31 Hudson Yards | 11th Floor | New York, NY 10001
+1 212 620 2770 | **VOZAdvisors.com**

Summit on Sleep Disruption
White Paper

In many disease states, treatment is a balance of – or decision between – managing symptoms and addressing the underlying cause of the disease. This balance is informed by typical progression of the disease, availability of effective or curative treatments, severity of symptoms, patient/caregiver preferences, 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. If the former are less well known or not as readily manifested as the latter, therapeutic plans to address one symptom may be less effective than anticipated because a secondary, but synergistic, symptom has not been addressed. Often in rare diseases, one such "hidden" symptom is sleep disruption, including excessive daytime sleepiness (EDS).

The impact of EDS is well known in the rare disorder narcolepsy, with documented deleterious effects on a wide range of activities, from learning in school to being able to drive a car.[1] A study of children and adolescents with narcolepsy showed significantly reduced health-related quality of life (HrQoL) as well as elevated stress, impaired adaptive skills, and reduced social and conceptual abilities.[2] A more recent study in adults noted similar reduction in HrQoL, with elevated scores on the Patient Reported Outcomes Information System (PROMIS) for anxiety, depression, and fatigue.[3]

Less well recognized, however, is the significance of EDS in other disease states, even though some form of sleep disruption is reported in a wide range of diseases, many of which are neurologic, rare, and impacting children. Studies suggest that while 25% of very young children have issues with sleep, that number increases to over 80% among children with neurodevelopmental disorders.[4] In many cases, the disease is relatively well characterized with regard to the primary manifestations, yet the role of sleep disruption in the severity and/or frequency of those manifestations may be underestimated or ignored by health care providers.

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[1] Raggi, Alberto MD*; Plazzi, Giuseppe MD†‡; Ferri, Raffaele MD§ Health-Related Quality of Life in Patients With Narcolepsy, The Journal of Nervous and Mental Disease: February 2019 - Volume 207 - Issue 2 - p 84-99 doi: 10.1097/NMD.0000000000000918

[2] Attila Szakács, John Eric Chaplin, Pontus Tideman, Ulf Strömberg, Jannie Nilsson, Niklas Darin, Tove Hallböök, A population-based and case-controlled study of children and adolescents with narcolepsy: Health-related quality of life, adaptive behavior and parental stress, European Journal of Paediatric Neurology, Volume 23, Issue 2, 2019, Pages 288-295, ISSN 1090-3798

[3] Jason C. Ong, Rina S. Fox, Rylee F. Brower, Sophia Mazurek & Cameron Moore (2021) How Does Narcolepsy Impact Health-Related Quality of Life? A Mixed-Methods Study, Behavioral Sleep Medicine, 19:2, 145-158, DOI: 10.1080/15402002.2020.1715411

[4] Dosier, Laura B.M.; Vaughn, Bradley V.; Fan, Zheng. 2017. "Sleep Disorders in Childhood Neurogenetic Disorders" *Children* 4, no. 9: 82. https://doi.org/10.3390/children4090082

In December 2020, a group of patient advocates representing a variety of rare diseases with reported complications around sleep convened in a virtual summit to discuss the role EDS plays in their respective patient communities. In particular, the group was interested in determining whether their constituents might benefit from shared learning across these disease states.

Participants included:

- Terri Jo Bichell, PhD, MPH, Executive Director, COMBINEDBrain
- Casey Gorman, Executive Director, Parents and Researchers Interested in Smith-Magenis Syndrome
- Lindsay Jesteadt, PhD, Director of Development, Wake Up Narcolepsy
- Jeremy Kelly, Board Chair & Lifetime Trustee, Myotonic Dystrophy Foundation
- Erica Kelly, person with myotonic dystrophy
- Rebecca King, Board Member, Hypersomnia Foundation
- Steve Maier, President, KLS Foundation Board of Directors
- Sharon O'Shaughnessy, Board Member, Narcolepsy Network
- Lara C. Pullen, PhD, President and Co-Founder, Chion Foundation
- Paige Rivard, Chief Executive Officer, Prader-Willi Syndrome Association USA
- Theresa Strong, PhD, Director of Research Programs, Foundation for Prader-Willi Research

The goal of the Summit was to describe the challenges faced by patients with EDS, including:

- Physical, emotional, social, and cognitive challenges of EDS and the impact of these challenges on daily functioning
- Challenges patients with EDS face in having this symptom diagnosed/recognized amidst the constellation of other symptoms experienced in different patient populations
- Overall impact of EDS and related symptoms on burden of illness, caregiver and family burden, and financial/economic challenges

Four primary themes evolved over the course of the summit:

- Multiple disorders, many of which are in the rare disease space, are impacted by sleep disruption issues that are not adequately recognized or addressed.
- Sleep disruption and its concomitant impacts are usually not the primary symptoms but can have significant impact on daily life.
- Conventional means to measure sleep are not well suited to many of these disorders:
    - Tools that work for some areas are not recognized by regulators.
    - Some of those tools do not work in other disease states.
- Healthcare providers rarely effectively address sleep issues even when brought to their attention by patients and caregivers.

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

While the impact of EDS is well known in patients diagnosed with narcolepsy, participants in this Summit report that sleep disruption, and EDS in particular, is common in many different disease states, many of which are congenital rare diseases. Limited data is available to understand how many diseases share this issue, what percentage of patients within each disease area is

impacted, or the range of severity of EDS that patients face. In the absence of such data, most information on EDS beyond narcolepsy is anecdotal and incomplete. Summit participants report, however, that numerous patients within their respective disease areas have some form of sleep disruption. Further, collaborations with other groups in the rare disease space suggest that EDS almost certainly impacts patients beyond the disease states represented in the Summit.

Literature shows, and Summit participants report, that improper sleep has wide-ranging consequences.[5] Some are physiological, including high blood pressure, diabetes, obesity, heart disease, stroke, poor balance, and a weakened immune system. Sleep also impacts mental and emotional health, with lack of sleep being associated with depression, poor decision making, memory issues, and mood swings. Beyond this, EDS has a negative effect on socialization, on the ability to build and maintain a support network, and on professional advancement. Summit participants reported that patients have little time or energy to make social connections, to spend time with friends, even to interact with people at work. Sleepiness during school or while at work impairs academic and career development and contributes to social isolation. Teenagers with myotonic dystrophy, for example, may sleep several hours in the afternoon, wake for two or three hours, then go to bed for the night and sleep another 10 hours. They have little or no waking time for schoolwork, much less for interacting with peers.

Sleep also has a significant impact on cognitive ability, as has been shown in studies with children[6], with the elderly[7], and with victims of traumatic brain injury[8], among others. The nonprofit COMBINEDBrain works with 21 different diagnoses, the majority of which have some significant sleep issue. For patients who are more significantly cognitively impaired, communicating about sleep is almost impossible, possibly masking the extent to which their cognition is impacted by EDS or other aspects of sleep disruption. Indeed, addressing sleep disruption may not even be a consideration for the treatment team. Improper sleep impacts the ability to focus, to learn, and to remember, yet the connection between EDS and cognitive delay is not typically considered in patients of diseases known to involve such delays.

Patients diagnosed with narcolepsy and idiopathic hypersomnia report that current treatment practices do not adequately address the real-world issues they face. Not surprisingly, then, research into addressing EDS beyond the narcolepsy community—particularly in rare diseases--is woefully inadequate. Some studies examine the issue of sleep as part of specific diagnoses, and some biopharmaceutical companies have focused drug development efforts in EDS. To date, however, no-one has undertaken a clinical trial that is agnostic to disease state. Such studies have been conducted in oncology, most notably resulting in a tumor-agnostic approval of TRK-fusion inhibitors.[9] A similar cross-disease study, available to any patient meeting criteria

[5] See, e.g., Medic, Goran et al. "Short- and long-term health consequences of sleep disruption." *Nature and science of sleep* vol. 9 151-161. 19 May. 2017, doi:10.2147/NSS.S134864

[6] Tham, Elaine Kh et al. "Infant sleep and its relation with cognition and growth: a narrative review." *Nature and science of sleep* vol. 9 135-149. 15 May. 2017, doi:10.2147/NSS.S125992

[7] Theresa E. Gildner, Aarón Salinas-Rodríguez, Betty Manrique-Espinoza, Karla Moreno-Tamayo, Paul Kowal, Does poor sleep impair cognition during aging? Longitudinal associations between changes in sleep duration and cognitive performance among older Mexican adults, Archives of Gerontology and Geriatrics, Volume 83, 2019, Pages 161-168, ISSN 0167-4943

[8] Larson, Eric B. 'Sleep Disturbance and Cognition in People with TBI'. 1 Jan. 2018 : 297 – 306.

[9] See, e.g., Looney, Ann-Marie et al. "Tumor-Agnostic Therapies" *Nature Reviews Drug Discovery* January 28, 2020. https://www.nature.com/articles/d41573-020-00015-1

for EDS and/or sleep disruption could prove an effective, efficient approach to treating these issues in a manner reflective of the relative impact they have in the lives of patients and caregivers.

The fact that minimal data exists outlining the significance of EDS outside a formal diagnosis of narcolepsy is indicative of how little importance has been given to the issue. Patients report being told they are lazy, are faking being tired, are shirking their responsibility. They are accused of being unreliable and become isolated when their lack of proper sleep results in irascibility or impatience. Children struggle to form friendships and to focus during class time. Because many of these patients have rare diseases with other, well-known characteristics, the aspect of sleep is often ignored or considered peripheral.

The issue of sleep is not typically addressed in treatment guidelines

EDS not only has significant impact on physical health and quality of life, it can also exacerbate other symptoms. The extent and severity of this impact has not been well studied or described. Based on conversations with their constituents, however, advocacy leaders believe it is more pervasive than is widely recognized. Prader-Willi Syndrome (PWS), for example, is characterized by constant hunger, typically leading to obesity. People with PWS often also struggle with sleep disruption, including EDS. The general connection between sleep and eating is well known, with researchers describing links between sleep cycles and the body's ability to process food, the role of sleepiness in maintaining dietary discipline, and impulse to eat that is driven by tiredness rather than actual hunger. Further, EDS and short sleep duration correlate with obesity, regardless of diet and exercise.[10] Despite this clear association, in PWS, as well as other diseases, the two issues are seldom addressed in a holistic fashion. Indeed, no evidence in the literature addresses if sleep issues drive hunger issues or if the reverse is true. Participants noted that no clarity exists regarding if one of these factors causative or are they independent, yet synergistic, reflections of the underlying disease state. Studies evaluating the role of circadian rhythms in hunger and sleep might help clarify this issue.

Similarly, several diseases, e.g., Smith-Magenis Syndrome (SMS) and mucopolysaccharidoses (MPS) disorders, manifest both behavioral issues and sleep disruption. As with hunger, the connection generally between behavioral issues and sleep is clear. How they are related in specific diseases is not typically studied, however. As a result, Summit participants note that, in their experience, the pervasive influence of improper sleep is not typically considered in treatment plans. Children with EDS have trouble making friends, and struggle to achieve academic goals. This impact on socialization has a related effect on behavior. In many cases, including PWS, patients are described as not having control of their emotions, yet little thought is given to the role of disruptive sleep in the loss of emotional control or in behavior problems. Parents of children with Angelman syndrome (AS) described devastating effects on the household of having a child who is hyperactive and cannot sleep well. Not only is the physical, mental, and emotional well-being of the patient challenged, caregivers and siblings rapidly

[10] Maugeri, Andrea; Medina-Inojosa, Jose R.; Kunzova, Sarka; Agodi, Antonella; Barchitta, Martina; Sochor, Ondrej; Lopez-Jimenez, Francisco; Geda, Yonas E.; Vinciguerra, Manlio. 2018. "Sleep Duration and Excessive Daytime Sleepiness Are Associated with Obesity Independent of Diet and Physical Activity" *Nutrients* 10, no. 9: 1219. https://doi.org/10.3390/nu10091219

become sleep deprived as well. As a result, these family members have their own behavior issues and/or lack of emotional control.

Even motor function can be linked to sleep disruption. Aromatic 1-amino acid decarboxylase (AADC) is a rare disorder manifested in poor motor function, as well as cognitive and speech issues. An effort to create descriptive vignettes for these children included sleep disruption as part of behavioral characteristics, along with irritability and excessive crying. When caregivers reviewed the matrix, they flagged sleep disruption as underreported, something not mentioned at all by health care providers.[11]

The consequences of EDS are significant and far-reaching, yet the capacity of patients and caregivers to address such issues is limited. Parents of children with rare disorders face significant burden of disease, including psycho-social and financial stress. Caregivers report having little time or energy to address even basic aspects of life — cleaning, balancing a checkbook, or preparing meals. If they do notice EDS in their children, they have minimal capacity to address this issue, even if they can find a physician who will treat their concerns seriously. Adults with EDS have similar constraints, with little energy for pursuing what many consider to be a peripheral issue. Some literally have too little wake time in a day to do much more than maintain their life; indeed, some patients report that they lack the energy even to maintain the quality of life they currently experience. Absent the intervention, or even support, of health care providers, sleep issues may not be addressed at a level concomitant with their life impact.

Measuring sleep is challenging

In part, the lack of understanding around the role of sleep disruption in various diseases is due to challenges in measuring sleep. Sleep researchers evaluate sleep through polysomnography, a combination of electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG). More recently numerous activity trackers have come on the market, positioned as tools to measure sleep. While sleep experts debate the relative benefits of these two approaches[12], in reality, neither is practical for many patients.

Participants discussed some of the challenges they face in measuring sleep problems in a way that reflects their experience. Some diseases impact cognitive ability, at times to the extent that the patients cannot tolerate either leads from an EEG or having a device on their wrist. Other diseases result in hyperactivity even while sleeping. Activity trackers require inactivity for a minimum set period of time in order to record that the wearer is in deep sleep. For patients whose disease causes them to be restless even while asleep these devices never register a sleep time, though they demonstrably are asleep. Measuring EDS is even more challenging, particularly if the intent is to determine the impact of EDS on a normal day in a normal life. Children will not wear a device on their head during school, and are not likely to be undisturbed

[11] Hanbury, Andria et al. "Deriving Vignettes for the Rare Disease AADC Deficiency Using Parent, Caregiver and Clinician Interviews to Evaluate the Impact on Health-Related Quality of Life." *Patient related outcome measures* vol. 12 1-12. 7 Jan. 2021, doi:10.2147/PROM.S278258

[12] See, e.g., Pedro Carazo-Vargas, Joshua Salazar-Obando, Andrea Vargas-Montero, Ricardo Alvarado-Barrantes, Francisco Siles-Canales & José Moncada-Jiménez (2020) Lack of Agreement between Polysomnography and Accelerometry Devices for Measuring Sleep Efficiency and Movement in University Students, Measurement in Physical Education and Exercise Science, 24:4, 291-302, DOI: 10.1080/1091367X.2020.1819814

long enough for a sleep-evaluation wearable to be effective. One Summit participant expressed frustration that sleep is even woefully underrepresented in PEC cards, with the result that patients with limited verbal skills have almost no way to communicate that they are struggling with sleep issues.

The lack of effective measurement of sleep parameters in patients with, for example, PWS, AS, or SMS, means that the impact sleep has on the patient and on the course of their disease is not well documented.

Healthcare providers are not adequately addressing EDS and other sleep issues

Another topic discussed by participants was the difficulty they have in getting health care providers to take sleep issues seriously. Even participants with narcolepsy describe challenges in having their EDS taken seriously by the medical community. Finding a sleep expert is challenging and time consuming and is no guarantee that all aspects of sleep disruption will be understood or deemed significant. Particularly in the United States, these patients face biases in a society that does not value sleep. Entrepreneurs characteristically boast about how much they accomplish on little sleep, and lack of sleep is seen as a hallmark of hard work and dedication. People pride themselves on their reliance on coffee as an alternative to good rest. Sleep is identified with a lack of ambition, with lethargy and sloth. Data is clear that sufficient sleep is critical for proper health, yet the stereotypes remain. Indeed, some participants wondered whether an unhealthy culture of sleep is particularly acute among physicians, noting challenges faced by the medical community in addressing the impact of sleep among their members.[13]

Patients for whom EDS is a secondary, less well-known, aspect of their disease face even more difficulty in being treated seriously, perhaps due, in part, to the difficulty of measuring sleep in these populations. Without data to support the prevalence or severity of EDS, medical professionals can easily marginalize concerns raised by patients or caregivers. Several participants reported encounters with health care providers who diminished their concerns. They also said that while some doctors may request a sleep test, sometimes they are unaware that those tests do not work well in some populations. When the test does not demonstrate a problem, the problem is dismissed.

Many participants reported that some patients face disease-related symptoms that are severe, even life-threatening. In comparison, issues of sleep are deemed insignificant and ancillary. For patients with seizure disorder, sleep and seizure activity may be connected. A characteristic of AS, for example, is head-bobbing, which is typically noticed around eating. Some of this may be tied to EDS or, even if it is seizure-like activity, may be related to lack of rest. Lack of sleep can trigger a seizure, but the focus is almost always on the seizure or pre-seizure activity rather than on sleep dysregulation.

Caregivers and patients must, at times, become advocates for their own health and convince the treatment team that what they are observing and reporting is both real and significant. Arguing with providers about sleep is daunting, and when patients or their caregivers do try to raise the issue, they report often being dismissed by the treatment team. While rare diseases

[13] Kancherla BS, Upender R, Collen JF, et al. What is the role of sleep in physician burnout? *J Clin Sleep Med*. 2020;16(5):807–810.

are often treated by multi-disciplinary teams, those teams almost never include sleep specialists, even for those diseases in which EDS is a known factor.

Conclusions and Recommendations

Consistently, participants in the Summit discovered areas of commonality around sleep issues across the different disease states that had not previously been identified. EDS and other forms of sleep disruption significantly impact the lives of patients and their families yet sleep issues—and their impact on daytime functioning—these populations is poorly understood. Collecting data is challenging due to the wide variety of conditions involved and to the lack of practical tools for measuring sleep in special needs patients.

An important first step is to raise awareness among the rare disease community about the potential importance of sleep in managing a wide array of diseases. Summit participants recommend a session focused on sleep at a rare disease conference, e.g., NORD, Global Genes, EURORDIS, and World Orphan Drug. These meetings are attended by advocates, patients, and caregivers impacted by a plethora of rare diseases. Some are diseases involving circadian rhythm disorders, and others are characterized as involving sleep disruption at some level. The consensus, however, is that many other diseases may be impacted by EDS than is currently recognized. Elevating the profile of sleep as a complicating factor among the rare disease community is an important first step toward understanding the scope of the problem.

One way to quantify the problem of EDS is through a survey instrument. Several sleep surveys are currently in use and could be modified for use in the rare disease community. This approach can be particularly useful in identifying additional diseases that may have not yet been identified as being impacted by sleep disruption. A similar survey designed to improve knowledge of juvenile Huntington's Disease resulted in 87% of respondents mentioning sleep disruption as a common symptom — a phenomenon previously unreported.[14] A broad, global survey distributed through advocacy groups should provide sufficient data to support more focused additional studies.

If new areas are uncovered through the survey, a next step would be to secure more detailed, real-time feedback from patients and/or their caregivers. An app that prompts participants to record daily the status of sleep in the past 24 hours will provide a detailed picture of how often patients experience daytime sleepiness, nighttime wakefulness, etc. Such data will provide patients, caregivers, and advocates with the information needed to approach their health care providers for support in addressing sleep issues. Such activities are best conducted through a coalition comprised of patient advocates, perhaps with the support of a medical advisory committee. Results should be published and shared broadly among patient communities, with the goal that EDS be give the level of attention proper to an issue that can have such a significant impact on quality of life. The participants also discussed publishing information about patient experiences and burdens in a medical journal toward the goal of educating health care providers to test for and recognize sleep disorders in these rare disease populations.

[14] Moser, Amelia D, et al. A survey-based study identifies common but unrecognized symptoms in a large series of juvenile Huntington's disease. *Neurodegenerative Disease Management* 2017 7:5, 307-315

This same coalition could be involved in approaching the FDA to discuss different models for clinical trials of drugs designed to address EDS or sleep disruption. Such a model would reflect the reality that many sleep issues cut across multiple disease states. A study's inclusion criteria could define specific characteristics of a sleep disorder, then accept all patients meeting those criteria regardless of their specific overall diagnosis. The result would be a trial that reflects the real-world experience of patients and caregivers and that would accrue quickly. Further, trials with this design provide the opportunity to gather correlative data on the possible role of sleep disruption on other aspects of life in these communities.

Greater attention in peer-reviewed and popular literature to the role of sleep disruption will help elevate awareness of this phenomena; indeed, Summit participants hope this paper will contribute to such progress. Participants in this summit identified critical gaps in knowledge and in treatment of EDS and sleep disruption. Disseminating information about sleep disorders in rare diseases in the literature is a critical first step, starting with the publication of this and future papers. Participants resolved to continue the dialogue begun during the meeting, with the anticipation that collectively they can help ensure that some, if not all, of these recommendations become reality.