 rare, genetic neurological disorders.

**Results:** The overwhelming response was that disordered sleep, particularly EDS, is a major health problem within their populations that they feel is not adequately diagnosed or treated. Participants felt that burdens associated with sleep disturbances were underrecognized as a treatable medical issue and were not effectively addressed by health care providers. Participants noted the following unmet needs: patient and physician education on sleep disturbance, effective medications approved for these disease populations, and medically acceptable patient-centered devices to measure sleep parameters. Participants described impacts of disordered sleep and EDS on behavior and school performance, describing impaired wakefulness as an interference with normal daytime functioning. Participants also revealed tremendous burdens on the caregivers and family members who live with people experiencing sleep-wake instability.

**Conclusions:** These results provide real-world insights that disordered sleep including EDS and subsequent impaired daytime functioning are major burdens in these rare disease communities. Furthermore, these burdens are underrecognized for caregivers and, for some rare diseases, among the patients themselves. Participants identified gaps in knowledge and treatment of sleep disorders and resolved to continue the dialog to find ways to raise awareness of disordered sleep and reduce burdens in these patient populations.

**Background**

In many therapeutic areas, treatment is a balance of managing symptoms and addressing the underlying cause of the disease. This balance is informed by clinical knowledge of the disease, availability of effective or curative treatments, severity of symptoms, patient preferences, FDA approval, and other considerations. Treatment strategies are complicated further when the disease has multiple symptoms, some of which may mask others. More significantly, some symptoms may exacerbate other aspects of the same disease. Therapeutic plans to address one symptom may be less effective than anticipated because a secondary, but synergistic, symptom has not been addressed. One such “hidden” factor, particularly in rare neurological diseases, is disordered sleep-wake stability.
Excessive daytime sleepiness (EDS) and other disorders of sleep-wake stability can have a tremendous negative impact on physical and mental health, and on overall quality of life (1). Sleep-wake stability, in contrast to the sleep-wake cycle, relates to the ability to maintain sleep or wakefulness. Quantity and quality of sleep plays a vital role in regulating many bodily functions, with abnormal reductions in quantity and quality of sleep causing physical effects, such as increased activity of the sympathetic nervous system (2), increased inflammatory responses (3), and changes in metabolism (4–7). For example, a recent study reported that children experiencing narcolepsy with cataplexy had increased occurrence of obesity and night eating (8). Disordered sleep also has a significant impact on cognitive ability, as has been shown in studies with children, with the elderly, and with victims of traumatic brain injury, among others (9). Reduced sleep quality can also increase emotional distress, mood swings, behavioral problems, and deficits in cognitive performance (10–12). The cumulative effect of disrupted sleep can lead to severe impairments in daytime wakefulness and cognitive functioning. Such impairments can negatively impact school and job performance with long-term educational and economic impacts (13).

Among people with rare diseases, there is evidence that sleep disorders may be an underrecognized component of their disease burdens, particularly for neurological diseases (14). Studies suggest that while 25% of very young typical children have issues with sleep, that number increases to over 80% among children with neurodevelopmental disorders (15). In almost every case, the disease is relatively well characterized with regard to the primary manifestations, yet the role of sleep disruption on severity and/or frequency of those manifestations is undervalued or overlooked. For example, Prader-Willi syndrome (PWS) is a rare genetic disorder primarily viewed as an endocrine and metabolic disease, (16,17) but there is published evidence that a variety of sleep disorders may be common in this patient population; (18) yet disorders of sleep-wake stability are not adequately addressed by the medical community. There is also growing evidence that sleep disorders, including EDS, are a feature of other neurological diseases like Angelman syndrome (19), myotonic dystrophy (20), and Smith-Magenis syndrome (21).

Quantitative and qualitative studies based upon information collected from patients and caregivers are becoming more accepted as real-world data (RWD) that contributes to the evidence of disease burdens, effectiveness of treatments, and impacts on daily life(22). Recording and analyzing the primary evidence of patient experiences can help shed light on their full patient journey, from initial symptoms through diagnosis, treatment, daily life, and disease burden. In some cases, patient perspectives can provide new insights that are overlooked or not known to the medical community. The US Food and Drug Administration (FDA) recognizes value in RWD (23) and incorporates it into evaluations and decision making. For instance, the FDA provides patients and patient advocates the opportunity to participate in drug development and approval through the Patient-Focused Drug Development initiatives which began in 2012 and were reinforced with the passage of the 21st Century Cures Act in 2016 (23).

To collect RWD regarding burdens of disorders of sleep-wake stability across rare diseases, Harmony Biosciences sponsored a Summit on Sleep Disruption with leading representatives from seven rare
neurological disease patient advocacy groups. The goal of the summit was to learn about burdens related to EDS from those patients and caregivers experiencing it. Attendees were representatives of: Angelman syndrome, idiopathic hypersomnia, Kleine-Levin syndrome, myotonic dystrophy, narcolepsy, Prader-Willi syndrome, and Smith-Magenis syndrome. One person represented COMBINEDBrain, a patient advocacy consortium of 25 additional rare genetic neurological disorders.

Results

**EDS and other sleep disorders are significant in a wide array of diseases**

The overwhelming response across all of the represented patient communities was that disorders of sleep-wake stability are a major health burden, with symptoms unrecognized and/or unaddressed by health care providers. Whereas some impacts of EDS are known in patients diagnosed with idiopathic hypersomnia (24), Kleine-Levin syndrome (25), Smith-Magenis syndrome (26), and narcolepsy (27,28), participants in this Summit reported that sleep disruption, and EDS in particular, is common in many different therapeutic areas including the rare diseases represented at this summit. Summit participants reported that numerous patients within their respective disease areas have some form of sleep disruption, and many are coping with EDS. The nonprofit COMBINEDBrain works with 25 different neurodevelopmental disease communities, and, anecdotally, a majority of communities in the group have reported some type of significant sleep issue. Furthermore, collaborations with other groups in the rare disease space suggest that EDS almost certainly impacts patients beyond the represented therapeutic areas. This anecdotal data suggests that more research is needed to understand how many diseases share this issue, what percentage of patients within these disease areas are impacted, and the range of severity of EDS patients face.

**Burdens stemming from disorders of sleep-wake stability**

Participants described how disrupted sleep and the resulting EDS, has wide-ranging consequences and impacts (Table 1). People with EDS can spend many hours sleeping and yet feel tired when they are awake. Together, these behaviors result in the inability to perform activities of daily living as many patients and caregivers report irritability and overwhelming fatigue when awake, as well as bouts of daytime sleepiness. Fatigue and EDS often lead to difficulties with social interactions and emotional regulation, missed meals, weight loss, loss of muscle mass, and physical pain from lying in bed for hours. Patients and caregivers also frequently report anxiety and depression with participant quotes shown in Figure 1.

Participants commented on how these sleep-related conditions have a negative effect on socialization, on the ability to build and maintain a support network, and on professional advancement. For example, some participants shared stories of people having little time or energy to make social connections, to spend time with friends, and even to interact with work peers. Sleepiness during school or while at work impairs academic and career development and is a major isolating factor. Teenagers with myotonic dystrophy, for example, may sleep several hours in the afternoon, wake for two or three hours, then go to
bed and sleep another 10 hours. In addition, emotional regulation can be impaired such that the patient is not able to live in group homes, presenting an additional burden on caregivers to arrange for care long-term.

EDS can negatively impact cognitive performance, with participants describing conditions ranging from “brain fog” to severely impaired memory and attention. For instance, one participant with adult-onset sleep problems has an advanced degree that they can no longer use because of poor memory and other medical issues. For patients with significant cognitive impairments, communicating about sleep is almost impossible. One participant expressed frustration that Picture Exchange Cards (PECS), used as a tool for individuals with communication disorders, do not include topics related to sleep. These limitations in communication abilities and in alternative communication methods likely mask the extent to which individuals are impacted by EDS or other sleep-wake cycle disruptions.

Though improper sleep is known to impact cognitive abilities, participants said that a connection between EDS and cognitive delay is not typically considered by physicians of patients with diseases known to have such delays. Participants questioned whether their cognition might improve with successful treatment of their sleep disorders. Participants noted that they had seen positive changes in cognition when EDS was controlled in PWS. As an extension, if the sleep disorders are treated early, participants hypothesized that patients might have less of a cognitive impairment than is traditionally accepted as an unavoidable part of the disorder.

Effects of EDS on physical health can have high costs as well. Participants described how some people have no energy to exercise, though some are able to push themselves to exercise, with positive effect. For others, exercise reduces their energy stores. Participants also noted connections between poor sleep and digestive problems, slowed growth, physical endurance, and muscle tone and strength. Another person said that their blood pressure goes up when their sleep disorder is not treated. They also described how the physical fatigue ties in with cognitive functioning, e.g., it can be difficult to mentally focus on tasks that require high level thinking while sleepy.

Financial burdens can be substantial for the people who experience disorders of sleep-wake stability (including EDS) and their caregivers. Participants shared experiences with difficulties in finding the right doctors and accessing regular care, a process that sometimes involved air travel and associated expenses. Moreover, participants described how some people face difficulties getting insurance coverage for sleep medications. Difficulties in finding and keeping jobs, as discussed above, adds additional financial strains for people living with sleep disorders. Aside from reduced productivity and capacity to work, people with sleep disorders also may be forced to pay others to do their household chores. Furthermore, some people cannot live independently, and families have to plan for long-term care in facilities when families are no longer able to provide care.

Taken together, the mental, physical, cognitive, emotional, and financial burdens stemming from disordered sleep, particularly EDS, can be tremendous. Participants agreed that there is a great need for better recognition of these burdens by physicians and by regulators.
Caregiver burdens

Participants also shared information about the tremendous burdens sleep disorders impart on caregivers. Caregivers, typically parents of patients, understand that patients’ sleep patterns affect the entire household. For instance, one participant described how her son calls loudly for her in the middle of the night when he awakens, waking everyone in the household. As such, caregivers can experience many of the same burdens stemming from their own lack of sufficient sleep, e.g., falling asleep at work. In addition, caregivers often have burdens related to caring for other family members in addition to the patient, which can limit their ability to care for their own personal, financial, social, and physical needs.

Health care providers and diagnosis

Participants agreed that interactions with healthcare providers can be very challenging, sometimes feeling insurmountable. Many experienced difficulties in getting health care providers to recognize the importance of their sleep problems, the need for testing and diagnosis, and the need for treatments. The process of finding knowledgeable, effective doctors can be arduous. Some patients and caregivers travel long distances to see effective doctors who are knowledgeable and willing to help them. Participants voiced vigorous agreement about experiences with doctors who blamed parents for their child’s poor sleep hygiene or described patients as lazy and undisciplined. Several participants described their health care providers incorrectly suggesting that cataplexy was a behavioral issue or a tantrum.

Cataplexy is not a behavioral manifestation; it is a neurological symptom of narcolepsy where patients suddenly and unexpectedly lose muscle tone while awake(29). The most prevalent cause of cataplexy may be rare neurological disorders including Angelman syndrome and PWS (31,32). Participants noted that doctors sometimes lack knowledge regarding the etiology of cataplexy, and may not recognize the symptoms in children, especially those with developmental disorders. For instance, one participant recalled a physician stating incorrectly that four-year-old children cannot have cataplexy (30). Another parent discussed how narcolepsy in very young children with neurodevelopmental disorders such as Angelman syndrome may have been misdiagnosed as epilepsy, rather than a sleep disorder, with the sleep disruption actually preceding or provoking subsequent seizures. Participants delineated specific suggestions for educating physicians and providing them with resources that might improve patient-physician interactions and speed diagnosis (Figure 2). Educating physicians, and providing them with tools to recognize symptoms, screen patients for sleep disorders at office visits, and recognize burdens and impacts could increase the likelihood of patients getting a diagnosis and treatment sooner. Participants agreed that physician education around sleep is a key element to improving care.

Treatments

Participants noted that patients needing FDA-approved and effective medications for disorders of sleep-wake stability face several challenges. Participants noted that getting approved and effective medications for disorders of sleep-wake stability is a challenge. For example, patient advocates for people diagnosed with narcolepsy report that current treatment practices do not adequately address the
real-world issues they face. Participants noted that not only is it difficult to get healthcare providers to recognize the significance of EDS, but that it can be difficult in rare diseases to recruit the numbers of patients required to measure primary outcomes necessary to achieve an FDA-approved indication for a given rare disease. Part of this is due to the rarity of the disorders, and part may be due to the burdens associated with clinical trial participation.

To increase participation and speed the clinical trial process, summit participants suggested that trials for EDS treatments might include patients across multiple rare diseases that experience sleep disorders. In other words, EDS clinical trials in the rare disease space might be agnostic to therapeutic area. Such studies have been successfully conducted in oncology, most notably resulting in a tumor-agnostic approval of TRK-fusion inhibitors (33). Participants proposed that a cross-disease study, available to any patient meeting criteria for EDS and/or other sleep disorders, has potential to be an effective, efficient approach to finding effective treatments for these disorders more quickly. Participants proposed the idea that whether treatments for EDS could be approved across diseases.

Participants also revealed difficulties in getting access to medications known to help disorders of sleep-wake stability for themselves or their children, due to lack of insurance coverage. Many insurance companies will not pay for medications that are not approved for the treatment of sleep issues. Participants suggested that label expansions by the FDA could help them rapidly gain access to potentially effective medications. Several participants agreed that patients also face high costs to get the treatments they need. From their perspective, factors contributing to costs included absence of FDA approval for their disease, and limited insurer coverage for off-label prescriptions, especially expensive specialty medications commonly used to treat EDS.

Furthermore, participants noted that health care providers should understand the need for a diagnosis and treatment of sleep disruption as part of comprehensive care for a person with a rare disease. Taken together, participants suggested improving collaboration between patients, caregivers, physicians, insurers, and regulators to facilitate improved access to treatments in rare disease communities living with disordered sleep.

**Diagnostic tools to validate patient burdens with sleep disorders**

Participants discussed several areas of unmet needs related to addressing sleep disruption and daytime functioning outlined in Figure 2. Many participants noted that there is an unmet need for medically acceptable devices to accurately measure sleep parameters in the home setting. For example, they noted that currently available actigraphy may not be accurate for measuring sleep because patients can have limited activity during the day when they are awake because of fatigue. Conversely, they might have excessive physical movements during sleep that would confound the algorithms for measurement. In addition, patient compliance with other modalities can be very difficult for some people with sensory or cognitive disorders. Many patients with Angelman syndrome will not tolerate wrist actigraphy, attempting repeatedly to remove the device, further interrupting sleep and accurate measurement. Stringent
requirements for diagnosis and insurance coverage based on inadequate diagnostic tools can leave some patients suffering from EDS without treatments.

Participants agreed that improved actigraphy tools are needed to accurately measure sleep disorder symptoms and patient and caregiver burdens. They discussed how tools need to be easily manageable in the home setting to conduct decentralized clinical trials and to increase patient compliance. Given modern technologies, participants hope that research is being performed in these areas.

**Insurers and regulators**

Coverage of sleep diagnostic procedures and medications from public and private insurers is also necessary to get patients the treatments they need and to reduce financial burdens on families (Figure 2). Participants shared experiences, describing excessive efforts required to get approval from insurers for coverage. Some patients and caregivers pay high costs for medications while also expending tremendous time and effort in the approval process. Caregiver costs include impacts on careers or lost income due to time spent in these efforts. Participants suggested that diagnostic tools for sleep disorders that are validated across diseases might ease the process for getting approval from insurers for medications that improve sleep.

**Discussing next steps**

Participants discussed working collaboratively to 1) encourage sleep disorder treatment trials that are agnostic to the disease type, and 2) urge the FDA to consider expanding labels to focus on symptoms across diseases. Some patient advocates have experience working with the FDA, and the FDA has been exploring ways to better incorporate patient voices into their decision-making processes. The group agreed to pursue the possibility of requesting a listening session or critical path innovation meeting with the FDA (34) to begin the conversations.

Summit participants reached consensus on action items and initiatives toward two major goals: 1) increase awareness of disorders of sleep-wake stability in the medical and regulatory communities; 2) identify strategies to expedite the FDA-approval and label expansion process. Participants hope that the combination of these two initiatives will be impactful and effective for patients and caregivers. The information gathered from this summit provides real-world insights into the patient and caregiver experiences and their unmet needs. Publishing these insights amplifies patient voices in the medical literature to help educate physicians and researchers. This information might also serve as real-world evidence for the FDA to utilize in their decision-making process.

**Discussion**

This summit provides valuable real-world insights into patient and caregiver experiences in rare neurological disease communities that face heavy burdens from underrecognized disorders of sleep-wake stability, particularly EDS, and its impact on daytime functioning. Members of patient advocacy
groups often share information and provide support to each other through a variety of experiences and formats, such as meeting in-person, online support groups, and educational events. All participants said that, based on their interactions in the community, they think that sleep disorders are common and yet underrecognized by the medical community and regulatory agencies. There is increasing evidence that sleep disorders are common in rare disease communities, particularly for neurological diseases. These sleep disorders are often secondary to the primary symptoms of a rare disease which are more commonly recognized and managed, but the disorders of sleep-wake stability have significant impacts on patients’ lives. However, even though reports exist in the literature (32) patients and caregivers still face challenges in getting the symptoms of sleep disruption and their sequelae recognized and treated by their physicians. Participants with known sleep disorders such as narcolepsy shared similar concerns with the other disease communities. For example, a recent survey documented delays in diagnosis of narcolepsy, particularly for pediatric patients (35).

By asking open-ended questions, summit organizers sought to learn from the patients and caregivers without any bias imposed by asking pointed questions, such as in surveys. The open conversations allowed participants to exchange details while also finding common ground and shared experiences. This manuscript documents the participants’ collective voice regarding the conversations throughout the summit to inform the medical community and regulatory authorities. Participants agreed that optimal awareness and improved treatment options for children with impairments in sleep-wake stability requires collaboration between patients and caregivers, advocacy groups, healthcare professionals, and regulators (Figure 3).

The FDA is increasingly finding ways to incorporate patient voices into their decision-making processes. For example, the FDA developed Project Patient Voice, which is an online platform containing patient-reported symptom data collected during cancer clinical trials (36). Starting with a pilot of one clinical trial, the goal of the program is to provide more patient experience data, in addition to other trial data, so the public and health care providers can learn about potential side effects of certain drugs. The FDA also developed a series of guidance documents related to patient-focused drug development (PFDD) (37). The guidance includes information on how to elicit and collect information from patients. Methods include qualitative analysis, most commonly collected through interviews and focus groups. The approach used in this study is consistent with the PFDD qualitative analysis approach, similar to semi-structured interviews by using open-ended questions while allowing participant priorities to emerge during conversations (37). Summit organizers collected notes and comments to document conversations, and then organized the information by topics and themes to present in a comprehensive manuscript. This work provides valuable insights into the unfiltered patient and caregiver voices regarding their experiences with sleep disorders. The difficulty for these disease communities lies in getting the information disseminated to the medical community and regulators. This publication is a step in that process.

Mechanisms to amplify patient voices are becoming more common (35,36,38–40). Surveys have a long-standing history for gathering information but are often limited in scope and structure. The open-ended
questions in this summit enabled participants to lead the discussion. Social listening is another strategy for collecting RWD regarding disease burdens in an unbiased manner. Social listening is an analytics tool that similarly probes conversations by analyzing social media content for counts of specific words and phrases (39). This approach can be especially valuable for rare disease communities who connect through online support groups from around the world. Social listening confirmed that a PWS support group was discussing sleep issues more frequently than hyperphagia, a primary PWS symptom (39), leading to further inquiries into the problem in PWS. Patient voices can be critical for drug development for rare diseases, particularly in developing endpoints for clinical trials (40). Rare neurological diseases which share sleep disturbances could be candidates for “basket” clinical trials, where an intervention is tested in multiple diseases with a shared outcome measure (i.e. sleep disturbances). This design reduces personnel and financial resources and expedites a path to effective treatments.

The participants’ suggestion that clinical trials for new sleep medications be agnostic to disease type does have precedence, albeit under very different conditions. Three tumor-agnostic therapies have received regulatory approval after clinical trials that included patients regardless of the origin of their tumors; in one case the therapy was approved across 15 tumor types (33) based on tumor genomic signatures rather than standard disease classification. Thus, it is theoretically plausible to use a similar approach to conduct clinical trials for sleep disorders across rare disease populations as long as they all exhibit the sleep disorder that is being targeted for treatment. With this approach, researchers would also benefit by more quickly gathering data about effectiveness and side effects across disease types. Consolidating different diseases has potential to reduce the time and costs of clinical trials. It may be worthwhile to expand beyond the disorders considered here, to include other patients which might experience defined sleep problems that could be considered in such agnostic clinical trials (41).

The US FDA has been working to help people with rare diseases by adapting regulatory approaches through a number of programs, including hosting patient-focused meetings and listening sessions (34). For example, orphan drug designation can be obtained if a sponsor can provide rationale for the use of a drug for a specific rare condition (42). The FDA also requires a shorter review period for orphan drugs when a sponsor applies to expand the label to another rare disease. Some of the participants discussed these options as mechanisms to speed drug treatment approval for their communities, and some had experience in helping obtain such approvals. By combining their efforts as advocates for a number of rare diseases, summit participants hope to be more effective in increasing recognition that disorders of the sleep-wake cycle are an important aspect of the symptomatology of the diseases they represent. Amplifying their voices through this publication of the summit outcomes can help bring awareness to the medical and research communities. Furthermore, the group resolved to pursue an application for a meeting with the FDA (34) to move toward approvals for treatments across disorders.

**Conclusions**

Our work provides first-hand evidence of the impact of EDS, disorders of sleep-wake stability, and their sequelae on patient and caregiver quality of life. Participants in the summit, advocacy group leaders, and
patients representing patient communities with rare neurological diseases passionately described patient and caregiver burdens and needs as they relate to disrupted sleep. They agreed that sleep problems are common in their disease areas. They identified critical gaps in knowledge, diagnostics, and treatments of EDS and sleep disruption. This paper documents this information as real-world insights into patient experiences that can provide important information to health care providers and researchers. Participants resolved to continue their dialogue and explore initiatives with the anticipation that collectively they can help ensure that sleep disorders are clinically recognized and better managed for people with rare diseases. As a step towards this goal, participants will pursue an application for a meeting with the FDA (34).

Methods

The Summit on Sleep Disruption was held via a recorded online group meeting on December 14, 2020, with all participants visible on screen together. The moderator asked 12 open-ended questions (described in Table 2) which focused on three areas: 1) the physical, emotional, social, and cognitive challenges of EDS and the impact of these challenges on daily functioning; 2) the challenges associated with EDS in patients with other primary symptoms; and 3) the overall impact of EDS and related symptoms on burden of illness, caregiver and family burden, and financial/economic challenges. Responses were synthesized, major points of agreement were extracted, and quotes were captured to represent the voices and viewpoints of participants.

Participants included: Casey Gorman, Executive Director, Parents and Researchers Interested in Smith-Magenis Syndrome; Erica Kelly, person with myotonic dystrophy; Jeremy Kelly, Board Chair & Lifetime Trustee, Myotonic Dystrophy Foundation; Lara Pullen, PhD, President and Co-Founder, Chion Foundation; Lindsay Jesteadt, PhD, Director of Development, Wake Up Narcolepsy; Paige Rivard, Chief Executive Officer, Prader-Willi Syndrome Association USA; Rebecca King, Board Member, Hypersomnia Foundation; Sharon O'Shaughnessy, Board Member, Narcolepsy Network; Steve Maier, President, KLS Foundation Board of Directors; Theresa Strong, PhD, Director of Research Programs, Foundation for Prader-Willi Research; and Terry Jo Bichell, PhD, MPH, Executive Director, COMBINEDBrain. COMBINEDBrain is a patient advocacy consortium that supports 25 rare genetic neurodevelopmental disorders.

Declarations

Ethical approval, consent to participate and publish: All summit participants provided their written and verbal consent to record the summit with the purpose of publishing the main concepts of the summit.

Consent for Publication: Not Applicable.

Data Availability: Any data generated from the summit can and will be made publicly available to any interested researcher by contacting the corresponding author.
Competing Interests and Funding: The authors declare no conflicts of interest related to this manuscript. The summit was sponsored by Harmony Biosciences.

Authors’ contributions: All authors participated in the summit. MP, MN, TJB and ACP drafted the manuscript with all authors reviewing the draft and providing written consent of their approval to submit.

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**Tables**

**Table 1. Burdens Reported by the Summit on Sleep Disruption Participants**
| Category                  | Burdens                                                                                       |
|--------------------------|-----------------------------------------------------------------------------------------------|
| Physical Health/Fatigue  | Weight loss, muscle loss, pain from lying in bed for many hours, poor nutrition, high blood pressure, frequent fatigue, reduced physical endurance, reduced strength, falling asleep during the day |
| Activities of Daily Living | Dependent upon others for housecleaning and cooking, missed school, little time for homework, poor quality homework, lost jobs |
| Socialization/Emotional  | Anxiety, depression, emotional outbursts, behavioral outbursts, reduced emotional regulation, stress from poor school performance, social isolation, missed social opportunities, isolation from depression, moods that stress relationships, limits to caregiver social life, avoids dating |
| Cognition/Neurological   | Foggy brain, reduced attention span, memory loss, slowed processing speed, loss of consciousness, drop attacks interpreted as tantrums, poor concentration during work and school |
| Financial                | Reduced or no income, reduced ability to work, costs to pay others to do daily tasks like housework and cooking, costs associated with reduced independence, and reliance on care, costs of travel to disease specialists, costs of finding specialized doctors, high credit card bills to pay for medications |

**Table 2. Open-Ended Questions Discussed During Summit on Sleep Disruption**

1. How does EDS impact physical health?
2. If you think about the day-to-day life of sleep disruption, how would you describe to someone how this affects your life day to day?
3. When you think about being a parent of a child with sleep issues – how do you separate behavioral issues that are normal from things that are based on sleepiness?
4. How is the workforce and advancement impacted?
5. Do people not have control of their emotions? Is this a real problem?
6. Does it make it easier because you go through long periods of normality or harder because out of the blue your life is disrupted?
7. How does that impact relationship building?
8. What is the financial impact of EDS?
9. What kinds of resources and support are available to you to deal with EDS? What is missing?
10. In your experience in talking to doctors about sleep issues, how has that gone?
11. How common is it in a sleep issue to have a multidisciplinary team to coordinate issues?
12. How do patients choose what treatments to use?
Figure 1: Quotes Reflecting Reported Patient Burdens Associated with Disorders of Sleep-Wake Stability

| Physical Health/Fatigue          | Activities of Daily Living                  | Socialization/Emotional          | Cognition/Neurological       | Financial               |
|---------------------------------|---------------------------------------------|----------------------------------|-----------------------------|-------------------------|
| “How we feel at the end of a long week is how they feel on a Monday morning having had ten hours of sleep” | “Exercise is almost impossible, and it takes almost an hour to get out of bed with multiple alarms and people calling you and shaking you.” | “My son who is 20 had a robust dating history in high school and in college. After he graduated...it was too much energy and felt he needed to straighten his disease out.” | “He can’t stay awake long enough to complete a task – his memory is gone and he has no idea where he is often.” | “The mental health part is brutal – he is one step away from being fired.” |
| “I know people who sleep so long that they have issues with their joints because they sleep in certain positions without moving for hours at a time.” | “I am sleepy taking care of him. I drink so much coffee, have fallen asleep at red lights, I don’t exercise...daytime sleepiness for caregivers is a huge problem.” | “In terms of partner or spouse, they have to sign up for it – they are signing up for the spouse’s illness but maybe also a child’s” | “The daytime sleepiness really affects her processing speed - she struggles to retrieve information or do simple things like tell time.” | “Our nest will never be empty. Our parenting will go on for a long, long time.” |

Figure 1

Quotes from Summit participants which reflect the burdens associated with disorders of sleep-wake stability.

Figure 2: Rare Disease Community Needs Related to Sleep Disruption and Daytime Functioning

**Patient and caregiver needs**

- Tools that accurately reflect burden of sleep disruption and its impact on daily functioning
- Access to knowledgeable doctors and treatments to manage symptoms of sleep disruption and its sequelae
- Removal of barriers impeding insurance coverage for medications
- Participation in clinical trials to accelerate data generation needed for approval of new treatment options
- Recognition that other symptoms of a disease (e.g. behavioral, cognitive) may be ‘downstream’ effects of sleep disruption and excessive daytime sleepiness (EDS)

**Physician needs to improve care of patients with disorders of sleep-wake stability**

- Understanding that disorders of sleep-wake stability are common in rare diseases
- Resources to improve physician recognition of disorders of sleep-wake stability across diseases
- Tools to screen for disorders of sleep-wake stability at time of diagnosis and follow ups
- More information on medications to treat EDS

**Regulatory actions to facilitate improved care of patients with disorders of sleep-wake stability**

- Incorporate real-world evidence into decision-making processes
- Accept clinical trials for rare diseases that are agnostic to disease type to speed access to effective treatments
- Provide flexibility in clinical trial outcomes to facilitate effective and efficient trial design
- Expansion of FDA approvals
Figure 2

Rare Disease community needs related to sleep disruption and daytime functioning. These needs are identified as those corresponding to: i) patients and caregivers, ii) physicians, and iii) regulators.

Figure 3: Collaborations to Facilitate Awareness Around Disorders of Sleep-Wake Stability

Patients, Caregivers & Advocacy Groups

Healthcare Providers

Regulators

Figure 3

Summit participants outlined ways in which patients, caregivers, advocacy groups, healthcare providers, and regulators could facilitate increased awareness around disorders of sleep-wake stability in rare diseases. Patients, Caregivers & Advocacy groups provide increasing awareness of symptoms (AoS) to Healthcare Providers. Both groups provide real-world data (RWD) to Regulators to highlight burdens. Patients, Caregivers & Advocacy Groups organized listening sessions (LS) with Regulators to increase awareness. Healthcare providers provide insights into biomarkers and outcome measures (BOM) for disease.