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 (QoL). There is evidence that sleep disorders and their sequelae may be underrecognized burdens 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 disorders of sleep-wake stability and excessive daytime sleepiness (EDS) on people with rare disorders, Harmony Biosciences organized a Summit on Sleep Disruption.

Methods: Summit attendees were from 8 patient advocacy groups, each representing a rare, neurological disorder for which patients report sleep disturbances. The Summit occurred via video teleconference, and video recordings and audio transcripts of the entire meeting were generated. The contents of the audio transcripts were analyzed for concepts representing areas of unmet need and underrecognized secondary symptoms of rare diseases and their burden.

Results: The overwhelming response among the Summit participants was that disordered sleep, including EDS, is a major health problem within their populations. Participants felt that burdens associated with sleep disturbances were underrecognized as a treatable medical issue and were not effectively diagnosed or

addressed by healthcare professionals. They described the impacts of disordered sleep and EDS on behavior and school performance, namely, the interference of impaired wakefulness with normal daytime functioning and QoL. Participants also communicated the tremendous strains on caregivers and family members who live with people experiencing sleep-wake instability.

Conclusions: These results provide real-world insights into the major burdens related to disordered sleep, including EDS and subsequent impaired daytime functioning, in these rare disease communities. These concerns are underrecognized by healthcare professionals, caregivers, and, for some rare diseases, even the patients themselves. Participants identified gaps in the treatment of sleep disorders and resolved to use further dialog to raise awareness of disordered sleep and reduce burdens for those living with the aforementioned rare diseases.

Background

In clinical practice, treatment is often a balance of managing symptoms and addressing the underlying cause of a disease. This balance is informed by clinical knowledge of the disease, the availability of effective or curative treatments, the severity of symptoms, patient and caregiver preferences, US Food and Drug Administration (FDA) approval, and other considerations. Treatment strategies are further complicated by—and sometimes less effective for—diseases presenting with multiple symptoms and comorbidities, some of which may mask others or, more significantly, exacerbate other aspects of the same disease. An example of such a "hidden" factor, particularly in rare neurological diseases, is disordered sleep-wake stability.

Excessive daytime sleepiness (EDS) and other disorders affecting 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. The quantity and quality of sleep have vital roles in regulating many bodily functions, and abnormal reductions in these have physical effects, such as increased activity of the sympathetic nervous system,[2] increased inflammatory response,[3] and changes in metabolism.[4-7] Reduced sleep quality can also increase emotional distress, mood swings, behavioral problems, and deficits in cognitive performance.[8-10] Such impairments can negatively affect school and job performance, with long-term educational and economic impacts.[11]

Among people with rare diseases, sleep disorders may be an underrecognized component of their disease burdens, particularly for neurological diseases.[12] For example, Prader-Willi syndrome (PWS) is a rare genetic disorder that is primarily viewed as an endocrine and metabolic disease,[13,14] but recent findings indicate that a variety of sleep disorders may be common in this patient population.[15,16] Growing evidence shows that sleep disorders, including EDS, are often a feature of other neurological diseases, such as Angelman syndrome,[17] myotonic dystrophy,[18] and Smith-Magenis syndrome.[19] Despite this evidence, disorders of

sleep-wake stability unfortunately are not adequately addressed by the medical community; therefore, different types of data are needed to characterize the patient and caregiver experiences of sleep disorders to best inform treatment.

Findings from quantitative and qualitative studies that collect information from patients and caregivers are increasingly accepted as real-world data (RWD) that contribute to the evidence of disease strain, effectiveness of treatments, and effects on daily life.[20] Recording and analyzing the primary evidence that is the patient experience can help shed light on the entire patient journey from initial symptoms to diagnosis, treatment, daily life, and disease burden.

Methods

The Summit on Sleep Disruption was held via a recorded online group meeting on December 14, 2020, with all participants visible onscreen together, sponsored by Harmony Biosciences. Summit participants included:

- Casey Gorman, Executive Director, Parents and Researchers Interested in Smith-Magenis Syndrome
- Erica Kelly, a person with myotonic dystrophy
- Jeremy Kelly, Board Chair and Lifetime Trustee, Myotonic Dystrophy Foundation
- Lara C. 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 V. Strong, PhD, Director of Research Programs, Foundation for Prader-Willi Research
- Terry Jo Bichell, PhD, MPH, Executive Director, COMBINEDBrain

The moderator asked 12 open-ended questions (see Table 1) focused on 3 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 disorders of sleep-wake stability in patients with other primary symptoms; and (3) the overall impact of sleep-wake instability and related symptoms on burden of illness, caregiver and family strain, and financial/economic challenges.

Table 1. Open-ended questions discussed during the 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?

Video and audio transcripts of the Summit were analyzed to gather data on novel disease burdens associated with sleep-wake instability as well as unmet needs within these communities experiencing sleep disturbances (Figure 1). Our data analysis aligns with the standards outlined by O'Brien et al for qualitative research.[21]

Results

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

The overwhelming response across all represented Summit patient communities was that sleep disruption, and EDS in particular, is common in many therapeutic areas, including the rare diseases represented at this Summit. Some impacts of EDS are known in patients diagnosed with idiopathic hypersomnia,[22] but also in conditions such as Kleine-Levin syndrome,[23] Smith-Magenis syndrome,[19] narcolepsy,[24-26] and those represented by COMBINEDBrain. More research is needed to understand how many diseases share this issue, what percentage of patients within these disease areas are affected, and the range of symptom severity of patients with EDS face.

Burdens stemming from disorders of sleep-wake stability

Participants described how disrupted sleep and the resulting EDS have wide-ranging consequences and impairment (Table 2).

Table 2. Burdens reported by summit participants related to sleep disruption

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, avoiding 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

Physically, people with EDS can sleep for many hours and yet still feel tired when they are awake. Fatigue and EDS often lead to difficulties with missed meals, weight loss, loss of muscle mass, and physical pain from lying in bed for hours. Participants noted connections between poor sleep and digestive problems, slowed growth, lower physical endurance, and reduced muscle tone and strength. Participant quotes on various domains of life are shown in Figure 2.

Participants commented on the negative effects of sleep-related conditions on their social interactions, ability to build and maintain a support network, and academic and career development. Patients and caregivers frequently report experiencing anxiety and depression. These effects can also be very isolating; for example, teenagers with myotonic dystrophy may sleep for several hours in the afternoon, wake for 2 or 3 hours, and then go back to bed and sleep another 10 hours.

EDS can impair cognitive performance, with participants describing conditions ranging from “brain fog” to severely decreased memory and attention. They also described how physical fatigue ties in with cognitive functioning; for example, it can be difficult to focus on tasks that require high-level thinking while one feels sleepy. Patients with significant cognitive impairments report that it is almost impossible to communicate about their experiences with sleep, even with aids such as Picture Exchange Cards (PECS), which do not include topics related to sleep experiences. These communication limitations likely mask the extent to which individuals are affected by EDS or other sleep-wake cycle disruptions.

Financial burdens can be substantial for the people who experience sleep-wake stability disorders (including EDS). Summit participants shared difficulties in finding doctors who could adequately address

their needs, a process that sometimes involved significant travel expenses in their search for a suitable clinician. They described difficulties obtaining insurance coverage for sleep medications, likely because of a lack of FDA approval and limited coverage for the off-label prescriptions typically used to treat sleep disorders. Other expenses, resulting from participants' reduced productivity and capacity to work, were having to hire others to complete household chores.

Caregiver burdens

Participants also shared information about the tremendous burdens that sleep disorders impart on caregivers. Caregivers, who are typically parents of patients, related how patients' sleep patterns affect the entire household. For instance, 1 participant described how her son calls loudly for her in the middle of the night, waking everyone in the household. As a result, these caregivers can experience many of the same hardships stemming from their own lack of sleep—for example, falling asleep at work. In addition, caregivers often report challenges related to caring for family members other than the patient as well as addressing their own personal, financial, social, and physical needs. Caregivers may also experience a loss in income resulting from time spent on these efforts. Long term, patients' physical, social, and emotional challenges may preclude them from living in group homes, presenting an additional burden on caregivers to arrange for long-term care.

Healthcare professionals and their role in diagnosis

Participants agreed that challenges in interactions with healthcare professionals (HCPs) can be very difficult, if not insurmountable. The process of finding knowledgeable, effective doctors can be arduous. Many described difficulties in getting HCPs to recognize the significance of the sleep problems experienced by their loved ones, as well as the need for appropriate testing, accurate diagnosis, and effective treatments.

Some experiences were symptom specific; for instance, 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. One such participant recalled a physician stating incorrectly that 4-year-old children cannot have cataplexy; however, research has shown that children indeed can have cataplexy.[27] Another parent discussed how narcolepsy in very young children with neurodevelopmental disorders such as Angelman syndrome may be misdiagnosed with epilepsy, rather than a sleep disorder, with the sleep disruption actually preceding and provoking subsequent seizures. Participants were in strong agreement about experiences in which doctors blamed parents for their child's poor sleep hygiene or described patients as lazy and undisciplined. They delineated specific suggestions for educating physicians and providing them with resources that might improve patient/caregiver–physician interactions and expedite diagnosis (Figures 1 and 3).

Diagnostic tools to validate patient burdens with sleep disorders

Summit participants noted that there is an unmet need for acceptable devices that accurately measure sleep parameters in the home setting. Challenges with currently available actigraph devices are that

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 measurement algorithms. In addition, patient compliance with other modalities can be very difficult for some people with sensory or cognitive disorders. For example, many patients with Angelman syndrome will not tolerate wrist actigraphy and will repeatedly attempt to remove the device. This further interrupts sleep and accurate measurements. Stringent requirements for diagnosis and insurance coverage mean adequate diagnostic tools are necessary for patients with EDS to procure proper treatment.

Treatments

Participants noted several challenges for patients needing FDA-approved and effective medications for disorders of sleep-wake stability, with patient advocates reporting that current treatment practices do not adequately address the real-world issues faced by individuals living with narcolepsy. In addition, when developing treatments in rare disease communities, it has been difficult to recruit the numbers of patients required to measure primary outcomes necessary to achieve an FDA-approved indication for the given rare disease. To increase participation and speed the clinical trial process, Summit participants proposed that a cross-disease study that is available to any patient meeting the criteria for EDS and/or other sleep disorders has potential to be an effective, efficient approach.

Discussing next steps

When discussing next steps, participants mentioned the need to work collaboratively to (1) encourage sleep disorder treatment trials that are agnostic to disease type and (2) urge the FDA to consider expanding labels to focus on symptoms that are present across diseases. The group agreed to pursue the possibility of requesting a listening session or critical path innovation meeting with the FDA[27] to begin those conversations.

Summit participants reached consensus on action items and initiatives toward 2 major goals: (1) increase awareness of disorders of sleep-wake stability in the medical and regulatory communities and (2) identify strategies to expedite the FDA approval and label-expansion process. Participants hope that the combination of these 2 initiatives will be effective for patients and caregivers in these efforts. as well as agreeing that optimal awareness and improved treatment options for children with impairments in sleep-wake stability require collaboration among patients and caregivers, advocacy groups, HCPs, and regulators (Figure 3).

Discussion

This Summit provides valuable real-world insights into patient and caregiver experiences in rare neurological disease communities. All these individuals face significant burdens related to underrecognized disorders of sleep-wake stability, particularly EDS. Summit organizers collected notes and comments to

document conversations and then organized the information by topic and theme to present in a comprehensive manuscript. Publication of these insights will amplify patient voices in the medical literature to help educate physicians and researchers; this could be a crucial step in the development of drugs for rare diseases, particularly in developing endpoints for clinical trials.[29] The FDA is increasingly finding ways to incorporate patient voices into their decision-making processes. For example, the FDA developed a series of guidance documents related to patient-focused drug development (PFDD).[30] The guidance includes information on how to elicit and collect information from patients. The approach used in this study is consistent with the PFDD qualitative analysis approach, which began in 2012 and was reinforced with the passage of the 21st Century Cures Act in 2016.[31]

The FDA has also been working to help people with rare diseases by adapting regulatory approaches through a number of programs.[28] 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.[32] The FDA also requires a shorter review period for orphan drugs when a sponsor applies to expand the label to another rare disease. By combining their efforts as advocates for a number of rare diseases, Summit participants hoped to be more effective in increasing recognition that sleep-wake cycle disorders are an important aspect of the symptomatology of the diseases they represent.

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 1 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 ("basket" trials). Consolidating research for different diseases has potential to reduce the time and cost requirements of clinical trials.[34]

Social listening is an analytics tool that similarly probes conversations by analyzing social media content to collect RWD regarding disease burden in an unbiased manner.[35] This approach can be especially valuable for rare disease communities who connect through online support groups from around the world. Social listening in a PWS support group confirmed that participants were discussing sleep issues more frequently than hyperphagia, a primary PWS symptom[35]; this led to further inquiries into sleep problems in PWS.

Conclusions

Our work provides first-hand evidence of the impact of EDS, sleep-wake stability disorders, and their sequelae on patient and caregiver QoL. 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. Participants 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 HCPs and researchers. Participants resolved to continue their dialogue and explore initiatives with the anticipation that they can collectively ensure that sleep disorders are clinically recognized and better managed for people with rare diseases. As a step toward this goal, the group resolved to pursue an application for a meeting with the FDA to move toward approvals for treatments across disorders.[28]

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.

Data availability: Any data generated from the Summit can and will be made publicly available to any interested researcher by contacting the corresponding author.

Author disclosure statements: Ms Picone is a co-owner of TREND Community. TREND Community extracts and analyzes information from social media for the benefit of rare disease communities and to further clinical research that leads to improvements in their quality of life. TREND is a Public Benefit Corporation, an entity that allows it to be self-supporting without needing to fundraise. The results of the analyses have no bearing on the revenue incurred, thus avoiding any pressure to introduce bias into the analysis. The analyses provide information to TREND Community clients who choose what to do with the information.

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References

1. Medic G, Wille M, Hemels M. Short- and long-term health consequences of sleep disruption. *Nat Sci Sleep*. 2017;9:151-161. doi:10.2147/NSS.S134864

2. Seravalle G, Mancia G, Grassi G. Sympathetic nervous system, sleep, and hypertension. *Curr Hypertens Rep*. 2018;20(9):74. doi:10.1007/s11906-018-0874-y

3. Hurtado-Alvarado G, Domínguez-Salazar E, Pavon L, Velázquez-Moctezuma J, Gómez-González B. Blood-brain barrier disruption induced by chronic sleep loss: low-grade inflammation may be the link. *J Immunol Res*. 2016;2016:4576012. doi:10.1155/2016/4576012

4. Mohammadi S, Moosaie F, Saghazadeh A, Mahmoudi M, Rezaei N. Metabolic profile in patients with narcolepsy: a systematic review and meta-analysis. *Sleep Med*. 2021;81:268-284. doi:10.1016/j.sleep.2021.02.040

5. Mohammadi S, Dolatshahi M, Zare-Shahabadi A, Rahmani F. Untangling narcolepsy and diabetes: pathomechanisms with eyes on therapeutic options. *Brain Res*. 2019;1718:212-222. doi:10.1016/j.brainres.2019.04.013

6. Reutrakul S, Punjabi NM, Van Cauter E. Impact of sleep and circadian disturbances on glucose metabolism and type 2 diabetes. In: Cowie CC, Casagrande SS, Menke A, et al, eds. *Diabetes in America*. 3rd ed. National Institute of Diabetes and Digestive and Kidney Diseases; 2018. Accessed May 6, 2021. http://www.ncbi.nlm.nih.gov/books/NBK568006/

7. Kim CE, Shin S, Lee H-W, et al. Association between sleep duration and metabolic syndrome: a cross-sectional study. *BMC Public Health*. 2018;18(1):720. doi:10.1186/s12889-018-5557-8

8. Taillard J, Sagaspe P, Philip P, Bioulac S. Sleep timing, chronotype and social jetlag: Impact on cognitive abilities and psychiatric disorders. *Biochem Pharmacol*. 2021;191:114438. doi:10.1016/j.bcp.2021.114438

9. Modi AC, Mara CA, Schmidt M, Smith AW, Turnier L, Wade SL. Pilot executive functioning intervention in epilepsy: behavioral and quality of life outcomes. *J Pediatr Psychol*. 2021;46(4):363-374. doi:10.1093/jpepsy/jsaa119

10. Difrancesco S, Penninx BWJH, Riese H, Giltay EJ, Lamers F. The role of depressive symptoms and symptom dimensions in actigraphy-assessed sleep, circadian rhythm, and physical activity. *Psychol Med*. 2022;52(13):2760-2766. doi:10.1017/S0033291720004870

11. Skaer TL, Sclar DA. Economic implications of sleep disorders. *Pharmacorconomics*. 2010;28(11):1015-1023. doi:10.2165/11537390-000000000-00000

12. Agar G, Brown C, Sutherland D, Coulborn S, Oliver C, Richards C. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. *Mol Autism*.

2021;12:18. doi:10.1186/s13229-021-00426-w

13. Fermin Gutierrez MA, Mendez MD. Prader-Willi syndrome. In: *StatPearls*. StatPearls Publishing; 2021. Accessed May 21, 2021. http://www.ncbi.nlm.nih.gov/books/NBK553161/
14. Emerick JE, Vogt KS. Endocrine manifestations and management of Prader-Willi syndrome. *Int J Pediatr Endocrinol*. 2013;2013(1):14. doi:10.1186/1687-9856-2013-14
15. Cataldi M, Arnaldi D, Tucci V, et al. Sleep disorders in Prader-Willi syndrome, evidence from animal models and humans. *Sleep Med Rev*. 2021;57:101432. doi:10.1016/j.smrv.2021.101432
16. Duis J, Pullen LC, Picone M, et al. Diagnosis and management of sleep disorders in Prader-Willi syndrome. *J Clin Sleep Med*. 2022;18(6):1687-1696. doi:10.5664/jcsm.9938
17. Spruyt K, Braam W, Curfs LM. Sleep in Angelman syndrome: a review of evidence. *Sleep Med Rev*. 2018;37:69-84. doi:10.1016/j.smrv.2017.01.002
18. Romigi A, Franco V, Placidi F, et al. Comparative sleep disturbances in myotonic dystrophy types 1 and 2. *Curr Neurol Neurosci Rep*. 2018;18(12):102. doi:10.1007/s11910-018-0903-x
19. Shayota BJ, Elsea SH. Behavior and sleep disturbance in Smith-Magenis syndrome. *Curr Opin Psychiatry*. 2019;32(2):73-78. doi:10.1097/YCO.0000000000000474
20. Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: the changing landscape of the regulatory approval process. *Pharmacoepidemiol Drug Saf*. 2020;29(10):1201-1212. doi:10.1002/pds.4932
21. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med*. 2014;89(9):1245-1251. doi:10.1097/ACM.0000000000000388
22. Bollu PC, Manjamalai S, Thakkar M, Sahota P. Hypersomnia. *Mo Med*. 2018;115(1):85-91.
23. Arnulf I, Groos E, Dodet P. Kleine-Levin syndrome: a neuropsychiatric disorder. *Rev Neurol (Paris)*. 2018;174(4):216-227. doi:10.1016/j.neurol.2018.03.005
24. Zhang M, Inocente CO, Villanueva C, et al. Narcolepsy with cataplexy: does age at diagnosis change the clinical picture? *CNS Neurosci Ther*. 2020;26(10):1092-1102. doi:10.1111/cns.13438
25. Abad V, Guilleminault C. New developments in the management of narcolepsy. *Nat Sci Sleep*. 2017;9:39-57. doi:10.2147/NSS.S103467
26. Kornum BR, Knudsen S, Ollila HM, et al. Narcolepsy. *Nat Rev Dis Primers*. 2017;3:16100. doi:10.1038/nrdp.2016.100
27. Pillen S, Pizza F, Dhondt K, Scammell TE, Overeem S. Cataplexy and its mimics: clinical recognition and management. *Curr Treat Options Neurol*. 2017;19(6):23. doi:10.1007/s11940-017-0459-0

28. FDA patient listening sessions. US Food and Drug Administration (FDA). Updated March 29, 2023. Accessed April 6, 2023. https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions

29. Deal LS, Goldsmith JC, Martin S, Barbier AJ, Roberds SL, Schubert DH. Patient voice in rare disease drug development and endpoints. *Ther Innov Regul Sci*. 2017;51(2):257-263. doi:10.1177/2168479016671559

30. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients: Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. Food and Drug Administration (FDA), US Department of Health and Human Services. Published February 2022. Accessed April 6, 2023. https://www.fda.gov/media/131230/download

31. Real-world evidence US Food and Drug Administration (FDA). Updated April 5, 2023. Accessed April 3, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

32. Ahmed MA, Okour M, Brundage R, Kartha RV. Orphan drug development: the increasing role of clinical pharmacology. *J Pharmacokinet Pharmacodyn*. 2019;46(5):395-409. doi:10.1007/s10928-019-09646-3

33. Looney A-M, Nawaz K, Webster RM. Tumour-agnostic therapies. *Nat Rev Drug Discov*. 2020;19(6):383-384. doi:10.1038/d41573-020-00015-1

34. Lu C, Li X, Broglio K, et al. Practical considerations and recommendations for master protocol framework: basket, umbrella and platform trials. *Ther Innov Regul Sci*. 2021;55(6):1145-1154. doi:10.1007/s43441-021-00315-7

35. Picone M, Inoue S, DeFelice C, et al. Social listening as a rapid approach to collecting and analyzing COVID-19 symptoms and disease natural histories reported by large numbers of individuals. *Popul Health Manag*. 2020;23(5):350-360. doi:10.1089/pop.2020.0189

Figure 1. 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

- **An 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

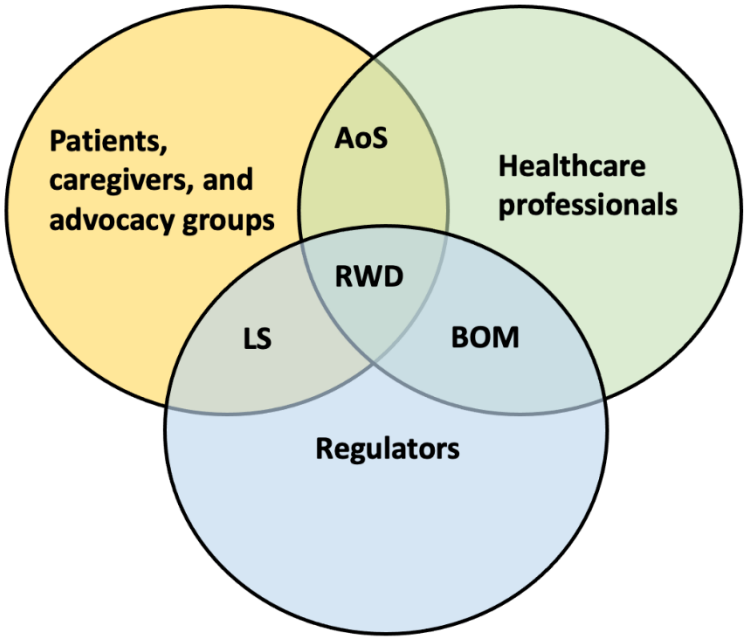
- **Incorporate real-world evidence into decision-making processes**
- **Accept clinical trials for rare diseases that are agnostic to disease type to speed access to effective treatments**
- **Provide flexibility in clinical trial outcomes to facilitate effective and efficient trial design**
- **Facilitate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

Needs are identified as those corresponding to (i) patients and caregivers, (ii) physicians, and (iii) regulators.

Figure 2. Quotes from Summit participants that reflect the 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 10 hours of sleep." "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."	"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." "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."	"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." "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."	"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 daytime sleepiness really affects her processing speed; she struggles to retrieve information or do simple things like tell time."	"The mental health part is brutal – he is 1 step away from being fired." "Our nest will never be empty. Our parenting will go on for a long, long time."

Figure 3. Ways that various parties can facilitate awareness of sleep disorders in rare diseases



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