



# Sleep Disorders in Children with Prader Willi Syndrome: Current Perspectives

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**Abstract:** Children with Prader-Willi syndrome (PWS) face a multitude of potential health challenges including life-threatening obesity, endocrinopathies, behavioral and emotional dysregulation, developmental delays, and sleep disorders. In the current perspective piece, we provide a focused review of the condition's etiology and clinical findings, as well as a more in-depth discussion of sleep disorders frequently associated with PWS. In particular, we highlight and discuss difficult clinical scenarios frequently encountered by the pediatric sleep physician caring for this patient population, including diagnosis and treatment of complex sleep-related breathing disorders, considerations for sleep apnea surgery, the interplay between growth hormone and sleep apnea, diagnostic challenges in hypersomnia/narcolepsy, and current and emerging therapies for hypersomnia/narcolepsy. Overall, although there are many areas that need further research, sleep disorders remain a fruitful target for improving quality of life of children with PWS and their families.

**Keywords:** Prader-Willi syndrome, narcolepsy, growth hormone, sleep apnea

## Introduction

Children with Prader-Willi syndrome (PWS) experience a multitude of health challenges, including sleep disorders. These children are at risk for the full spectrum of sleep disruption, including sleep-related breathing disorders, narcolepsy and hypersomnia, chronic insomnia, and sleep-related movement disorders such as periodic limb movement disorder and restless leg syndrome. Left untreated, these sleep disorders can result in important health consequences, including deleterious effects in physical health, neurocognitive function, and overall quality of life. Experts in PWS have recently published an extensive and helpful review of the literature and provided recommendations for diagnosis and management.<sup>1</sup> In the current review, we aimed to augment the literature by presenting not only a general narrative review of the condition and literature, but more importantly a state-of-the-art discussion of current clinical challenges commonly encountered by sleep providers caring for patients with PWS.

## Epidemiology, Genetics, and Clinical Characteristics

PWS is the most common genetic disorder that causes life-threatening obesity in childhood.<sup>2</sup> The prevalence ranges from 1 in 8000 to 1 in 30,000 (~400,000 individuals) worldwide. Males and females are affected equally, and all ethnic groups represented, although there is an increased prevalence in Caucasians.<sup>3</sup>

PWS arises from errors of genomic imprinting with lack of expression of paternally inherited imprinted genes in the chromosome 15q11-q13 region. Paternal deletion of the chromosome 15q11-q13 region accounts for about 60% of cases. Maternal uniparental disomy of chromosome 15 in which both chromosome 15s are inherited from the mother accounts for 35%. Micro-deletions and epimutations within the imprinting center in the chromosome 15q11-q13 region account for 5% of cases.<sup>2</sup> A DNA methylation study is the first-line screening test for PWS and can identify 99% of PWS genotypes.<sup>4</sup> If positive, a chromosomal microarray can be done to help identify the genetic subtype. Determining the

subtype allows for anticipatory guidance to families regarding possible genotype–phenotype correlations and recurrence risk.

Many of the typical features of Prader-Willi syndrome can be explained by the impaired development and function of the hypothalamus. The hypothalamus controls endocrine and metabolic function, appetite regulation, emotion, and behavior and is linked to the autonomic nervous system. Additionally, pituitary hypoplasia has been observed in 63–74% of patients with Prader-Willi syndrome.<sup>5</sup> Physical features of PWS include a narrow bifrontal diameter, almond-shaped eyes, small mouth and chin, generalized hypotonia, small genitalia, and small hands/feet. PWS is a complex disorder that affects many body systems. In neonates, severe hypotonia and poor feeding leads to failure to thrive and developmental delays. In early childhood, intellectual disabilities, impaired growth, and abnormal body composition with rising body mass index become increasingly apparent. Hyperphagia becomes more apparent in later childhood. Other endocrinopathies include hypothyroidism, adrenal insufficiency, and hypogonadism. Scoliosis and low bone mineral density are orthopedic problems seen in PWS. Emotional lability, behavioral outbursts and compulsive tendencies are some of the psychiatric concerns seen in PWS. Patients with PWS are at an increased risk for many metabolic disturbances including severe obesity, diabetes mellitus, dyslipidemia, and liver steatosis. Central and obstructive apnea are common along with other sleep-related breathing disorders.

## Sleep-Related Breathing Disorders

Children with PWS are at increased risk for a variety of different sleep-related breathing disorders. Many features of PWS predispose these children to snoring and obstructive sleep apnea, including obesity, narrow upper airway and micrognathia, low tone of the upper airway, and weak respiratory muscles related to generalized hypotonia.<sup>6</sup> All these features likely contribute to the increased sleep apnea prevalence of around 80%,<sup>7</sup> compared to 2% to 3% in the general population.<sup>8</sup> In addition to the multifactorial etiology of their OSA, children with PWS tend to have disproportionately more associated hypoventilation compared to neurotypical children.<sup>9</sup> Finally, practitioners may consider evaluating for evidence of possible pulmonary hypertension in the setting of PWS and significant OSA.<sup>10,11</sup> The complex interplay between recombinant human growth hormone (rhGH) and sleep-related breathing disorders is discussed in detail later in the manuscript.

Treatment of OSA in this population needs to be individualized depending on severity, patient-specific findings, and family preferences. Surgical options are discussed in more detail below, but a recent meta-analysis<sup>12</sup> found that T/A results in an average improvement in AHI of 7/hr with nearly two-thirds of children decreasing OSA severity category, but only about 20% achieving complete resolution. Orthognathic options can also be considered depending on patient anatomy, including LeFort osteotomy, tongue reduction, or orthodontic treatment.<sup>13,14</sup> Besides surgery, non-invasive positive airway pressure (PAP) can be efficacious, but only if worn by the child. While PAP adherence data in children with PWS are not well published, our anecdotal experience is that adherence remains a challenge for many children with PWS and requires a high degree of family commitment; the involvement of behavioral sleep psychology and/or PAP educator can sometimes be a helpful resource. Working on fitness and nutrition for optimal weight management is an adjuvant treatment for OSA, although obviously also challenging in this patient population. Those children with mild OSA may benefit from medical therapy with intranasal steroids and/or leukotriene inhibitors.<sup>1</sup> Other adjuvant treatment options to consider for selected patients include positional therapy and myofunctional therapy.

Central sleep apnea (CSA) is also encountered frequently in children with PWS. This is particularly the case in infants, and longitudinal studies have demonstrated that this can either resolve, convert to OSA, or persist with time as they get older.<sup>15</sup> A Cheyne-stokes respiratory pattern is also possible as a particular subtype of CSA, and was previously reported in one child with PWS.<sup>16</sup> The CSA observed in children with PWS may be a manifestation of a more generalized dysfunction of ventilatory control in the condition. Previous studies have demonstrated that individuals with PWS may have abnormal ventilatory responses to hypoxia (absent or blunted response), hyperoxia (increased ventilation response), and hypercapnia (absent or blunted response).<sup>17–19</sup> Treatment with supplemental oxygen in infants with CSA and PWS has been shown to be efficacious.<sup>20,21</sup> Older children with CSA and/or ventilatory control issues may respond to supplemental oxygen or may require more advanced modes of non-invasive ventilation with a backup rate.

## Sleep Apnea Surgery

First-line surgical treatment for OSA in children with PWS is T/A. T/A in patients with PWS and OSA helps to decrease severity of disease, with about 20% achieving total cure and 60–70% having substantial decrease in severity of OSA.<sup>22</sup> While surgery can decrease OSA severity, about 80% of PWS patients continue to have some degree of OSA after surgery. With the likelihood of persistent OSA following T/A, it is important to repeat polysomnogram (PSG) 3–4 months after surgery. Studies have shown an increased rate of perioperative complications for patients with PWS undergoing T/A.<sup>22–24</sup> For patients with PWS, hypotonia, restricted lung volume second to obesity, scoliosis, abnormal ventilatory responses to hypoxia and hypercarbia, as well as central apneas due to hypothalamic anomalies can all contribute to worse outcomes and more complications.<sup>22</sup>

A recent meta-analysis by Clements et al<sup>22</sup> reported 24% of patients with PWS had at least one reported complication following T/A; this is higher than the overall 7% reported incidence of complications in non-syndromic children.<sup>25</sup> The most common complication was the development of velopharyngeal dysfunction (VPD). Hypotheses as to why this occurs more readily in patients with PWS include their generalized hypotonia affecting the palatal musculature.<sup>23</sup> VPD occurred in 14% of patients and studies recommend consideration for preoperative resonance speech evaluation.<sup>22,23</sup> Performing tonsillectomy alone or with partial/superior adenoidectomy may also be considered to mitigate the risk for developing postoperative VPD. Additional complications reported included hemorrhage and the need for additional supplemental oxygen support. Increased risk for complications following T/A, particularly VPD, should be discussed with the family during preoperative counseling. Additionally, children with PWS should be monitored closely after surgery for acute perioperative complications; low threshold should be given to observe overnight after T/A in a setting where care can be escalated to an ICU setting if additional respiratory support is needed.<sup>22</sup>

When significant OSA persists despite T/A and the cause for OSA is not completely clear and/or PAP is not tolerated or effective, consideration may be given to performing drug-induced sleep endoscopy (DISE). Lan et al<sup>26</sup> evaluated DISE in nine patients with PWS and found 66% to have multilevel obstruction. Obstruction at the level of the velum was the most common site. Partial or complete collapse of the base of tongue was also common and this site was associated with a higher AHI. DISE may be useful when considering additional surgical interventions for OSA, although the success rate of these secondary sleep surgeries in patients with PWS is not well established.

## Growth Hormone Therapy

The rationale for the initial use of rhGH in the treatment of PWS was based on the significant overlap between findings in PWS and GH deficiency, including poor growth, low energy, increased fat mass, and reduced muscle strength. Indeed, extensive research has shown reduced GH response during stimulation testing and decreased daily spontaneous GH release in the majority of children with PWS<sup>27</sup> leading to Food and Drug Administration approval of GH treatment for PWS in the year 2000. The positive effect on growth velocity and body composition for children with PWS who are treated with rhGH has been well established.<sup>28</sup> As a result, consensus guidelines generally agree that optimal timing of rhGH start is prior to 2 years of age, when abnormal weight gain typically presents.<sup>4,29</sup> However, in clinical practice, many PWS physician experts and parents of children with PWS advocate for rhGH initiation as soon as possible.<sup>30</sup> This is based on additional research, albeit in small populations, demonstrating improved motor<sup>31–34</sup> and neurocognitive<sup>33–36</sup> development for children with PWS who receive rhGH therapy in infancy and toddlerhood. The urgency of this earlier rhGH initiation suggests that there is a critical window for achieving the possible lasting psychomotor benefits of rhGH therapy that may be otherwise missed if started later in childhood. Whether such a critical window truly exists is currently a topic of great research interest in the PWS community.

Despite its many benefits, there is also much controversy surrounding the rhGH use in patients with PWS as it relates to sleep disturbances. Following FDA approval of rhGH for PWS treatment, several cases of sudden death in children with PWS recently started on rhGH therapy were reported.<sup>37</sup> Given many of these children were markedly obese and/or had concurrent respiratory infection, it was hypothesized rhGH-induced increases in IGF-1 could increase lymphoid/tonsillar tissue leading to obstructive events<sup>38</sup> or that rhGH may have increased oxygen consumption due to increases in basal metabolic rate.<sup>39</sup> Since those cases, additional studies have been performed to evaluate the relationship between

rhGH therapy and obstructive and central sleep apnea in children with PWS. Recently, Zimmermann et al<sup>40</sup> took the approach of assessing sleep-disordered breathing for children with PWS who started rhGH before versus after the first year of life. Among the 62 patients studied, median OAHl was not significantly different after rhGH initiation, and there was also no difference in OAHl or OSA severity between the two age groups. However, a small subset of patients (2 patients in the younger group, 1 patient in the older group) developed moderate or severe OSA 3 months after starting rhGH. Similarly, Caudri et al<sup>41</sup> also showed no statistically significant differences in baseline and follow up OAHl among 94 children with PWS after rhGH initiation. Yet, it is notable that 12 subjects (13%) had no or mild OSA at baseline yet progressed to moderate or severe OSA which altered their clinical management after rhGH. For the youngest children, Miller et al assessed PSG before and 6 weeks following rhGH start in 20 infants 2 to 21 months of age. While no differences in overall AHI were found, they did note that among the 5 infants with marked increase in OAHl events (>50 events per hour), 3 had an active viral respiratory infection. Ultimately, this led authors to advocate for close OSA monitoring (eg, home pulse oximetry) in infants with PWS and respiratory illness on rhGH. Regarding central apneic events, most studies<sup>15,41–43</sup> demonstrate improvement following rhGH initiation. In the absence of placebo-controlled trials, it is not known whether these improvements would have been seen regardless of rhGH due to natural physiologic maturation. Reassuringly, none of the studies reviewed report additional instances of sudden death in children with PWS started on rhGH.

Ultimately, the relationship between rhGH and sleep-disordered breathing and/or sudden death is not fully understood. Therefore, current best practice recommendations advise baseline polysomnography prior to, and again within 3 to 6 months after rhGH start in patients with PWS.<sup>29</sup> For those children who are found to have concerning apnea on baseline evaluation, successful treatment (supplemental oxygen, PAP, T/A) should be pursued prior to rhGH initiation. However, limited access to pediatric polysomnography and challenges with interpretation of PSG results in infancy complicate adherence to these recommendations and may delay rhGH initiation for very young children. This is becoming more relevant as improved availability of genetic testing has increased the likelihood of PWS diagnosis in infancy.<sup>44</sup> Strong advocates of early initiation of rhGH therapy argue that lymphoid tissue is not developed in early infancy in non-snoring children,<sup>45</sup> thus the underlying hypothesis of IGF-1 mediated airway obstruction is not applicable to the youngest children who may have the most to benefit (eg, psychomotor advances) from rhGH initiation. Accordingly, prescribers of rhGH are left to deliberate between the possible increased risk of sleep-disordered breathing versus the risk of withholding a therapy that may positively alter the natural course of this complex, genetic syndrome.

As a result of these challenging treatment decisions, it is advised that a multidisciplinary team, experienced in PWS, determine timing and appropriateness of rhGH initiation.<sup>29</sup> Our standard practice is to have all children with PWS evaluated by a sleep medicine physician and outpatient polysomnography performed prior to rhGH start. Given the typically extended wait times for pediatric polysomnography, for infants we find it helpful to initiate the PSG on room air and then trial supplemental oxygen for the last few hours for comparison to evaluate this as a potential treatment option. In the very specific case of an infant with genetic confirmation of PWS who is unable to undergo polysomnography by 6 months of age, rhGH initiation without polysomnography may be considered. This is only in the instance of a full review of potential risks and benefits with the parents/guardian (who remain in favor of therapy), the child has been evaluated without concern by an expert in sleep-related breathing disorders, and the child has no other contraindications to rhGH therapy (untreated cortisol/thyroid hormone deficiencies). For hospitalized infants unable to undergo polysomnography, an additional possible evaluation is to perform at least 48 hours of continuous cardiorespiratory and pulse oximetry monitoring as a screen for significant sleep-related breathing disorders. Following rhGH therapy start, all infants and children should undergo polysomnography within 2–3 months to assess for development of sleep disturbances, regardless of what baseline assessment was done.

## Sleep-Related Movement Disorders

The most common clinically relevant sleep-related movement disorders encountered in children are restless leg syndrome (RLS), periodic limb movement disorder (PLMD), and restless sleep disorder (RSD). While all three of these disorders likely share similar pathophysiology related to dopamine dysfunction and relative iron deficiency, their clinical presentations and diagnoses differ. Specifically, RLS is a clinical diagnosis based on the child verbalizing an

urge to move feeling in the legs, and is many times accompanied by sleep-onset difficulties. In contrast, the diagnosis of PLMD is rendered based on the presence of an elevated number of periodic limb movements during polysomnography in conjunction with restless, unrefreshing sleep. Finally, RSD is a relatively new diagnostic entity that is diagnosed when a child has restless, disturbed sleep (not typically sleep-onset difficulties), in conjunction with a large muscle movement index of at least five per hour on polysomnography.<sup>46</sup> Treatment of these sleep-related movement disorders typically starts with optimization of iron stores, which can be accomplished via oral or intravenous routes.<sup>47</sup> While much is known about RLS, PLMD, and RSD in children, there is very little published regarding these disorders in individuals with PWS. A single case report of a young child with PWS and excessive sleepiness mentioned mildly elevated PLMS as a part of the presentation, although that child was found to have narcolepsy.<sup>48</sup> Finally, a case series of children with PWS who had undergone PSG demonstrated that only one child out of 37 included in analysis had elevated PLMS (>5/hr).<sup>49</sup>

Bruxism may occur either during wakefulness or during sleep, and in the latter case it is classified as a sleep-related movement disorder. Interestingly, children with PWS appear to be at increased risk of bruxism. A previous case-control study performed by Saeves et al found evidence of increased tooth wear with erosion and attrition in individuals with PWS.<sup>50</sup> Subsequent data have shown that children with PWS have decreased salivary secretion, increased viscosity, and increased mouth breathing that likely contribute to tooth wear.<sup>51</sup> It has been hypothesized that there is a shared underlying mechanism related to epigenetic differences underlying bruxism and PWS.<sup>52</sup> Treatment of sleep-related bruxism should include enlisting the aid of a pediatric dentist as well as treatment of any underlying sleep apnea. Studies have demonstrated that treatment of sleep apnea with either positive airway pressure or mandibular advancement decreases severity of bruxism.<sup>53</sup> This was also demonstrated in a case report of a 9 year old with PWS, OSA, and bruxism that improved with use of a mandibular advancement oral device.<sup>14</sup>

## Hypersomnia and Narcolepsy

Excessive daytime sleepiness is very common in individuals with PWS. There can be multiple possible contributors to their daytime sleepiness including sleep-related breathing disorders as well as disorders of central hypersomnolence. The hypersomnia of PWS is felt to be related to differences in the hypothalamus that result in excessive sleepiness and a predisposition for intrusion of REM sleep into wakefulness.<sup>1,54–56</sup> This hypothesis is bolstered by results of a mouse model of PWS which demonstrates that differences in the small nuclear RNA 116 (SNORD116) cluster within the PWS locus results in REM-intrusion.<sup>54,55</sup> The Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) has been validated in children with PWS down to age 6 years of age, and therefore provides a useful tool for screening for excessive daytime sleepiness in the clinical setting.<sup>57</sup>

There are multiple challenges in the diagnostic evaluation of the child with PWS and hypersomnia. While the diagnostic work-up for hypersomnia and narcolepsy in the child without PWS may consist of multiple sleep latency testing (MSLT), narcolepsy antigen testing, and possible cerebrospinal fluid (CSF) hypocretin testing, these diagnostic tools may have different test characteristics within the PWS population. Specifically, HLA testing in patients with Prader-Willi syndrome has not been found to be clinically useful as a diagnostic marker of narcolepsy.<sup>54</sup> A recent review of the literature found four studies that have been previously published examining hypocretin levels in individuals with PWS. Overall, the studies found that individuals with PWS had an average CSF hypocretin level between 150 and 200 pg/mL, as opposed to those individuals with type I narcolepsy who had levels on average around 50 pg/mL. In contrast, control samples were on average between 350 and 400 pg/mL. It is not currently felt that a decreased number of hypocretin neurons are the principal culprit for narcolepsy in individuals with PWS,<sup>58</sup> and therefore testing CSF hypocretin levels is not typically diagnostically of value or commonplace in this population.<sup>1</sup>

Best practice for evaluation of hypersomnia in the child with PWS that is otherwise unexplained includes diagnostic testing with MSLT.<sup>1</sup> In generally healthy children, appropriate performance and interpretation of MSLT data is a challenge even for experienced pediatric sleep physicians and adding the extra layer of PWS contributes to the challenge. Studies of adults with PWS demonstrate a high prevalence of hypersomnia based on MSLT based on mean sleep latency (SL) and number of sleep onset REM periods during napping opportunities (SOREMS). While 67% report subjective daytime sleepiness, approximately 35% meet criteria for narcolepsy (SL <8 min + >1 SOREM), 12%



hypersomnia without narcolepsy (SL <8 minutes + <2 SOREMS), and 53% have a borderline picture (either: >1 SOREM + SL >8 mins OR SL 8–10 mins + <2 SOREMS).<sup>59</sup>

While the MSLT is typically not performed in children under the age of 5 years, when napping during the day is still physiologically normal, children with PWS may present with hypersomnia and/or narcolepsy before the age of 5 years. Although the test characteristics of the MSLT are not as well understood below the age of 5 years, it is noteworthy that there are published cases of children under the age of 5 years with PWS who successfully underwent MSLT testing. Williams et al<sup>49</sup> reported on a series that included 7 children with PWS under the age of 5 years who completed MSLT testing, four of which had a mean sleep latency less than 8 minutes and two of which had at least 2 sleep onset REM periods; none of the children with mean sleep latency >8 minutes had multiple SOREMS. In that same series, MSLT sleep latency was not related to subjective sleepiness score, AHI, or BMI. Because the MSLT is not well validated in children under the age of 5 years, sleep providers may be hesitant to perform testing in younger children. That said, postponing diagnostic evaluation may result in significant diagnostic delays and a missed opportunity for providing intervention during a critical time of a child's development; this was well illustrated by a case report of a child who manifested symptoms of narcolepsy and cataplexy as early as infancy, but MSLT was not performed until the child was age 6 years.<sup>48</sup>

Cataplexy experienced in PWS warrants specific discussion as well. Cataplexy is common in children with PWS, ranging from 18% to 25% affected, and a possible presentation unique to PWS is the occurrence of cataplexy in association with eating solid food.<sup>1</sup> While in a generally healthy child, the presence of true cataplexy is almost pathognomonic for type I narcolepsy, this is not necessarily the case for PWS, where cataplexy without other symptoms of narcolepsy may be a manifestation of underlying PWS.<sup>60–62</sup> Furthermore, cataplexy and hypersomnia may begin at a very young age in children with PWS, with cases reported in the literature of cataplexy and/or narcolepsy beginning in children with PWS as young as two years of age.<sup>48,63</sup> The differential diagnosis of cataplexy includes atonic seizures, which have been reported in children with PWS and consideration should be given to formal EEG in the evaluation of a child with PWS and drop episodes.<sup>64</sup>

Management of narcolepsy and hypersomnia in children with PWS is a complex and evolving landscape. A recent best practice publication<sup>1</sup> suggested treatment per published clinical practice guidelines from the American Academy of Sleep Medicine.<sup>65</sup> While these general guidelines are based on the best available evidence to-date, the experienced pediatric sleep physician will recognize that patient and PWS-specific factors must be taken into consideration. Traditional stimulants including methylphenidate have been successfully used in children with PWS and narcolepsy.<sup>2,66</sup> Modafinil has positive experience published in a 6-year-old child with PWS and narcolepsy<sup>48</sup> as well as an open-label study of nine children with PWS and hypersomnia.<sup>67</sup> Families should be educated that modafinil is not approved for use in those children under the age of 17 years related to black box warning for Stevens-Johnson syndrome and psychosis, may decrease effectiveness of oral contraception, and may cause fetal harm.<sup>65</sup> Nevertheless, modafinil is frequently used in children with narcolepsy provided family is educated regarding possible risks. Oxybate has been shown to be effective for treatment of narcolepsy in children, although it should be used with caution in children with PWS given their underlying propensity for SRBDs.<sup>1</sup>

Carnitine is a less well-established therapy for hypersomnia/narcolepsy in PWS, although anecdotally has been used with success. Carnitine is needed for transport of long-chain fatty acids in mitochondria, and deficiency of which may result in multiorgan symptoms. Individuals with PWS have been hypothesized to have alterations in carnitine metabolism and utilization,<sup>68,69</sup> and it is sometimes prescribed at 50 mg/kg/day.<sup>70</sup> Interestingly, individuals with narcolepsy or hypersomnia without PWS have recently been found to have altered acylcarnitine profiles and carnitine palmitoyltransferase 1B was an independent risk factor.<sup>71</sup> Furthermore, a recent systematic review found that carnitine supplementation was well tolerated, without side effects, and had some efficacy as a pharmacologic therapy for patients with narcolepsy.<sup>72</sup> This may be a particularly attractive option that is relatively benign compared to other pharmaceutical alternatives for hypersomnia in very young patients with PWS. To be sure, this is an area worthy of further investigation.

Finally, although not yet approved for hypersomnia in children with PWS, there has been intense interest in pitolisant. This medication works as a histamine-3-receptor inverse agonist and has strong evidence of efficacy for treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy.<sup>65</sup> In children with PWS, there have been initial successes with this

medication, including a case series of three children who had improved sleepiness and cognition with use<sup>73</sup> as well as a case report of a 15 year old with PWS who experienced improved cognition, behavior, muscle tone, and alertness.<sup>74</sup> A randomized, double-blind placebo-controlled trial of pitolisant in children and adults is currently underway with results highly anticipated by families and providers alike.<sup>1</sup>

## Conclusion

Children with PWS are at high risk for a multitude of different sleep disorders, identification and treatment of which may substantially improve health and quality of life. There are unique characteristics of diagnostic and therapeutic strategies that should be taken into consideration when providing care to these children. Examples of this include the performance and interpretation of multiple sleep latency testing when there is clinical presentation of a narcolepsy-like picture in PWS, the role of wake-promoting medications and supplements for treatment of hypersomnia, and the need for individualized therapy for sleep apnea given the lower surgical cure rates and challenges with PAP adherence. Even for experienced pediatric sleep physicians, challenges remain regarding complex sleep apnea and ventilatory control management, the interplay between growth hormone and sleep apnea, and appropriate diagnosis and treatment of hypersomnia and narcolepsy in PWS. Complex sleep apnea (sleep apnea with both obstructive and central components) is related to the underlying abnormal ventilatory control in addition to airway obstruction and may require more advanced modes of positive airway pressure and/or the addition of supplemental oxygen. Supplemental oxygen can also be effective for infants with PWS and predominantly central sleep apnea. Due to concern that rhGH may cause worsening of existing obstructive sleep apnea in a subset of PWS patients, the performance of follow-up sleep studies is clinically helpful. These are all areas that need additional study in order to ultimately improve care for these children and their families.

## Abbreviations

CSA, central sleep apnea; CSF, cerebrospinal fluid; DISE, drug-induced sleep endoscopy; ESS-CHAD, Epworth Sleepiness Scale for Children and Adolescents; MSLT, multiple sleep latency testing; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; PSG, polysomnogram; PWS, Prader-Willi syndrome; rhGH, recombinant human growth hormone; RLS, restless leg syndrome; RSD, restless sleep disorder; SL, sleep latency; SOREMS, sleep onset REM periods during napping opportunities; SNORD116, small nuclear RNA 116; T/A, tonsillectomy and adenoidectomy; VPD, velopharyngeal dysfunction.

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