

## SPECIAL ARTICLES

### Diagnosis and management of sleep disorders in Prader-Willi syndrome

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Clinical experience and a growing body of evidence suggest that sleep disturbances are common in people with Prader-Willi syndrome (PWS). PWS is a rare neuroendocrine disorder characterized by early hypotonia and feeding difficulties; developmental delays; endocrinopathies; and behavioral concerns, especially rigidity, anxiety, and behavioral outbursts. PWS is also characterized by decreased resting energy expenditure and transition to hyperphagia and obesity. We propose that, for many people with PWS, clinical diagnosis and management of sleep disorders is an unmet need. We present current information to suggest disordered sleep is a significant burden for individuals with PWS and often overlooked. While central and obstructive sleep apnea are more widely recognized in PWS, other sleep disorders have increasingly gained recognition, including hypersomnia, narcolepsy-like phenotypes, and insomnia. Sleep disorders can impact behavior, cognition, and quality of life and health for individuals with PWS. Our goal is to bring sleep disorders to the forefront of therapeutic intervention for patients with PWS. This paper presents a review of the literature and recommendations for clinical practice based on published research and our clinical experience as sleep specialists, geneticists, psychiatrists, pediatricians, otolaryngologists, and pulmonologists with extensive experience with this patient population. We recommend that management of sleep be considered an integral part of successful medical management of PWS. Further research concerning sleep problems in PWS is urgently needed to develop best practices and work toward a consensus statement for medical management to meet the needs of people with PWS.

**Keywords:** Prader-Willi syndrome, sleep-disordered breathing, imprinting disorder, obstructive sleep apnea, excessive daytime sleepiness, hypersomnolence, narcolepsy, cataplexy

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#### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Clinical experience and growing evidence suggest that sleep disturbances are common in people with Prader-Willi syndrome (PWS). While clinical focus has been largely on central and obstructive sleep apnea, perspectives need to shift to recognize the array of sleep abnormalities in PWS to include excessive daytime sleepiness, narcolepsy- and cataplexy-like phenotypes, and insomnia. This paper presents a review of the literature and recommendations for clinical practice based on published research and multidisciplinary clinical experience.

**Study Impact:** We recommend that health care providers consider the significant impacts and potential relationships between sleep and many features of PWS, such as behavioral concerns. It is vitally important that clinicians immediately recognize and acknowledge sleep disturbances in this population and consider sleep management an integral part of successful medical management of PWS.

#### INTRODUCTION

Prader-Willi syndrome (PWS), a rare neuroendocrine disorder present in 1/10,000–1/15,000 individuals,<sup>1,2</sup> is caused by a loss of expression of paternal chromosome 15q11.2–q13. It appears that there is an interplay between many genes in this region, but a small, isolated deletion of the small nucleolar ribonucleic acid-116 (*SNORD116*) noncoding RNA has been associated with a PWS phenotype.<sup>3–7</sup>

Sleep disorders are a common burden for people with PWS.<sup>8,9</sup> Moreover, disordered sleep likely contributes to more commonly recognized features of PWS. For example, excessive sleepiness could be impacting feeding in infancy and the unique

behavioral profile in older children. However, to the extent that clinical assessments of sleep disorders in patients with PWS do occur, they often focus on the well-established connection between PWS and central sleep apnea (CSA) and obstructive sleep apnea (OSA).<sup>9,10</sup> Concerns regarding OSA arise immediately from the time of diagnosis due to profound hypotonia<sup>11</sup> and increased risks associated with weight gain and tonsillar hypertrophy exacerbating OSA when growth hormone (GH) therapy is started.<sup>9</sup> In this paper, we review the literature related to sleep and PWS, and provide evidence for a variety of neurological sleep disorders in PWS in addition to OSA. For example, clinical evidence suggests that excessive daytime sleepiness (EDS), also called hypersomnolence, affects many

individuals with PWS.<sup>9</sup> EDS is present in > 50% of individuals with PWS and persists despite adequate treatment of OSA,<sup>12,13</sup> with occurrence possibly as high as 95%.<sup>14</sup>

The most common early features in PWS are hypotonia and feeding difficulties.<sup>1,2</sup> Notably, infants are also excessively sleepy and do not awaken or express interest in feeding. Over time, other features of PWS develop as children progress through nutrition phases, including decreased resting energy expenditure, increased weight without a change in calories, and later, an inability to feel full, called hyperphagia.<sup>1,2</sup> Developmental delays are common, including childhood apraxia of speech. Endocrinopathies include GH deficiency, hypothyroidism, and hypogonadism. Behavioral concerns are common and include anxiety, behavioral rigidity, and behavioral outbursts.<sup>15,16</sup> Based on this array of well-established features, PWS has predominantly been considered an endocrine and metabolic disorder with hyperphagia and obesity. Sleep disorders have been considered as possible concerns in some patients.<sup>2</sup> The aim of this review is to highlight the importance of recognizing and treating sleep disorders in PWS.

### IDENTIFYING SLEEP DISORDERS IN PWS

Several studies demonstrate that *SNORD116* plays a role in sleep.<sup>17-19</sup> For example, 2 individuals with small deletions in *SNORD116* exhibited increased rapid eye movement/non-rapid eye movement (REM/non-REM) ratio, increased REM fragmentation, and increased amplitude of theta waves during REM sleep during the light phase.<sup>17</sup> Furthermore, mice lacking *SNORD116* had reduced gray matter volume in the ventral hippocampal areas and regions of the septum, which are important structures for maintaining theta rhythms in the brain.<sup>17</sup> Consistent with these findings, research in different mouse models have revealed that *SNORD116* plays a role in the orexin-hormone system within the lateral hypothalamus.<sup>18</sup> Furthermore, orexin plays important roles in feeding modulation and wakefulness.<sup>20</sup> Research in yet another mouse model of PWS demonstrated dysregulation of genes related to circadian rhythm such as *Clock*, *Cry1*, and *Per2*.<sup>19</sup> Taken together, these animal studies indicate that multiple factors related to sleep can be affected by *SNORD116* and underscores the possibility of a variety of sleep disorders that may be clinically underrecognized in PWS.

Caregivers recognize that sleep problems are pervasive in PWS and real-world evidence for other sleep disorders in PWS comes from social listening and surveys of caregivers of patients with PWS. One study using social listening revealed that caregivers not only discussed apnea, tiredness, and narcolepsy with or without cataplexy, but some of these terms were more frequently discussed than terms related to hyperphagia.<sup>21</sup> Furthermore, a 2014 survey showed that 65% of caregivers reported sleep problems such as apnea or daytime sleepiness in people with PWS—a percentage higher than the percentage of caregivers reporting hyperphagia (51%).<sup>22</sup> These data provide evidence from patient communities that sleep abnormalities are an important feature of PWS and may extend beyond OSA to include EDS, insomnia, narcolepsy, and cataplexy.

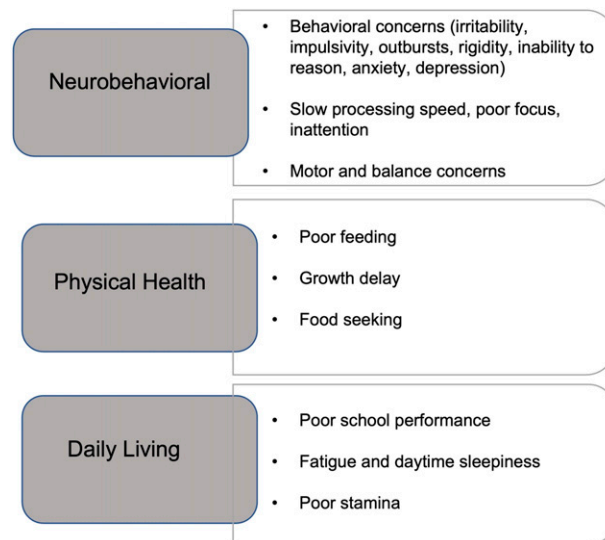
While there is growing recognition in the PWS community that sleep disorders may contribute to many clinical features of PWS (Figure 1), including the irritability and behavioral features of PWS, the connection remains poorly studied.<sup>16</sup> In typically developing children, impaired sleep has been associated with negative impacts on cognitive performance and behavior.<sup>23</sup> Perhaps even more importantly, the medical literature lacks a consensus statement on how best to diagnose and manage these symptoms in the PWS population. Until such a necessary consensus can be formed and published, we offer this review of the literature as well as our considered recommendations for the medical diagnosis and treatment of sleep disorders in PWS (Figure 2).

### VENTILATORY CONTROL DURING SLEEP

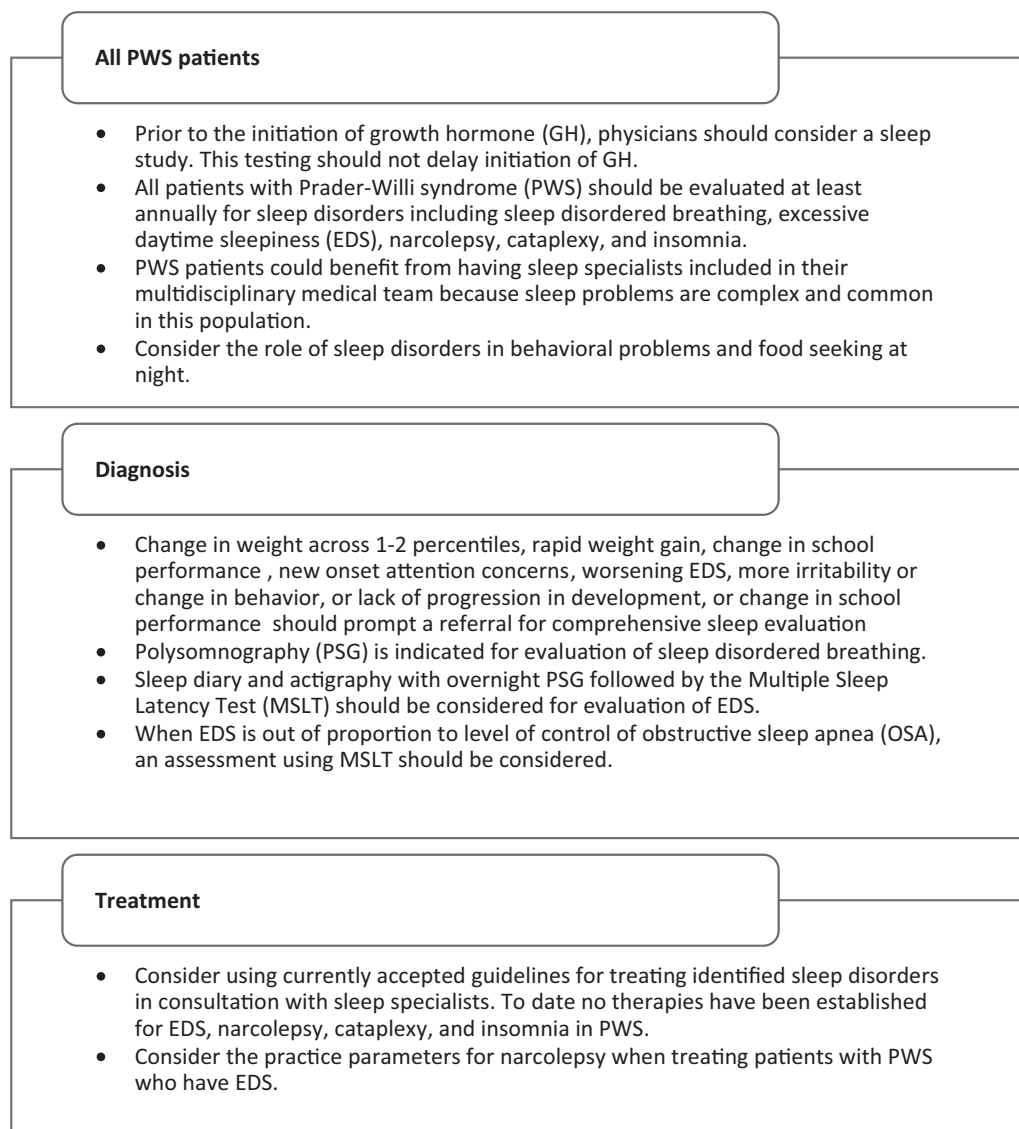
Many adults with PWS have an abnormal hypercapnic ventilatory response, although there are some adults in whom the hypercapnic ventilatory response is absent,<sup>24</sup> a situation that likely contributes to an increased risk of morbidity and mortality.<sup>25</sup> Children with PWS are also hypercapnic.<sup>26</sup> Moreover, the severity of abnormality of the hypoxic ventilatory response is independent of the degree of obesity.<sup>24,27</sup> Individuals with PWS also have a significantly higher arousal threshold to hypercapnia compared with controls.<sup>28</sup> Likewise, individuals with PWS have lower nocturnal basal blood oxygen saturation level (SpO<sub>2</sub>) than controls and tend to have clusters of desaturations.<sup>29</sup> Because of this abnormal ventilatory response, health care providers should have a low threshold to screen for respiratory disturbances during sleep.

One study suggests that the lack of ventilatory response is due to primary peripheral chemoreceptor dysfunction and/or

**Figure 1**—Symptoms of PWS that may be associated with disordered sleep.



PWS = Prader-Willi syndrome.

**Figure 2**—Recommendations for clinical approaches.

defective afferent pathways to central controllers.<sup>30</sup> In this study of 17 adults with PWS, researchers paired individuals with PWS to controls matched for age, sex, and body mass index and found that, while the response to hyperoxia in the control group was decreased, individuals with PWS demonstrated a paradoxical reaction of 100% O<sub>2</sub> in which minute ventilation increased. Moreover, after vital capacity breathing of 15% CO<sub>2</sub> in O<sub>2</sub>, or breathing 100% nitrogen, patients with PWS experienced no change in breathing as opposed to controls, who showed a marked increase in minute ventilation under each of those conditions.

Multiple studies have revealed increased nocturnal hypoventilation in PWS as a result of poor ventilatory control.<sup>24,26,27</sup> Children with PWS have disproportionately longer periods of hypoventilation when compared with typically developing children with the same apnea-hypopnea index (AHI).<sup>26</sup> In 1 study,

investigators assessed arousal from sleep by providing inspired O<sub>2</sub> partial pressure of only 80 mmHg for a maximum of 3 minutes and found that only 1 of 13 patients with PWS were aroused during the challenge. Furthermore, those individuals with PWS had a blunted response in heart rate and no change in respiratory rate.<sup>24</sup>

GH, the only Food and Drug Administration–approved treatment for individuals with PWS, should be initiated at the time of diagnosis and maintained through life. While GH has metabolic benefits, it also appears to improve ventilatory control. For example, GH treatment of 9 patients aged 7–14 years has been shown to improve ventilation and inspiratory drive.<sup>31</sup> GH also improved the coupling of heart rate and pulse transit time, an index of blood pressure. The 2 measures taken together suggest that GH may also improve cardiovascular function during sleep.<sup>32</sup>

## CENTRAL SLEEP APNEA

PWS increases the risk of CSA, a condition that is more common in infants with PWS as opposed to adults with PWS.<sup>33–35</sup> Recent reports suggest that 43% of infants with PWS have CSA compared with closer to 5% for kids between the ages of 2 and 18.<sup>36</sup> Poor ventilatory control in PWS may contribute to CSA.<sup>9</sup> An additional risk factor for CSA as well as generalized sleep-disordered breathing is scoliosis or other spinal abnormalities—which impacts anywhere from 15% to 86% of individuals with PWS.<sup>37</sup> Polysomnography (PSG) should be performed in infants with PWS at the time of diagnosis to rule out central apnea. There may be an association between central adrenal insufficiency and central apnea index,<sup>38</sup> and continued monitoring with frequent PSGs approximately every 6 months may be indicated for these individuals with central adrenal insufficiency.<sup>34,36,39</sup> Supplemental oxygen has been shown to be an effective treatment in infants and is the therapy of choice for this age group.<sup>36,40</sup> For older individuals, the use of positive airway pressure is the standard of care.<sup>9</sup>

## OBSTRUCTIVE SLEEP APNEA

More than 80% of children with PWS exhibit sleep-disordered breathing including OSA,<sup>41</sup> and most apneas are in REM sleep and are not associated with arousals.<sup>12</sup> The body mass index percentile for the individual's age and sex has been associated with more severe hypoxemia during sleep and more sleep disruptions. In addition, untreated OSA has been associated with more severely delayed developmental milestones in adolescents and young adults.<sup>42</sup> Worsening OSA has also been associated with EDS and autistic-related behavior with worsening impulsivity in children.<sup>41,43,44</sup> These behavioral changes should prompt concern for worsening OSA. In addition, developmental milestones may be more severely delayed in individuals with untreated OSA.<sup>44</sup>

There remains much controversy regarding the potential of GH therapy to exacerbate OSA. There are case reports of pediatric deaths in the first months of GH therapy and risk factors included severe obesity, history of upper airway obstruction or sleep apnea, and respiratory infection.<sup>45,46</sup> Multiple studies showed no increase in OSA-related mortality in GH-treated individuals with PWS.<sup>47–49</sup> GH treatment also does not appear to negatively impact overall apnea-hypopnea index (AHI), central apnea index, or obstructive apnea index in adults with PWS.<sup>47,50</sup> Moreover, in children with PWS aged 0–2.5 years old (21 children started on GH before age 1 year and 41 children started after age 1 year), investigators found no correlation between GH treatment and the onset of OSA.<sup>48</sup> An additional study that conducted overnight PSG in 20 infants aged 2–21 months at 6 weeks post-initiation of GH found no significant changes in OSA.<sup>51</sup> There may be a vulnerable time during which OSA worsens after initiation of therapy,<sup>52</sup> but this is often resolved by 2 years on therapy.<sup>9,32</sup> In this study, the subset of participants who worsened with GH therapy had underlying respiratory issues, chronic respiratory infections, and elevated

serum insulin-like growth factor 1 (IGF-1).<sup>52</sup> It is likely that those participants with OSA and underlying respiratory conditions may have increased mortality.

Current recommendations include monitoring for symptoms of OSA before initiation and while continuing GH therapy.<sup>49,53</sup> Participants with moderate to severe OSA preinitiation may still receive GH therapy but should receive more frequent evaluations. Specifically, some groups have recommended annual sleep studies, as well as adenotonsillar evaluation for patients with PWS prescribed GH.<sup>54</sup> We recommend that, prior to the initiation of GH, physicians should screen via a sleep study. This testing should not, however, delay initiation of GH. In addition, approximately 6–10 weeks post-initiation of GH, a follow-up sleep study may be needed if any worsening symptoms (such as, but not limited to, snoring, witnessed apnea, daytime sleepiness) or signs (such as, but not limited to, weight gain) occur.<sup>52</sup> It is reasonable to repeat a sleep study independent of a marked worsening of symptoms—as changes in sleep apnea are less apparent in kids with PWS. Findings of worsening obstructive AHI should expedite evaluation and treatment, but not necessarily stop or delay GH treatment.

Clinical management of patients on GH who are diagnosed with OSA remains highly variable among endocrinologists and sleep specialists across medical centers. While controversy remains as to whether a PSG is required in this population, a guideline has been put forth for children<sup>55</sup> that, in part, recommends PSG when clinical assessment suggests OSA. Snoring, witnessed apneas, rapid weight gain, change in school performance, new-onset attention concerns, worsening EDS, more irritability or change in behavior, or lack of progression in development should prompt a referral for PSG. Given the high prevalence of sleep disorders in PWS, routine PSG should be performed soon after diagnosis, at age 3 years and at the time of puberty in children.<sup>56</sup>

When OSA is diagnosed based on PSG, referral to otolaryngology is suggested. A recent consensus statement on the role of drug-induced sleep endoscopy suggests this procedure should be performed when an infant is diagnosed with OSA prior to the development of tonsils and adenoids (Evidence Level 1b).<sup>57</sup> Multilevel obstruction, particularly at the level of the velum, is common in the population and AHI has been correlated to complete tongue-base collapse.<sup>58</sup> In addition, research indicates that not only should PSG be performed prior to adenotonsillectomy (T&A) but repeat PSG should be performed following T&A to assess for residual OSA. While T&A can be effective, particularly if tonsils and/or adenoids are enlarged, it is common for residual OSA to be present in patients with PWS.<sup>59–63</sup> In addition, there may be an increased risk of velopharyngeal insufficiency in PWS postsurgically after T&A.<sup>64,65</sup>

When utilized consistently, continuous positive airway pressure (CPAP) can be effective in improving EDS, school performance, achievement of developmental milestones, and daytime blood gases.<sup>43,66</sup> It can also be used for residual OSA post-T&A, or for people who want to avoid surgery. For individuals with PWS; however, CPAP adherence can be challenging.<sup>13</sup> Behavioral therapy with desensitization to assist in the use of CPAP should be considered upon initiation of therapy. In the case of mild OSA, a trial of intranasal fluticasone with or without montelukast can be used as an alternative to CPAP.<sup>67</sup>



## NARCOLEPSY WITH OR WITHOUT CATAPLEXY

Narcolepsy is a neurological sleep disorder characterized by abnormal regulation of the sleep-wake cycle. The typical symptoms of narcolepsy type 1 include EDS, cataplexy (loss of muscle tone with strong emotion), hypnagogic/hypnopompic hallucinations, sleep paralysis, and fragmented sleep.<sup>68</sup> Pediatric presentations of narcolepsy and cataplexy can differ from adult presentations. Children can have profound baseline facial hypotonia and some patients experience motor tics.<sup>56,68–72</sup> Automatic behavior (repetitive and common behaviors done at night) and disrupted nighttime sleep also commonly occur in patients with narcolepsy.

In children, cataplexy may resemble clonic, atonic, and/or myoclonic seizures<sup>72</sup>; however, the loss of consciousness is absent with cataplexy. Alternatively, at onset, cataplexy may present as loss of tone and/or complex hyperkinetic movements. Often, children with cataplexy have prominent facial involvement that can include active movement of the tongue and perioral muscles. Moreover, unlike adults, children may experience cataplexy without a clear emotional trigger.<sup>69</sup> Obesity is also common in children with narcolepsy, such that more than half of children who first present with signs of narcolepsy are obese.<sup>73</sup> In addition, approximately one-third of children with narcolepsy also have symptoms of attention-deficit/hyperactivity disorder.<sup>56</sup> Cataplexy or sudden onset of atonia provoked by emotion appears relatively commonly in PWS,<sup>74</sup> with incidence estimates ranging from 18% to 25%.<sup>74</sup> For example, head drops in young children as they eat solid food is likely an example of cataplexy.<sup>75</sup>

Type 1 narcolepsy (formerly narcolepsy with cataplexy) is caused by the degeneration of hypothalamic neurons that make orexin.<sup>76</sup> Consequently, the cerebrospinal fluid of patients with narcolepsy has very low or no evidence of orexin. While patients with PWS have been found to have lower levels of orexin in the cerebrospinal fluid, their levels were not as low as those of a patient with narcolepsy type 1.<sup>77</sup> Moreover, while there appears to be a negative correlation between Epworth Sleepiness Scale and orexin levels in the cerebrospinal fluid of individuals with PWS,<sup>77,78</sup> decreases in the number of hypocretin neurons do not seem to play a role in the PWS narcolepsy phenotype, unlike in narcolepsy in typically developing children.<sup>79</sup> Testing for orexin levels in cerebrospinal fluid is not diagnostic or therapeutically useful and is not common practice in the PWS population.

By some estimates, half of individuals with PWS have REM sleep disorders that are likely phenotypic variations of narcolepsy.<sup>14</sup> The REM sleep disruptions include sleep-onset REM periods, REM sleep during daytime naps, many arousals during REM sleep, and a significant increase in total REM sleep.<sup>14,80</sup> Individuals with PWS also have decreased REM latency and decreased duration of non-REM sleep stage N3.<sup>27,73</sup> It is common for individuals with PWS to not only display sleep-onset REM periods but also score abnormally on a Multiple Sleep Latency Test.<sup>81</sup> While this presentation is suggestive of a narcoleptic phenotype,<sup>82</sup> it has also been suggested that the primary mechanism is a generalized 24-hour state of hypoarousal.<sup>83</sup>

There are several diagnostic criteria for narcolepsy.<sup>69,70,84–88</sup> In 2014, the American Academy of Sleep Medicine released

the *International Classification of Sleep Disorders*, third edition (ICSD-3).<sup>87</sup> The American Academy of Sleep Medicine notes that, in young children, narcolepsy may sometimes present as excessively long night sleep or as resumption of previously discontinued daytime napping. In 2013, the American Psychiatric Association published the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), which contains diagnostic criteria for sleep-wake disorders, including narcolepsy, and is designed for use by mental health and medical clinicians who are not experts in sleep medicine.<sup>88</sup> While the ICSD-3 criteria require results from a sleep study, the DSM-5 criteria do not. The DSM-5 notes that, in children, cataplexy can present as spontaneous grimaces or jaw-opening episodes with tongue thrusting or global hypotonia, without any obvious emotional triggers. Of note, a sudden onset of movement abnormality along with significant affective or behavioral change can be a harbinger of cycloid psychosis. Usually, the differentiating sign would be a co-occurring insomnia rather than hypersomnolence.<sup>89</sup> We therefore recommend that a Multiple Sleep Latency Test should be obtained in all patients with PWS who report disproportionately pervasive EDS even in the setting of mild to moderate OSA.

Since a diagnosis of narcolepsy also requires that a patient's EDS is not caused by insufficient sleep or another sleep disorder, such as OSA, it can be difficult to obtain a formal diagnosis of narcolepsy in PWS. Often patients with PWS and OSA have difficulty adhering to their prescribed positive airway pressure (mainly CPAP or bilevel positive airway pressure therapy). This means that, per clinical guidelines, OSA cannot be excluded as a cause of their EDS. This situation may contribute to the underdiagnosis of narcolepsy in the PWS population. Because EDS is often out of proportion to OSA, we recommend that screening for narcolepsy-type features should be undertaken in individuals with PWS despite residual OSA.

We recommend treatment for narcolepsy per practice parameters in individuals with PWS.<sup>90</sup> Stimulants and antidepressants have all been used to treat EDS and cataplexy associated with narcolepsy, with variable response. Amphetamine was the first compound to demonstrate significant improvement for excessive sleepiness in narcolepsy and it, as well as modafinil, has an indication by the Food and Drug Administration for this purpose. Given the dual indication of treating both narcolepsy as well as attention-deficit/hyperactivity disorder, stimulants such as amphetamine or methylphenidate may be considered.<sup>91</sup> Selective serotonin reuptake inhibitors and tricyclic antidepressants may be used to treat cataplexy. Care must be taken in consideration of the use of selective serotonin reuptake inhibitors in PWS as they may be activating and may precipitate mania or affective psychosis.<sup>89,92</sup> Sodium oxybate, the sodium salt of gamma hydroxybutyrate, and pitolisant are the only medications indicated for both EDS and cataplexy.<sup>93</sup> Sodium oxybate is the drug of choice for narcolepsy type 1 in children and adults. Use of sodium oxybate may cause respiratory depression and should be approached with much caution in this population. A clinical trial in PWS demonstrating safety and efficacy is necessary to help inform the use of the medication in this population.

Typical approaches to the treatment of narcolepsy<sup>90</sup> may be effective for individuals with PWS and should be considered.

A single case study reported that treatment with modafinil was able to improve sleep efficiency and REM sleep parameters in a 7-year-old child with PWS.<sup>94</sup> A case series of 9 adolescent and young-adult patients (6 of whom displayed at least 2 sleep-onset REM periods consistent with a narcolepsy-like phenotype) treated with modafinil at a starting dose of 100 mg/day responded with an improved Epworth Sleepiness Scale score from 14 (mild EDS) to 4 (no EDS).<sup>95</sup> Individuals treated with 100–200 mg modafinil in the morning experience an improvement not just in daytime alertness but also with respect to behavioral and attention concerns. While the precise biochemical mechanism of action of modafinil has not been clearly defined, modafinil acts similarly to other stimulants and produces significant dopaminergic activity. Modafinil is regulated by the US Drug Enforcement Administration as a schedule IV class drug<sup>96</sup> and abuse of modafinil may lead to limited physical dependence and psychological dependence.<sup>97</sup> Modafinil is not approved for use in individuals less than 17 years of age. Its use should be monitored with caution due to reports of serious side effects, including life-threatening development of Stevens-Johnson syndrome.

In a case series, researchers reported that a novel histamine-3-receptor inverse agonist pitolisant, when administered to adolescent individuals with PWS, decreased daytime sleepiness and improved processing speed and mental clarity.<sup>98</sup> Currently approved for the treatment of narcolepsy and cataplexy in adults, pitolisant also demonstrates the potential to treat EDS associated with cognitive impairment, epilepsy, and Alzheimer disease.<sup>99</sup> A phase 2 study evaluating the safety and efficacy of pitolisant in both pediatric and adult patients with PWS is currently underway.<sup>100</sup> The results of this trial will provide evidence for the beneficial effects of pitolisant in a pediatric population with PWS. Pitolisant is the first and only treatment approved for adult patients with narcolepsy with cataplexy that is not scheduled as a controlled substance by the US Drug Enforcement Administration.

### EXCESSIVE DAYTIME SLEEPINESS

A recent study of 60 adults with PWS found that 67% reported EDS.<sup>8</sup> The incidence of EDS in children with PWS is unclear, although there are several studies of sleep-wake patterns in children with PWS<sup>12,101</sup> that explore EDS among other sleep issues. In the case of PWS, EDS is exemplified by decreased wakefulness in combination with an increased percentage of sleep time and stage N3 sleep during the day and at night.<sup>83</sup> In practice, many individuals with PWS have EDS, which can be confirmed by long sleep duration in a 24-hour period and shortened sleep latency times on Multiple Sleep Latency Testing.<sup>102</sup> Multiple Sleep Latency Testing can also diagnose hypersomnia—which is distinct from presenting symptoms of EDS.

A variety of sleep disturbances, in particular OSA, can cause EDS and there is increasing evidence that other sleep abnormalities may contribute to EDS in individuals with PWS. For example, 1 study of weight loss in patients with PWS reported

improvement in sleep-related breathing disorders but still reported persistence of EDS.<sup>103</sup> Even in individuals with an established diagnosis of OSA, the correlation of AHI with EDS reveals an out-of-proportion finding suggestive of a narcolepsy-like phenotype or hypersomnia of PWS.<sup>104</sup>

EDS disrupts school performance and may be associated with irritability and behavioral disturbances commonly seen in individuals with PWS.<sup>16</sup> It is thus important to recognize and treat this sleep disorder. There are a variety of treatment practices reported for EDS in the PWS population. An open-label case series of 10 patients found that modafinil decreased sleepiness in patients aged 8–21 years with PWS.<sup>105</sup> EDS was successfully reduced in an 11-year-old boy with PWS when treated with clomipramine. He experienced a slight improvement in nocturnal hypoxemia although his OSA persisted.<sup>106</sup> In another case report, an 8-year-old girl with PWS and EDS was successfully treated with tryptophan.<sup>105</sup> A new wake-promoting agent, pitolisant, was shown to reduce sleepiness and improve cognitive function in case reports of children with PWS.<sup>24,107</sup> These medications are often considered and used off label when managing a patient with PWS despite limited data.

### DISTURBED SLEEP AND CHRONIC INSOMNIA

A recent study in 700 healthy adolescents (between 5 and 12 years of age) found that insomnia occurs in 19.3% of participants compared with 20.2% of participants with sleep-disordered breathing.<sup>108</sup> Thirty-three percent reported chronic insomnia.<sup>109</sup> Diagnosis of disrupted sleep often requires a thorough sleep history, including the use of sleep diaries, actigraphy, and consideration of precipitating factors that may include behavioral concerns, anxiety, or perseverative behaviors. For chronic insomnia, we recommend a sleep evaluation by a sleep medicine specialist to help assess potential underlying causes. Initiation of behavioral therapy may be beneficial in the treatment once underlying sleep pathology is ruled out.

In the case of PWS, disrupted sleep and awakenings may contribute to nighttime foraging for food. Improved food security in the home, including locking to prevent access to food, can improve anxiety and sleep disruptions. The prevalence of insomnia in PWS is approximately 29%.<sup>110</sup> A trial of melatonin, including extended-release melatonin,<sup>111</sup> should be considered for initiation of sleep. Benzodiazepines such as lorazepam and alprazolam are effective anxiolytic medications for adults, but can cause respiratory depression, ataxia, excessive sedation, memory impairment, and paradoxical disinhibition. Additionally, some second-generation antipsychotics such as quetiapine are often prescribed for insomnia.<sup>112</sup> However, they have significant side-effects including metabolic syndrome and should not be prescribed for the treatment of sleep disturbances alone. A recent study of pediatric psychiatrists indicated that the most popular first-choice treatment for sleep disturbances in pediatric populations was melatonin, followed by trazodone, mirtazapine, and zopiclone.<sup>113</sup> Fifty-seven percent of clinician respondents reported trazodone as their second-choice treatment.<sup>113</sup> In children with neurodevelopmental disorders,

insomnia was also treated with melatonin, antihistamines, such as hydroxyzine.<sup>114</sup>

## PERIODIC LEG MOVEMENTS AND RESTLESS SLEEP

Schaaf-Yang syndrome shares many clinical features with PWS. A recent study of 33 individuals with Schaaf-Yang revealed a high rate of sleep disorders, including periodic limb movement contributing to restless sleep.<sup>19,115</sup> Increased periodic limb movements has also been documented in PWS,<sup>94</sup> although there is a significant gap in knowledge around the prevalence of restless legs syndrome and generalized restless sleep in PWS. A recent Cochrane review found that iron supplementation probably improves restlessness and restless legs syndrome severity in comparison to placebo. Importantly, benefits were seen even when participants did not have low blood levels of iron.<sup>116</sup> Consider checking serum ferritin levels in individuals with periodic limb movements, restless legs syndrome, or restless sleep and, furthermore, consider that the minimum serum ferritin levels may not reflect adequate brain ferritin. With iron therapy, consider risks of constipation, which may be alleviated through supplements with higher absorption (ie, iron + vitamin C) and monitor ferritin to ensure appropriate dosing. Also, ensure iron is stored safely in a locked cabinet in the home as an acute overdose may be fatal.

## CONCLUSIONS

A variety of sleep abnormalities in the PWS population have the potential, if left untreated, to have tremendous negative impacts on their quality of life. As such, there needs to be increased awareness around the array of sleep abnormalities in PWS that include EDS, narcolepsy- and cataplexy-like phenotypes, and insomnia. We also recommend that health care providers consider the significant impact and potential relationships between sleep and many features of PWS (such as behavioral concerns) when deciding upon a course of treatment. Research is urgently needed to increase understanding of these features and their natural history in PWS to improve treatments for these individuals. While our evidence base grows, it is vitally important that clinicians immediately recognize and acknowledge sleep disturbances in this population. Additional research is needed to inform evidence-based practices toward a consensus statement for the treatment and diagnosis of sleep disorders in this population.

## ABBREVIATIONS

AHI, apnea-hypopnea index  
 CPAP, continuous positive airway pressure  
 CSA, central sleep apnea  
 EDS, excessive daytime sleepiness  
 GH, growth hormone  
 OSA, obstructive sleep apnea  
 PSG, polysomnography

PWS, Prader-Willi syndrome  
 REM, rapid eye movement  
 SNORD116, small nucleolar ribonucleic acid-116  
 T&A, adenotonsillectomy

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## SUBMISSION & CORRESPONDENCE INFORMATION

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## DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors gratefully acknowledge financial contributions from Harmony Biosciences for this initiative paid to TREND Community for writing services; Harmony Biosciences did not influence the writing of this paper or its content in any way. Ms. Picone is CEO and co-founder of TREND Community and TREND is a Public Benefit Corporation, an entity that allows it to be self-supporting without needing to fundraise. Drs. Glaze and Revana are consultants for TREND Community but do not receive any payments for services. They are also co-investigators in a pitolisant phase 2 clinical trial for Harmony Biosciences. Drs. Duis, Friedman, Sannar, and Shelton are also investigators in the pitolisant phase 2 clinical trial for Harmony Biosciences. Dr. Friedman is a member of the American Board of Internal Medicine (ABIM) Board of Directors and the ABIM Internal Medicine Exam Committee. To protect the integrity of Board Certification, ABIM strictly enforces the confidentiality and its ownership of ABIM exam content, and N.R.F. has agreed to keep ABIM exam content confidential. No ABIM exam content is shared or otherwise disclosed in this article. Chion Foundation (Dr. Pullen) received an unrestricted grant from Harmony Biosciences. Dr. Zee is a consultant and member of advisory committees for Eisai, Jazz, and Sanofi Aventis pharmaceutical companies. She is also a consultant for Harmony Biosciences and is the primary investigator for a research grant to Northwestern University funded by Harmony Biosciences and Vanda Pharmaceuticals. Drs. Hawkins, Pfalzer, Sannar, and Singh report no conflicts of interest.