

# Sleep in Children with Neurodevelopmental Disabilities

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## Abstract

### Keywords

- ▶ sleep disorders
- ▶ neurodevelopmental disabilities
- ▶ Down syndrome
- ▶ Fragile X syndrome
- ▶ Prader–Willi syndrome
- ▶ Angelman syndrome
- ▶ Rett syndrome
- ▶ Smith–Magenis syndrome
- ▶ cerebral palsy
- ▶ autism spectrum disorders

This review describes recent research in pediatric sleep disorders associated with neurodevelopmental disabilities (NDDs) and their treatment. NDDs affect more than 2% of the general population and represent more than 35% of the total cases of children referred to a neuropsychiatric center for sleep problems. Specific clinical and therapeutic aspects of sleep disorders associated with Down syndrome, Fragile X syndrome, Prader–Willi syndrome, Angelman syndrome, Rett syndrome, Smith–Magenis syndrome, cerebral palsy, and autism spectrum disorders are described. Furthermore, the drugs commonly used for sleep disorders in children with NDDs are described. The review clearly highlighted that children with NDDs are often affected by sleep disorders that require appropriate clinical and therapeutic approach to improve quality of life in both patients and families.

## Introduction

Sleep disorders in children with neurodevelopmental disabilities (NDDs) have raised increasing interest in recent years, especially some specific conditions such as Down syndrome (DS), Fragile-X syndrome, Rett syndrome (RS), Prader–Willi syndrome (PWS), Angelman syndrome (AS), tuberous sclerosis, and autism spectrum disorders (ASDs).

NDDs affect approximately 2% of the general population and are associated with varying degrees of cognitive, physical, and emotional impairment.<sup>1</sup>

Sleep disturbances in children with NDDs are highly prevalent and are linked to a multifactorial etiology with

different contributions of neurologic, medical, and psychiatric comorbidities. Sleep difficulties can result in additional learning and behavior problems, affecting the whole family's health and well-being.<sup>2</sup>

Furthermore, differently from age-related sleep disturbances in typically developing children, sleep disorders in patients with NDDs tend to be chronic, lasting into adolescence or adulthood.

Despite these conditions associated with different developmental disorders constitute more than 35% of total cases of children referred to a neuropsychiatric center for sleep problems, research on the treatment of sleep disorders in children with NDDs has been relatively scarce.<sup>3</sup>

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The pathophysiology of sleep disorders in children with NDDs might be linked to the specific syndrome genotype or phenotype, to an endogenous dysfunction in hormone and neurotransmitter release or to altered perception of the zeitgebers (light–dark cycle, food schedule, maternal inputs, etc.).

In some patients with NDDs, problematic sleep is a phenotypic characteristic of a particular disorder or genetic condition and the knowledge of the distinctive features of sleep disorders in patients with NDDs is crucial for their effective treatment.<sup>4</sup>

The main sleep complaints in children with NDDs are represented by difficulty in settling at night (51%) and nocturnal awakenings (67%).<sup>5</sup> Fragmented sleep throughout the day and night determines daytime sleepiness and irregular sleep schedule that may lead to a free-running rhythm or to a complete reversal of the night–day cycle.<sup>6</sup>

## Sleep Abnormalities in Children with Genetic Disorders

### Down Syndrome

Several studies have shown that children with DS are affected by different sleep disturbances. The most common of them is represented by obstructive sleep apnea syndrome (OSAS) that affects approximately 50 to 80% of people with DS.<sup>7,8</sup> This high prevalence is linked to the definite physical characteristics of DS, such as, craniofacial and upper airway abnormalities, obesity, generalized hypotonia, tonsil and adenoid hypertrophy, macroglossia, glossoptosis, hypoplastic trachea, midfacial, and mandibular hypoplasia.<sup>9–11</sup>

In addition, Ferri et al hypothesized a brain stem dysfunction in DS, responsible for the abnormal imbalance between the sympathetic and vagal systems and confirms the presence of central as opposed to obstructive apnea in subjects with DS without chronic respiratory pathology.<sup>12</sup> These central events were preceded by sighs, but they provoked significant oxygen desaturation.

Excessively fragmented sleep, problems with sleep maintenance, early waking, daytime sleepiness, and decreased leg motor activity have also been described in infants with DS versus typically developing infants.<sup>13–16</sup>

Sleep problems have been often described as correlated with other problems such as asthma, autism, and a history of enlarged adenoids and tonsils.

A recent study showed that although a questionnaire survey reported that 65% of the children had significant sleep problems in the preceding month, the parents often did not report sleeping difficulties in their children. About 46% of children with DS screened positive for sleep-related breathing problems and 21% for sleep-related movement disorders. Sleep disorders represent an underrecognized problem in children with DS and the knowledge of comorbidities may help to deal with sleep problems in this population.<sup>9</sup>

Polysomnographic (PSG) studies showed that children with DS had significantly less rapid eye movement (REM) sleep than typically developing children and presented a low R index (number of high-frequency REMs against number of low-frequency REMs).<sup>17</sup> In addition, they showed an increase

in wake after sleep onset, body movements, and fewer spindle bursts.<sup>18</sup>

Recent practice parameters of the American Academy of Pediatrics recommend to discuss with parents, at least once during the first 6 months of life, symptoms of obstructive sleep apnea (OSA), including heavy breathing, snoring, uncommon sleep positions, frequent night awakening, daytime sleepiness, apneic pauses, and behavior problems that could be associated with poor sleep. Moreover, screening for signs of OSA should be included in every cardiologic follow-up.<sup>19</sup>

### Angelman Syndrome

AS is a neurodevelopmental genetic disorder caused by the absence or loss of function of the maternally inherited allele at the 15q11–q13 domain; it occurs in 1:12,000 to 20,000 individuals and accounts for 6% of all children with severe cognitive disability and epilepsy.<sup>20,21</sup>

AS is characterized by developmental delay, severe speech impairment, profound intellectual disability, ataxic gait, and/or tremulous movements of limbs, a peculiar behavior with frequent laughter, apparently happy temperament, hand flapping and jerky movements (puppet-like movements), and severe epilepsy.<sup>22</sup> Other clinical features are widely spaced teeth, an open mouth, tongue protrusion, microcephaly, fair skin and hair, and hyperactivity.

Sleep disturbances are common in AS and are included in the diagnostic criteria established in 1995 and updated in 2005.<sup>23,24</sup>

The few studies available on sleep disorders in AS show a high frequency of disorders of initiating and maintaining sleep, prolonged sleep latency, prolonged wakefulness after sleep onset, high number of night awakenings, and reduced total sleep time.<sup>25</sup> In addition, snoring and parasomnias were frequently reported, including enuresis, bruxism, sleep terrors, somnambulism, and nocturnal hyperkinesia.<sup>26</sup> Sleep problems appear more relevant and severe during childhood but in some patients they may persist into adulthood.<sup>27,28</sup>

Frequent sleep complaints include the following: difficulty initiating or maintaining sleep; frequent nighttime awakenings; irregular sleep/wake cycles, and circadian rhythm disorders, reduced sleep duration and nocturnal behaviors, including nocturnal laughing, sleepwalking/sleep terrors, bruxism, and seizures.<sup>24,26,27,29–31</sup>

PSG studies showed a significant reduction in sleep efficiency and in percentage and duration of REM sleep, whereas the percentage of SWS was found to be significantly higher, because of the presence of the 1 to 3 Hz bursts that represent the typical electroencephalography (EEG) pattern of the syndrome<sup>25</sup>; no respiratory abnormalities were found, but a tendency for subjects with AS to present a higher periodic limb movement index versus the other two control groups with epilepsy and mental retardation (MR) was found.<sup>32</sup>

In children with AS, biological alterations are causes of insomnia; treatment with sleep hygiene, behavioral therapy, and reinforcing of the sleep wake rhythm was documented to be as effective as hypnotic drugs.<sup>33,34</sup> Furthermore, response to melatonin treatment in small trials suggests the possibility

of altered melatonin secretion.<sup>35</sup> In a recent study correlating sleep–wake pattern with serum melatonin levels, children with AS reported circadian rhythm sleep disorders (CRSDs), delayed sleep phase syndrome (DSPS), and free-running rhythm; the nighttime serum melatonin levels of patients with AS were significantly low and patients with AS with DSPS showed delayed melatonin peak.<sup>31</sup>

### Prader–Willi Syndrome

PWS is a genetic disorder affecting in 1/10,000 and 1/25,000 live births.<sup>36,37</sup> The genetic defect is linked to a deletion in the paternally inherited chromosome 15q11–q13 in 70 to 75% of individuals, to a maternal uniparental disomy in 20 to 25% of cases, and to abnormal methylation of the imprinting center on chromosome 15 in 1 to 2%.

The early symptoms are represented by feeding difficulties and hypotonia followed by developmental delay, hypogonadism, hyperphagia, obesity and behavioral, and learning and psychological problems during childhood and adolescence.<sup>38</sup>

Different studies have been performed to evaluate sleep in patients with PWS showing a decrease of sleep and REM latency and the presence of sleep–onset REM periods, corroborating the hypothesis of a primary disorder of vigilance.<sup>39</sup>

A recent study that evaluated sleep microstructure in children with PWS by means of Cyclic Alternating Pattern (CAP) analysis showed a decrease of nonrapid eye movement (NREM) sleep instability, further supporting the hypothesis of the presence of a primary disorder of vigilance and underlying the similarities with narcolepsy. In these patients, growth hormone (GH) therapy was able to increase the NREM sleep instability with the normalization in slow wave sleep.<sup>40</sup>

Obesity and hypothalamic dysfunction could be responsible for the primary abnormalities of ventilation during sleep that might contribute to excessive daytime sleepiness (EDS). Although EDS has similarity with narcolepsy, patients with PWS do not present the other typical symptoms of narcolepsy.<sup>39</sup>

Sleep-disordered breathing and a decreased response to hypoxia or hypercapnia has been described in patients with PWS.<sup>41</sup> The studies on the prevalence of OSAS in PWS showed conflicting results: some reported a prevalence of approximately 90% whereas other studies reported a lower prevalence.<sup>39</sup>

It seems that OSAS is a feature that appears during the development; in fact, infants with PWS, when compared with older children, were more likely to experience central sleep apnea other than obstructive events.<sup>42</sup>

With age, obesity increases and OSAS emerges—a recent review, analyzing 14 studies in children with PWS reported an OSAS prevalence of 79.91%—53.07% had mild OSAS, 22.35% moderate OSAS, and 24.58% severe OSAS. Narcolepsy was found to occur in 35.71% of children with PWS. Adenotonsillectomy was found to be effective in reducing OSAS for some children, but residual OSAS was present in the majority of cases after the surgery.<sup>43</sup>

Several studies reported that GH therapy in children with PWS might determine hypertrophy of tonsils or adenoids, increase OSA, and could be responsible for sudden death of

subjects with PWS.<sup>39,44,45</sup> In a recent study, it was reported that, although the percentage of patients with an obstructive apnea–hypopnea index > 1 increased during GH treatment, a decrease of respiratory disturbance index and the central apnea index were observed; the authors concluded that long-term GH treatment in patients with PWS is generally safe, recommending annual polysomnography and adenotonsillar evaluation.<sup>45</sup>

Because of the concurrent presence of different sleep disturbances (EDS, narcolepsy, and sleep-disordered breathing) in children with PWS, the approach should be multidisciplinary. GH treatment is now considered to be safe, but it is still contraindicated in patients with PWS who are severely obese or have a severe respiratory impairment. EDS can be successfully treated with modafinil that improves significant sleepiness and is well-tolerated, without adverse effects.<sup>46</sup> An improvement of EDS has been reported in a case following treatment with tryptophan, possibly by consolidation of fragmented sleep.<sup>47</sup>

### Fragile X Syndrome

Fragile X syndrome (FXS) is one of the most common causes of MR; it is characterized by mild-to-severe intellectual disability, epilepsy, abnormalities in language and communication, unusual responses to sensory stimuli, stereotypic behaviors, hyperactivity, and deficits in visual–spatial skills, attention, and executive functioning. Distinctive physical features include an elongated face, large ears, and protruding jaw.<sup>48</sup>

Very few studies examined sleep disorders in patients with FXS: in two different studies Kronk et al reported a prevalence of 32 to 50% of significant sleep problems with the more frequent complaints represented by sleep onset difficulties and frequent awakenings during the night.<sup>49,50</sup>

Data obtained from the Fragile X Clinical and Research Consortium Database showed that 27% of parents report sleep problems.<sup>48</sup> Also, OSA has been reported to be a frequent complaint (from 7% to more than 30% of patients).<sup>51</sup>

A neurophysiologic study of nine patients with FXS showed reduced total sleep time, decreased REM sleep percentage, and an increase in the first REM latency and in stage 3 to 4 NREM percentage.<sup>52</sup> Moreover, in the same study, an increase in twitch movements was observed during both stage 2 NREM and REM sleep. This may indicate a dysregulation of the cholinergic monoaminergic system during sleep, leading to an imbalance between the two neurochemically different mechanisms, which are known to be involved in other clinical manifestations of this genetic syndrome.<sup>53</sup>

Behavioral intervention for sleep problems (mainly extinction) may be effective in subjects with FXS reducing settling problems, night awakenings, and co-sleeping while early morning waking and night rocking do not improve.<sup>54</sup>

Recently, research has been focused on medical problems in FMR1 premutation carriers—FMR1 premutation occurs in 1:200 women and 1:400 men.<sup>55</sup> An association between this condition and fragile X tremor and ataxia syndrome (FXTAS) has been reported, but sleep problems in this population are overlooked. Hamlin et al showed increased prevalence of OSA in premutation carriers with FXTAS and a significant odds

ratio of sleep apnea for permutation carriers with FXTAS of approximately 3.4 times emerged.<sup>56</sup>

A recent study examined the relationship between fragile X premutation and restless legs syndrome (RLS)—individuals with premutation resulted 1.9 times as likely to meet criteria for RLS versus controls and premutation carriers with RLS experienced also significantly worse symptoms and higher scores at the International restless legs scale, insomnia severity scale, and Pittsburgh Sleep Quality Index.<sup>57</sup>

### Smith–Magenis Syndrome

Smith–Magenis syndrome (SMS) is a rare, complex multi-systemic disorder caused by a mutation or small interstitial deletion in a crucial transcriptional regulator gene of the mammalian circadian clock, *RAI1* (retinoic acid induced) on chromosome 17p11.2<sup>58</sup>; it occurs in 1:25,000 births, and is characterized by developmental delay with intellectual disability of variable degree, short stature, hoarse deep voice, obesity, scoliosis, distinctive facies (deep, close-set eyes, midfacial hypoplasia, cupid bow-shaped mouth, and broad, square-shaped face), and peripheral neuropathy.<sup>59</sup>

Maladaptive behaviors are typical of SMS—self-injury with low sensitivity to pain (hitting, biting, skin picking, inserting foreign objects into body orifices, and yanking nails); peculiar motor stereotypes, including upper body self-hugging, compulsive finger licking, and book or magazine page flipping; temper tantrums, oppositional defiant behaviors, and attention deficit/hyperactivity disorder (ADHD) and a 24-hour sleep disturbance.

The diagnosis of SMS is based on clinical recognition of this constellation of physical, developmental, and behavioral features in combination with a sleep disorder characterized by inverted circadian rhythm of melatonin secretion with peaks during the day.<sup>60</sup>

Sleep disorders characterize all ages of patients with SMS—in infants' sleep disturbance is manifest by EDS or lethargy, as well as by decreased sleep duration. Older toddlers and children show fragmented and shortened sleep cycles, frequent and prolonged nocturnal awakenings, early morning awakening, EDS, daytime napping, snoring, and enuresis. Decreased nocturnal sleep, early awakenings, and daytime naps extend into adolescence.<sup>61</sup>

Data derived from actigraphy indicate a sleep disturbance that begins as early as 6 months of age during infancy, with fragmented sleep and reduced 24-hour sleep compared with healthy control subjects. This pattern persists in preschool (3 years), early school (5 years), and later school children (6–8 years) that sleep 1 to 2 hours less per 24 hours than healthy age-matched control children. Reduced 24-hour sleep stems largely from the reduction of night sleep in all age groups. The sleep debt is compensated for by daytime napping.<sup>60</sup>

PSG studies revealed reduced sleep time in virtually all SMS patients; they showed an abnormally reduced latency for falling asleep during the daytime, a finding that is consistent with increased daytime napping; in addition, abnormalities of REM sleep have also been reported in 43 to 50% of patients with SMS.<sup>62</sup>

As somatic features like such as hypoplasia and obesity predispose patients with SMS to OSAS, also this disorder should be screened.

CRSD in SMS are thought to be related to the disturbed regulation of downstream circadian clock genes.<sup>58,63</sup>

A series of studies have found that 96% of SMS children had inverted endogenous melatonin secretion, peaking in the day rather than at night.<sup>64</sup>

In a small group of patients with SMS, oral acebutolol was given in the early morning to suppress the daytime melatonin secretion and was coupled with an evening dose of melatonin to improve sleep/wake complaints.<sup>65,66</sup>

### Rett Syndrome

RS is a rare neurodevelopmental disorder associated, in 99% of cases, with a de novo mutation of the *MECP2* (methyl-CpG binding protein 2) gene on the X chromosome (Xq28) producing the MECP2 protein.<sup>67</sup> It affects mainly females with a prevalence of 1:10,000 to 20,000.<sup>68</sup> It is the second most common cause of genetic intellectual disability in females (after DS) and is characterized by severe MR, autistic features, muscle hypotonia, deceleration of head growth, ventilatory abnormalities during wakefulness (alternating apnea and hyperventilation), and motor apraxia of unknown etiology.<sup>69</sup>

Epilepsy occurs in 50 to 90% of patients with RS, with drug-resistant nocturnal seizures.<sup>70</sup>

Early studies on RS showed characteristic sleep dysfunctions, that are included as part of the diagnostic criteria for RS, represented by irregular sleep/wake patterns, excessive daytime naps, and problematic nighttime behaviors, such as, nocturnal laughter, bruxism, long spells of screaming and/or inconsolable crying, nocturnal seizures, sleep terrors, and sleep talking.<sup>71</sup>

Studies using polysomnography revealed alterations in sleep architecture such as lower sleep efficiency, long sleep-onset latency, and short total sleep time, increased wake after sleep onset (WASO), decreased REM sleep, fewer spindles, and K complexes similar to other forms of MR.<sup>72–74</sup> Patients with RS commonly show irregular breathing during wakefulness consisting of episodes of hyperventilation interspersed by breath-holding spells, sometimes associated with severe oxygen desaturation. On the contrary, usually, the respiratory pattern during sleep is normal, although some central or obstructive events and irregular breathing in later stages of the disorder were also reported.<sup>73</sup>

A recent study showed, in a sample of more than 300 cases followed over 12 years, that the prevalence of any sleep disturbance was very high (more than 80%) and decreased with age (less common in individuals older than 18 years).<sup>75</sup> Night laughing represented the most frequent problem occurring in 60 to 88% of younger girls followed by night screaming (less than 50%). The authors also demonstrated that, after adjusting for age, a higher prevalence of night laughing was associated with a larger gene deletion in patients with RS.

Treatment strategies for respiratory disturbances included 1 to 2 hours per day of continuous positive airway pressure (CPAP) while awake.<sup>76</sup>

Behavioral insomnia and problematic nighttime behaviors in RS are usually treated with a combination of behavioral treatments (graduated extinction) and oral melatonin (range, 2.5–7.5 mg) that reduced mean sleep latency.<sup>77</sup>

## Sleep Abnormalities in Children with Autism Spectrum Disorders

Sleep disorders and sleep alterations are common in children with ASDs, including Asperger syndrome.<sup>78</sup> Studies based on parental surveys reported a 50 to 80% prevalence of sleep problems in children with ASD compared with a 9 to 50% prevalence rate in typically developing children.<sup>78–80</sup> The degree of cognitive impairment or the ASD subtype do not seem to be correlated with the prevalence of sleep problems but, on the contrary, sleep disturbance in these children seems to be correlated with aggressive behavior, developmental regression, and internalizing problems.<sup>81</sup> Sleep disorders were reported either in ASD children with severe MR or in high-functioning subjects, with intelligence quotients greater than 70.<sup>78</sup>

In a questionnaire-based study on 167 children with ASD, Liu et al revealed that approximately 86% of subjects had at least one sleep problem almost every day, including bedtime resistance (54%), insomnia (56%), parasomnias (53%), sleep-disordered breathing (25%), morning rise problems (45%), and daytime sleepiness (31%).<sup>82</sup> Recently, it has been reported that more than 50% of 2- to 5-year-old children with ASD have at least one sleep problem, take more than 1 hour to fall asleep, and have long-lasting nocturnal awakenings.<sup>83</sup> Furthermore, insomnia is 10 times more frequent in children with ASD and this symptom tends to persist until adolescence.<sup>84</sup>

Anxiety, autism symptom severity, and gastrointestinal problems were identified as the main risk factors for sleep disturbance in children with ASD.<sup>85</sup>

It is known that in ASD, there is an overall diminished pattern of nocturnal melatonin secretion or a delay in its secretion at night. Low levels of melatonin and/or its urinary metabolic derivatives correlate with sleep problems and autistic behaviors.<sup>86</sup>

Therefore, patients with ASD may be unable to fall asleep until late at night or may exhibit irregular sleep–wake rhythms with multiple naps distributed through day and night.<sup>87</sup>

Emotional difficulties (e.g., separation anxiety) or communication difficulties that may preclude them from comprehending parental instructions about falling asleep may be the cause of insomnia.<sup>88</sup> Also, daytime sleepiness was frequently observed in children with ASD—Bruni et al using the Pediatric Daytime Sleepiness Scale reported that 62% of children with Asperger syndrome exhibited scores > 16, denoting excessive sleepiness.<sup>89</sup>

PSG studies in children with ASD have focused on abnormalities related to REM sleep (decreased quantity and reduced eye movement density during REM), decreased sleep spindles in Stage 2, increased stage 1, and decreased SWS.<sup>78,87</sup>

Few studies have tried to analyze the sleep microstructure to characterize better sleep of autistic children. Miano et al

revealed that children with ASD, compared with typical developing children, showed a reduced total sleep, shorter REM latency, and lower CAP rate, mainly caused by a reduction of A1 CAP subtypes.<sup>87</sup> Bruni et al reported that in children with Asperger syndrome sleep architecture does not differ from that of children with autism, but, on the contrary, sleep microstructure presents several differences—increased CAP rate in SWS and a decrease in sleep stage 2, higher percentage of A1 subtypes, and lower A2%.<sup>89</sup>

A PSG study of two consecutive nights on ASD children showed that the ASD poor sleepers differed significantly from the ASD good sleepers and normal children, having lower sleep efficiency, and prolonged sleep latency.<sup>90</sup>

The management of sleep disturbance in ASD children depends on the type of sleep disorder, but, in general, behavioral therapy associated to melatonin supplementation is the most used.

**Behavioral therapy:** Children with ASD are very sensitive to noise, music, and daytime routine; thus, consistent sleeping environment and routine that do not vary from one night to another help the child relax down to sleep. Also, the avoidance of exciting or mentally stimulating activities in the hours before bedtime is important.<sup>81</sup> Behavioral insomnia and sleep onset association disorder require parents to practice techniques of behavioral extinction and/or decreasing the duration of the afternoon nap.<sup>91</sup>

**Melatonin:** Melatonin given its endogenous deficiency in a significant percentage of children with ASD, supplementation with melatonin is suggested for difficulties initiating and maintaining sleep. The time of management is generally 5 to 6 hours before the desired bedtime, on an empty stomach in doses of 1 to 6 mg.<sup>88,92,93</sup> In a study on 51 patients (aged 2–18 years) with NDDs, melatonin was provided 20 to 30 minutes before the desired bedtime and improved sleep in 47 of 51 subjects—both sleep latency and total sleep time improved by approximately 30 minutes and no significant treatment-related side effects were reported.<sup>94</sup>

## Sleep Abnormalities in Children with Cerebral Palsy

The appropriate diagnosis and treatment of sleep problems in children with cerebral palsy (CP) is extremely important, because of their consequences on both child and family.<sup>2</sup>

CP is defined as a group of disorders of movement and posture causing activity limitations that can be attributed to nonprogressive disturbances that occur in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, behavior, and/or concurrent epilepsy.

CP is estimated to occur in 1.5 to 2.5 children per 1,000 live births in developed countries and is the most common cause of childhood physical impairment.<sup>95</sup>

In children with CP, sleep may be affected by the following several factors: muscle spasms, muscle–skeletal pain, and decreased ability to change body position during the night may all contribute to sleep difficulties. Epilepsy is likely to

predispose to sleep disorders, and the antiepileptic drugs can cause daytime sleepiness and deeply modify sleep architecture. Approximately 20 to 50% of children with CP have a cortical visual impairment, which can affect the timing and maintenance of sleep through an effect on melatonin secretion and the lack of light perception, resulting in a free running circadian rhythm.<sup>96</sup>

The most frequent subtypes of sleep disorders in this population are disorders of initiation and maintenance of sleep, sleep-wake transition disorders, parasomnias, and OSA.<sup>97</sup>

The incidence and severity of motor impairment and comorbidities, including sleep disorders, is partially related to severity of brain damage and subtype of CP, where bilateral spastic CP or quadriplegia are the most impairing for the quality of life and of sleep. A recent questionnaire study showed that sleep disturbances were significantly associated with the presence of quadriplegia, of epilepsy, of internalizing and total CBCL score, and of level V on Gross Motor Function Classification System (GMFCS).<sup>98</sup>

Anatomical factors such as pharyngeal hypotonia, adenotonsillar hypertrophy, glossoptosis, and disproportionate midface anatomy or mandibular alterations, together with abnormal central control of respiration can contribute to the obstructive disorder, causing sleep fragmentation and intermittent hypoxemia. Moreover, patients with CP suffer from gastroesophageal reflux, which may determine sleep fragmentation. Scoliosis and restricted lung volumes may aggravate the risk of sleep-related hypoventilation.

A questionnaire-based survey of 233 CP children investigated the prevalence of respiratory disturbances during sleep; habitual snoring was reported in 63% and sleep apnea in 19.7%. In 48 of these children whose questionnaires revealed habitual snoring and sleep apnea, a screening sleep study using pulse oximetry showed that 27% of the children had an apnea-hypopnea index (AHI) > 5 and 58% had a level of oxygen saturation lower than 85%.<sup>99</sup>

Wiggs and Stores found a significant association between the diagnosis of CP and chronic sleep problems in a population of motor-disabled children<sup>100</sup>; in a questionnaire-based survey, 23% of the children with CP had an abnormal total sleep score and 44% had at least one clinically significant sleep disorder. Furthermore, 14.5% of the 173 children with CP had a pathologic score for sleep-related breathing disorders at the Sleep Disturbance Scale for Children, but the authors did not consider the presence of MR and behavioral problems, which are known to have a strong influence on sleep.<sup>97</sup>

One of the first reports exploring sleep organization in children with CP showed that 12 of 23 patients exhibited some abnormal sleep EEG pattern, such as absence of EEG characteristics indicative of wakefulness, NREM sleep and REM sleep, absence of REM sleep, extremely low incidence of sleep spindles or the presence of "extreme spindles" or abnormally high percentage of wake after sleep onset.<sup>101</sup>

An old study on 56 children with persistent snoring and OSA, 16 of whom were neurologically abnormal (two of them with CP), showed that neurologically abnormal children had significantly increased obstructive apnea indices, increased

desaturation events, and lower mean arousal indices compared with their neurologically normal OSA peers.<sup>102</sup>

A more recent questionnaire-based study of children with CP seems to indicate that this population is indeed at higher risk for different sleep disorders: more than 40% of children with CP presented with at least one sleep disorder, versus 5% in the normal population, with a strong association between the SDSC total scores, epilepsy, MR and level 5 on the GMFCS.<sup>103</sup>

No sleep interventions specifically designed to improve sleep of children with CP are reported in the literature, and only melatonin remains a commonly prescribed drug for disturbed sleep in children with neurologic dysfunction.

Treatment of OSA with adenotonsillectomy or CPAP may improve sleep and quality of life in children with CP<sup>104</sup>; surgical techniques for the treatment of sleep respiratory disturbances have been used in several patients with CP or anoxic brain injury with documented obstructive sleep apnea; improvement of respiratory symptoms was achieved in most of patients treated with a significant reduction of AHI.<sup>105,106</sup>

Comorbid epilepsy in these children might also affect sleep through a defect in sleep regulation, presence of nocturnal seizures, and side effects of the antiepileptic medication.<sup>107</sup> Furthermore, spasticity, contractures, and movement limitations, with associated pain may adversely affect sleep. The reduction of spasticity in CP patients can lead to an improvement of sleep maintenance through reduction of pain, and reduction of respiratory muscle spasticity, ameliorating the respiratory function during sleep. Intrathecal baclofen therapy in a patient with mixed spastic athetoid quadriparetic CP and sleep apnea, requiring nightly continuous positive airway pressure, determined a reduction of spasticity, as well as an improvement of sleep apnea.<sup>108</sup>

Published data about sleep disorders in CP were mainly obtained by using screening questionnaires; for this reason, additional studies with structured interview or objective assessment may provide adequate information on sleep disorders and allow us to identify effective treatments.

## Therapeutic Approach to Sleep Disturbances in Children with Neurodevelopmental Disabilities

Most reviews of the pharmacological treatment of sleep disorders in children with NDDs focused mainly on insomnia and not on the other frequent comorbid disorders, such as respiratory sleep disturbances, rhythmic movement disorders, RLS, or periodic limb movements during sleep.

It should be emphasized that each developmental disorder could be characterized by a specific type of sleep disorder that should be accurately diagnosed to carry out the correct treatment. Therefore, after an accurate history and physical examination, a PSG study is mandatory if there is a reasonable suspect of the presence of one of the sleep disorders aforementioned.

Besides the treatment of the specific sleep disorders, an overview of the cognitive behavioral treatment and of the

most commonly used drugs for sleep disturbances is reported in the following paragraphs.

### Behavioral Treatment

After excluding medical contributors and other primary sleep disorders, that is, epilepsy, gastroesophageal reflux, iron deficiency, OSA, periodic limb movements or CRSD, parent-based education, and behavioral interventions are the first-line treatment of insomnia in NDDs.

Although genetic and/or epigenetic abnormalities in sleep/wake regulation predispose patients with NDDs to insomnia, poor sleep hygiene, negative associations and lack of limit setting, contribute to maintaining sleep disruption. Therefore, all behavioral techniques aim to promote self-soothing skills that allow the child to fall and return to sleep independently.

Parents are fundamental active figures to implement behavioral treatment strategies, such as, promoting a dark, quiet, relatively cool, nonstimulating environment, and poor of visual and auditory stimuli (such as electronic devices); parents should establish a successful and consistently followed bedtime routine and maintain a consistent sleep/wake schedule, avoiding the child to go to bed earlier or sleeping later due to lost sleep.<sup>4</sup>

In the case of disruptive behaviors, parents must avoid responding because this would give a negative reward to such behaviors. In the case of difficulty to ignore the child, parents may establish a minimal checking protocol, periodically observing and reassuring the child if he/she accepts to stay quiet in bed. This technique should be reapplied for nighttime awakenings.

### Drugs Commonly Used for Sleep Disturbances in Children with Neurodevelopmental Disabilities

If insomnia in a child with NDDs remains problematic after cognitive behavioral therapy, initiating sleep-promoting agents while continuing behavioral intervention is recommended.

In a recent survey study by Owens et al, more than one-third of 1,273 child psychiatrist treating insomnia in children with psychiatric disorders and NDDs reported that they treated insomnia with medication at least half of the time in patients with ADHD, ASD, and with mental retardation/developmental disabilities (MR/DD). Moreover, they reported to treat 17% of preschoolers and at least one-quarter of school-aged and adolescent patients. Overall, 96% of respondents recommended at least one medication in a typical month, and 88% recommended an over-the-counter medication.<sup>109</sup>

In general, respondents were more likely to use herbal preparations in children with anxiety or mood disorders than in children with NDDs or ADHD; melatonin was recommended by more than one-third of respondents (39%) although it is unclear whether it was being used primarily at bedtime for its mild hypnotic effects or as a chronobiotic. The physicians recommended for sleep disorders (mainly insomnia) nonprescription antihistamines in 69% and  $\alpha$  agonists in 67% of children with MR/DD. Trazodone was the second most frequently prescribed medication for children with MR/DD (66%) while sedating antidepressants were used in 75.5% of MR cases. Atypical antipsychotics were used by more than half of the respondents in children with MR/DD (52%) and benzodiazepines were used in 21.6% of cases of MR/DD. Tricyclic antidepressants as a class were also used for children in these diagnostic groups (25.5%).

Despite the widespread use of pharmacological treatment, the lack of well designed, controlled studies concerning the efficacy, tolerability, dosing, and safety profile of hypnotic medications in children are still needed. ►Table 1 summarizes the most common drugs used for insomnia in children with NDDs.

### Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is a chronobiotic drug crucial for the regulation of the sleep-wake cycle. In

**Table 1** Selected medications for the treatment of insomnia in subjects with NDDs

Medication	Dosage	Indications
Dyphenidramine	0.5 mg/kg	Primary insomnia with delayed sleep onset and/or frequent nocturnal awakenings
Hydroxyzine	1 mg/kg	Primary insomnia with delayed sleep onset and/or frequent nocturnal awakenings
Niaprazine	1 mg/kg	Primary insomnia with delayed sleep onset and/or frequent nocturnal awakenings
Melatonin	0.5–6 mg	Circadian rhythm disorders
Zolpidem	5–10 mg	Primary insomnia with delayed sleep onset
Trazodone	50–150 mg	Primary insomnia; frequent nocturnal awakenings
Clonidine	0.05–0.1 mg	ADHD, disruptive behavior disorders
Gabapentin	300–900 mg	Restless legs syndrome, epilepsy, resistant sleep onset insomnia
Clonazepam	0.25–0.5 mg	Epilepsy, restless legs syndrome, resistant sleep onset insomnia, bruxism, rhythmic movement disorder

Abbreviations: ADHD, attention deficit/hyperactivity disorder; NDDs, neurodevelopmental disabilities.

older children and adults, its production and secretion begin in the evening and peak during the night between 2:00 and 4:00 AM; its production and release are inhibited by light. There is now a greater understanding that low doses (0.5 mg) can be effective for some children, with diminishing benefit with doses exceeding 6 mg and, unlike traditional hypnotics such as chloral hydrate and the benzodiazepines, melatonin does not affect sleep architecture.<sup>110</sup>

Melatonin is increasingly prescribed to many children, both with and without NDDs and using a wide range of doses, demonstrating efficacy in improving sleep quality, by reducing sleep-onset latency or slightly increasing total sleep time. These effects have been observed in typically developing children with delayed sleep-phase syndrome, but they appear to be stronger in children with visual impairment, NDDs, attention deficit, and ASD.<sup>111–113</sup>

A recent large clinical trial confirmed the efficacy of melatonin in the treatment of sleep impairment in children with NDDs, using different doses, ranging from 0.5 to 12 mg; the main effects of melatonin were reduced sleep latency (from 102 to 55 minutes in 12 weeks) and increased total sleep time (40 minutes).<sup>114</sup>

Mild side effects such as headache, confusion, dizziness, cough, and rashes have been reported with the use of melatonin, but systematic reviews and meta-analyses suggest that there are no significant adverse side effects.<sup>112,113</sup>

### Gabapentin

The Food and Drug Administration (FDA) approved gabapentin for treatment of partial seizures in 1993. It was originally designed as a precursor of  $\gamma$ -amino butyric acid (GABA) that easily enters the blood-brain barrier, and increases brain synaptic GABA. It has been approved for the treatment of neuropathic pain and RLS in addition to its original purpose as an anticonvulsant medication. However, its precise pharmacological mechanism in humans remains unknown.

In an open-label study in adults, gabapentin was found to improve sleep quality in patients with primary insomnia, as it increases slow-wave sleep and sleep efficiency; it also decreases WASO and spontaneous arousal.<sup>115</sup>

In a recent case series, gabapentin was found to be a safe and a well-tolerated treatment for sleep-onset and sleep maintenance insomnia in the majority of treated children, including those with neurodevelopmental or neuropsychiatric disorders. Overall, 78% of children showed improvement in sleep (as reported by parents). Furthermore, this beneficial response was noted at doses of 5 to 15 mg/kg orally at bedtime, much less than the recommended dose to treat epileptic seizures (40 mg/kg divided three times daily).<sup>116</sup>

Gabapentin may have the added benefit of treating also sleep maintenance insomnia in children with NDDs, although larger controlled trials will be needed to establish its efficacy.

### Clonidine

Clonidine is a central and peripheral  $\alpha$ -adrenergic agonist that acts on presynaptic neurons and inhibits noradrenergic release and transmission, approved by the FDA for the treatment of hypertension. Clonidine received notoriety for

being prescribed as a sleep aid in children, but currently, there are no well-controlled studies that address the effects of clonidine in children with sleep problems.<sup>117</sup>

It is hypothesized that clonidine produces sedation via decrease in norepinephrine via negative feedback by agonism of the  $\alpha_2$ -adrenergic receptors at the level of the locus coeruleus, which would increase REM sleep; there appears to be variable effects on sleep, which are dose dependent. Administration of low doses of clonidine (range, 0.025–0.05 mg) has little effect on sleep and can either increase or decrease the duration of REM sleep. At medium-to-high doses (range, 0.1–0.3 mg), clonidine appears to have postsynaptic activity on the  $\alpha_2$ -adrenergic receptors, which results in decrease of acetylcholine, which increases REM latency, stage 2 sleep, and slow-wave sleep.<sup>118</sup>

Clonidine presents the advantage of transdermal administration and the central nervous system side effects are typically less evident with the transdermal patch. The most commonly reported side effects of clonidine include drowsiness, transient sedation, headache, dizziness, fatigue, somnolence, insomnia, hypotension, and bradycardia. These side effects commonly subside or decrease variably over time and are thought to be dose dependent.

Ingrassia Turk in a retrospective chart review found clonidine to be an effective therapeutic intervention for alleviating sleep disturbances in six children, whose ages ranged from 6 to 14 years. Dose titration began at 0.05 mg and was gradually titrated up to 0.1 mg at bedtime. No severe side effects were reported.<sup>119</sup>

In a recent open label retrospective review, 19 children with ASD were treated with oral clonidine (range, 0.1–0.2 mg) 30 minutes before bed-reduced sleep latency and lessened nocturnal awakenings; this is especially important in children with ASD who are overly aroused or mildly anxious at bedtime.<sup>120</sup>

Moreover, Hollway et al performed a vast literature search, and clonidine was reported to be effective in children who experienced sleep disturbances with comorbid ASD and other neurodevelopmental disorders with behavioral problems at doses ranging from 0.05 to 0.225 mg/d.<sup>121</sup>

A small number of clonidine overdoses have been reported with resulting fatality and there is some evidence that the clonidine overdose may be becoming more frequent<sup>122</sup>; however, generally, clonidine is well tolerated in children and has been efficacious in treating pediatric insomnia.

Future trials with clonidine in children should be fully controlled with objective measures, including PSG recordings, to determine its effectiveness and safety.

### Clonazepam

Benzodiazepines bind to the benzodiazepine subunit of the GABA chloride receptor complex, facilitating the action of the inhibitory neurotransmitter GABA. These hypnotics have long been the first choice treatment for insomnia in adults, but they raise concerns about cognitive impairment, rebound insomnia, and the potential risk for dependence. These concerns and little evidence-based data availability in the pediatric population, contribute to limit their use in children.



Clonazepam is a benzodiazepine with strong anticonvulsant, muscle relaxant, and sedative properties.

Three uncontrolled studies of children with parasomnias and secondary sleep disturbance showed that clonazepam improved (1) nocturnal tongue biting, (2) REM sleep behavior disorder, and/or (3) periodic limb movement disorder (PLMD), with mild and tolerable side effects.<sup>123–125</sup>

In a fully controlled study of adults without NDDs, the investigators found that clonazepam significantly improved PLMD and decreased the number of nighttime arousals.<sup>126</sup>

From the available data, clonazepam may represent a treatment option in children with arousal disorders (parasomnias) or PLMD/RLS, but future trials focused on objective sleep measures and safety issues are needed.

## Conclusions

Insomnia in children with NDDs is much more prevalent than in typically developing children, has multifactorial origin, and tends to be chronic. Chronic sleep deprivation compromises quality of life of both children and families and is associated with poorer developmental outcome, overweight, and behavioral disturbances.

In some NDDs, problematic sleep is a phenotypic characteristic of a particular disorder and can be a clinical clue to the diagnosis.

The medical approach should follow the pathway of sleep medicine, examining medical and psychiatric contributing factors, primary sleep disorders and maladaptive behaviors related to sleep.

Some of the following treatment options are available: behavioral treatment strategies through the parents, circadian rhythm regulation through melatonin, and pharmacological treatment or specific treatment in the case of obstructive sleep apnea.

Awareness of features of sleep disorders in patients with NDDs is fundamental for the appropriate recognition and effective treatment of these often overlooked aspects.

Despite the widespread use of pharmacological treatment, the lack of well designed, controlled studies concerning the efficacy, tolerability, dosage, and safety profile of hypnotic medications in children raise the need of further research in this field of sleep medicine.

## References

- Zucconi M, Bruni O. Sleep disorders in children with neurologic diseases. *Semin Pediatr Neurol* 2001;8(4):258–275
- Zucconi M, Bruni O. Sleep in children with neurologic disease. In: Marcus C LG, Caroll J, Donnelly D, eds. *Sleep in Children*. Abingdon, Oxon: Taylor & Francis Group; 2008:261–296
- Stores G. Sleep studies in children with a mental handicap. *J Child Psychol Psychiatry* 1992;33(8):1303–1317
- Grigg-Damberger M, Ralls F. Treatment strategies for complex behavioral insomnia in children with neurodevelopmental disorders. *Curr Opin Pulm Med* 2013;19(6):616–625
- Quine L. Sleep problems in children with mental handicap. *J Ment Defic Res* 1991;35(Pt 4):269–290

- Okawa MSH. Sleep disorders in mentally retarded and brain-impaired children. In: CG, ed. *Sleep and its Disorders in Children*. New York, NY: Raven Press; 1987:269–290
- Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective polysomnographic analysis of obstructive sleep apnea in down syndrome. *Arch Pediatr Adolesc Med* 2003;157(7):655–660
- Ng DK, Hui HN, Chan CH, et al. Obstructive sleep apnoea in children with Down syndrome. *Singapore Med J* 2006;47(9):774–779
- Hoffmire CA, Magyar CI, Connolly HV, Fernandez ID, van Wijn-gaarden E. High prevalence of sleep disorders and associated comorbidities in a community sample of children with Down syndrome. *J Clin Sleep Med* 2014;10(4):411–419
- Allanson JE, O'Hara P, Farkas LG, Nair RC. Anthropometric cranio-facial pattern profiles in Down syndrome. *Am J Med Genet* 1993;47(5):748–752
- Aboussouan LS, O'Donovan PB, Moodie DS, Gragg LA, Stoller JK. Hypoplastic trachea in Down's syndrome. *Am Rev Respir Dis* 1993;147(1):72–75
- Ferri R, Curzi-Dascalova L, Del Gracco S, Elia M, Musumeci SA, Pettinato S. Heart rate variability and apnea during sleep in Down's syndrome. *J Sleep Res* 1998;7(4):282–287
- McKay SM, Angulo-Barroso RM. Longitudinal assessment of leg motor activity and sleep patterns in infants with and without Down syndrome. *Infant Behav Dev* 2006;29(2):153–168
- Ashworth A, Hill CM, Karmiloff-Smith A, Dimitriou D. Cross syndrome comparison of sleep problems in children with Down syndrome and Williams syndrome. *Res Dev Disabil* 2013;34(5):1572–1580
- Breslin JH, Edgin JO, Bootzin RR, Goodwin JL, Nadel L. Parental report of sleep problems in Down syndrome. *J Intellect Disabil Res* 2011;55(11):1086–1091
- Carter M, McCaughey E, Annaz D, Hill CM. Sleep problems in a Down syndrome population. *Arch Dis Child* 2009;94(4):308–310
- Diomedes M, Curatolo P, Scalise A, Placidi F, Caretto F, Gigli GL. Sleep abnormalities in mentally retarded autistic subjects: Down's syndrome with mental retardation and normal subjects. *Brain Dev* 1999;21(8):548–553
- Clausen J, Sersen EA, Lidsky A. Sleep patterns in mental retardation: Down's syndrome. *Electroencephalogr Clin Neurophysiol* 1977;43(2):183–191
- Bull MJ. Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics* 2011;128(2):393–406
- Bird LM. Angelman syndrome: review of clinical and molecular aspects. *Appl Clin Genet* 2014;7:93–104
- Kyllerman M. Angelman syndrome. *Handb Clin Neurol* 2013;111:287–290
- Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. *J Med Genet* 2003;40(2):87–95
- Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. *Am J Med Genet A* 2006;140(5):413–418
- Pelc K, Cheron G, Boyd SG, Dan B. Are there distinctive sleep problems in Angelman syndrome? *Sleep Med* 2008;9(4):434–441
- Miano S, Bruni O, Leuzzi V, Elia M, Verrillo E, Ferri R. Sleep polygraphy in Angelman syndrome. *Clin Neurophysiol* 2004;115(4):938–945
- Bruni O, Ferri R, D'Agostino G, Miano S, Roccella M, Elia M. Sleep disturbances in Angelman syndrome: a questionnaire study. *Brain Dev* 2004;26(4):233–240
- Didde R, Korzilius H, Smits MG, Curfs LM. Sleep problems in individuals with Angelman syndrome. *Am J Ment Retard* 2004;109(4):275–284
- Laan LA, den Boer AT, Hennekam RC, Renier WO, Brouwer OF. Angelman syndrome in adulthood. *Am J Med Genet* 1996;66(3):356–360

- 29 Conant KD, Thibert RL, Thiele EA. Epilepsy and the sleep-wake patterns found in Angelman syndrome. *Epilepsia* 2009;50(11):2497–2500
- 30 Walz NC, Beebe D, Byars K. Sleep in individuals with Angelman syndrome: parent perceptions of patterns and problems. *Am J Ment Retard* 2005;110(4):243–252
- 31 Takaesu Y, Komada Y, Inoue Y. Melatonin profile and its relation to circadian rhythm sleep disorders in Angelman syndrome patients. *Sleep Med* 2012;13(9):1164–1170
- 32 Miano S, Bruni O, Elia M, Musumeci SA, Verrillo E, Ferri R. Sleep breathing and periodic leg movement pattern in Angelman Syndrome: a polysomnographic study. *Clin Neurophysiol* 2005;116(11):2685–2692
- 33 Summers JA, Lynch PS, Harris JC, Burke JC, Allison DB, Sandler L. A combined behavioral/pharmacological treatment of sleep-wake schedule disorder in Angelman syndrome. *J Dev Behav Pediatr* 1992;13(4):284–287
- 34 Allen KD, Kuhn BR, DeHaai KA, Wallace DP. Evaluation of a behavioral treatment package to reduce sleep problems in children with Angelman Syndrome. *Res Dev Disabil* 2013;34(1):676–686
- 35 Braam W, Didden R, Smits MG, Curfs LM. Melatonin for chronic insomnia in Angelman syndrome: a randomized placebo-controlled trial. *J Child Neurol* 2008;23(6):649–654
- 36 Donaldson MD, Chu CE, Cooke A, Wilson A, Greene SA, Stephenson JB. The Prader-Willi syndrome. *Arch Dis Child* 1994;70(1):58–63
- 37 Kaplan J, Fredrickson PA, Richardson JW. Sleep and breathing in patients with the Prader-Willi syndrome. *Mayo Clin Proc* 1991;66(11):1124–1126
- 38 State MW, Dykens EM. Genetics of childhood disorders: XV. Prader-Willi syndrome: genes, brain, and behavior. *J Am Acad Child Adolesc Psychiatry* 2000;39(6):797–800
- 39 Bruni O, Verrillo E, Novelli L, Ferri R. Prader-Willi syndrome: sorting out the relationships between obesity, hypersomnia, and sleep apnea. *Curr Opin Pulm Med* 2010;16(6):568–573
- 40 Verrillo E, Bruni O, Franco P, et al. Analysis of NREM sleep in children with Prader-Willi syndrome and the effect of growth hormone treatment. *Sleep Med* 2009;10(6):646–650
- 41 Nixon GM, Brouillette RT. Sleep and breathing in Prader-Willi syndrome. *Pediatr Pulmonol* 2002;34(3):209–217
- 42 Cohen M, Hamilton J, Narang I. Clinically important age-related differences in sleep related disordered breathing in infants and children with Prader-Willi Syndrome. *PLoS ONE* 2014;9(6):e101012
- 43 Sedky K, Bennett DS, Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. *J Clin Sleep Med* 2014;10(4):403–409
- 44 Nixon GM, Rodda CP, Davey MJ. Longitudinal association between growth hormone therapy and obstructive sleep apnea in a child with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2011;96(1):29–33
- 45 Berini J, Spica Russotto V, Castelnuovo P, et al; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). Growth hormone therapy and respiratory disorders: long-term follow-up in PWS children. *J Clin Endocrinol Metab* 2013;98(9):E1516–E1523
- 46 De Cock VC, Diene G, Molinas C, et al. Efficacy of modafinil on excessive daytime sleepiness in Prader-Willi syndrome. *Am J Med Genet A* 2011;155A(7):1552–1557
- 47 Lee YJ, Marcu S, Berall G, Shapiro CM. Tryptophan for the treatment of excessive daytime sleepiness in Prader-Willi syndrome. *Indian Pediatr* 2011;48(4):319–321
- 48 Kidd SA, Lachiewicz A, Barbooth D, et al. Fragile X syndrome: a review of associated medical problems. *Pediatrics* 2014;134(5):995–1005
- 49 Kronk R, Bishop EE, Raspa M, Bickel JO, Mandel DA, Bailey DB Jr. Prevalence, nature, and correlates of sleep problems among children with fragile X syndrome based on a large scale parent survey. *Sleep* 2010;33(5):679–687
- 50 Kronk R, Dahl R, Noll R. Caregiver reports of sleep problems on a convenience sample of children with fragile X syndrome. *Am J Intellect Dev Disabil* 2009;114(6):383–392
- 51 Tirosh E, Borochowitz Z. Sleep apnea in fragile X syndrome. *Am J Med Genet* 1992;43(1-2):124–127
- 52 Musumeci SA, Elia M, Ferri R, Scuderi C, Del Gracco S. Evoked spikes and giant somatosensory evoked potentials in a patient with fragile-X syndrome. *Ital J Neurol Sci* 1994;15(7):365–368
- 53 Brown WT, Jenkins E, Neri G, et al. Conference report: Fourth International Workshop on the fragile X and X-linked mental retardation. *Am J Med Genet* 1991;38(2-3):158–172
- 54 Weiskop S, Richdale A, Matthews J. Behavioural treatment to reduce sleep problems in children with autism or fragile X syndrome. *Dev Med Child Neurol* 2005;47(2):94–104
- 55 Tassone F, Long KP, Tong TH, et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. *Genome Med* 2012;4(12):100
- 56 Hamlin A, Liu Y, Nguyen DV, Tassone F, Zhang L, Hagerman RJ. Sleep apnea in fragile X premutation carriers with and without FXTAS. *Am J Med Genet B Neuropsychiatr Genet* 2011;156B(8):923–928
- 57 Summers SM, Cogswell J, Goodrich JE, et al. Prevalence of restless legs syndrome and sleep quality in carriers of the fragile X premutation. *Clin Genet* 2014;86(2):181–184
- 58 Williams SR, Zies D, Mullegama SV, Grotewiel MS, Elsea SH. Smith-Magenis syndrome results in disruption of CLOCK gene transcription and reveals an integral role for RAI1 in the maintenance of circadian rhythmicity. *Am J Hum Genet* 2012;90(6):941–949
- 59 Smith ACM, Boyd KE, Elsea SH, et al. Smith-Magenis Syndrome. 2001 Oct 22 [Updated 2012 Jun 28]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews*® [Internet]. Seattle, WA: University of Washington; 1993–2015. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1310/>
- 60 Gropman AL, Duncan WC, Smith AC. Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). *Pediatr Neurol* 2006;34(5):337–350
- 61 Smith AC, Dykens E, Greenberg F. Sleep disturbance in Smith-Magenis syndrome (del 17 p11.2). *Am J Med Genet* 1998;81(2):186–191
- 62 Potocki L, Glaze D, Tan DX, et al. Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. *J Med Genet* 2000;37(6):428–433
- 63 Nováková M, Nevsímalová S, Příhodová I, Sládek M, Sumová A. Alteration of the circadian clock in children with Smith-Magenis syndrome. *J Clin Endocrinol Metab* 2012;97(2):E312–E318
- 64 De Leersnyder H. Smith-Magenis syndrome. *Handb Clin Neurol* 2013;111:295–296
- 65 Carpizo R, Martínez A, Mediavilla D, González M, Abad A, Sánchez-Barceló EJ. Smith-Magenis syndrome: a case report of improved sleep after treatment with beta1-adrenergic antagonists and melatonin. *J Pediatr* 2006;149(3):409–411
- 66 De Leersnyder H. Inverted rhythm of melatonin secretion in Smith-Magenis syndrome: from symptoms to treatment. *Trends Endocrinol Metab* 2006;17(7):291–298
- 67 Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23(2):185–188
- 68 Perry A. Rett syndrome: a comprehensive review of the literature. *Am J Ment Retard* 1991;96(3):275–290
- 69 Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002;8(2):61–65
- 70 Dolce A, Ben-Zeev B, Naidu S, Kossoff EH. Rett syndrome and epilepsy: an update for child neurologists. *Pediatr Neurol* 2013;48(5):337–345

- 71 Young D, Nagarajan L, de Klerk N, Jacoby P, Ellaway C, Leonard H. Sleep problems in Rett syndrome. *Brain Dev* 2007;29(10):609–616
- 72 Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK. Rett's syndrome: characterization of respiratory patterns and sleep. *Ann Neurol* 1987;21(4):377–382
- 73 Marcus CL, Carroll JL, McColley SA, et al. Polysomnographic characteristics of patients with Rett syndrome. *J Pediatr* 1994;125(2):218–224
- 74 Nomura Y, Segawa M. Natural history of Rett syndrome. *J Child Neurol* 2005;20(9):764–768
- 75 Wong K, Leonard H, Jacoby P, Ellaway C, Downs J. The trajectories of sleep disturbances in Rett syndrome. *J Sleep Res* 2015;24(2):223–233
- 76 Julu PO, Witt Engerström I, Hansen S, Apartopoulos F, Engerström B; ESSRA group. Treating hypoxia in a feeble breather with Rett syndrome. *Brain Dev* 2013;35(3):270–273
- 77 McArthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Dev Med Child Neurol* 1998;40(3):186–192
- 78 Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Med Rev* 2009;13(6):403–411
- 79 Allik H, Larsson JO, Smedje H. Insomnia in school-age children with Asperger syndrome or high-functioning autism. *BMC Psychiatry* 2006;6:18
- 80 Giannotti F, Cortesi F, Cerquiglini A, et al. An investigation of sleep characteristics, EEG abnormalities and epilepsy in developmentally regressed and non-regressed children with autism. *J Autism Dev Disord* 2008;38(10):1888–1897
- 81 Kotagal S, Broomall E. Sleep in children with autism spectrum disorder. *Pediatr Neurol* 2012;47(4):242–251
- 82 Liu X, Hubbard JA, Fabes RA, Adam JB. Sleep disturbances and correlates of children with autism spectrum disorders. *Child Psychiatry Hum Dev* 2006;37(2):179–191
- 83 Cortesi F, Giannotti F, Ivanenko A, Johnson K. Sleep in children with autistic spectrum disorder. *Sleep Med* 2010;11(7):659–664
- 84 Sivertsen B, Posserud MB, Gillberg C, Lundervold AJ, Hysing M. Sleep problems in children with autism spectrum problems: a longitudinal population-based study. *Autism* 2012;16(2):139–150
- 85 Hollway JA, Aman MG, Butter E. Correlates and risk markers for sleep disturbance in participants of the Autism Treatment Network. *J Autism Dev Disord* 2013;43(12):2830–2843
- 86 Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol* 2011;53(9):783–792
- 87 Miano S, Bruni O, Elia M, et al. Sleep in children with autistic spectrum disorder: a questionnaire and polysomnographic study. *Sleep Med* 2007;9(1):64–70
- 88 Johnson KP, Malow BA. Assessment and pharmacologic treatment of sleep disturbance in autism. *Child Adolesc Psychiatr Clin N Am* 2008;17(4):773–785, viii
- 89 Bruni O, Ferri R, Vittori E, et al. Sleep architecture and NREM alterations in children and adolescents with Asperger syndrome. *Sleep* 2007;30(11):1577–1585
- 90 Malow BA, Marzec ML, McGrew SG, Wang L, Henderson LM, Stone WL. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. *Sleep* 2006;29(12):1563–1571
- 91 Vriend JL, Corkum PV, Moon EC, Smith IM. Behavioral interventions for sleep problems in children with autism spectrum disorders: current findings and future directions. *J Pediatr Psychol* 2011;36(9):1017–1029
- 92 Andersen IM, Kaczmarek J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *J Child Neurol* 2008;23(5):482–485
- 93 Malow B, Adkins KW, McGrew SG, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord* 2012;42(8):1729–1737, author reply 1738
- 94 Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res* 2008;44(1):57–64
- 95 Bax M, Goldstein M, Rosenbaum P, et al; Executive Committee for the Definition of Cerebral Palsy. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol* 2005;47(8):571–576
- 96 Simard-Tremblay E, Constantin E, Gruber R, Brouillette RT, Shevell M. Sleep in children with cerebral palsy: a review. *J Child Neurol* 2011;26(10):1303–1310
- 97 Newman CJ, O'Regan M, Hensey O. Sleep disorders in children with cerebral palsy. *Dev Med Child Neurol* 2006;48(7):564–568
- 98 Romeo DM, Brogna C, Musto E, et al. Sleep disturbances in preschool age children with cerebral palsy: a questionnaire study. *Sleep Med* 2014;15(9):1089–1093
- 99 Shintani T, Asakura K, Ishi K, Yoshida M, Kataura A, Ogasawara H. Obstructive sleep apnea in children with cerebral palsy. *Nippon Jibiinkoka Gakkai Kaiho* 1998;101(3):266–271
- 100 Wiggs L, Stores G. Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. *J Intellect Disabil Res* 1996;40(Pt 6):518–528
- 101 Shibagaki M, Kiyono S, Takeuchi T. Nocturnal sleep in mentally retarded infants with cerebral palsy. *Electroencephalogr Clin Neurophysiol* 1985;61(6):465–471
- 102 Masters IB, Harvey JM, Wales PD, O'Callaghan MJ, Harris MA. Clinical versus polysomnographic profiles in children with obstructive sleep apnoea. *J Paediatr Child Health* 1999;35(1):49–54
- 103 Romeo DM, Brogna C, Quintiliani M, et al. Sleep disorders in children with cerebral palsy: neurodevelopmental and behavioral correlates. *Sleep Med* 2014;15(2):213–218
- 104 Hsiao KH, Nixon GM. The effect of treatment of obstructive sleep apnea on quality of life in children with cerebral palsy. *Res Dev Disabil* 2008;29(2):133–140
- 105 Kosko JR, Derkay CS. Uvulopalatopharyngoplasty: treatment of obstructive sleep apnea in neurologically impaired pediatric patients. *Int J Pediatr Otorhinolaryngol* 1995;32(3):241–246
- 106 Myatt HM, Beckenham EJ. The use of diagnostic sleep nasendoscopy in the management of children with complex upper airway obstruction. *Clin Otolaryngol Allied Sci* 2000;25(3):200–208
- 107 Becker DA, Fennell EB, Carney PR. Sleep disturbance in children with epilepsy. *Epilepsy Behav* 2003;4(6):651–658
- 108 McCarty SF, Gaebler-Spira D, Harvey RL. Improvement of sleep apnea in a patient with cerebral palsy. *Am J Phys Med Rehabil* 2001;80(7):540–542
- 109 Owens JA, Rosen CL, Mindell JA, Kirchner HL. Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. *Sleep Med* 2010;11(7):692–700
- 110 Braam W, van Geijlswijk I, Keijzer H, Smits MG, Didden R, Curfs LM. Loss of response to melatonin treatment is associated with slow melatonin metabolism. *J Intellect Disabil Res* 2010;54(6):547–555
- 111 Appleton RE, Gringras P. Melatonin: helping to MEND impaired sleep. *Arch Dis Child* 2013;98(3):216–217
- 112 Braam W, Smits MG, Didden R, Korzilius H, Van Geijlswijk IM, Curfs LM. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. *Dev Med Child Neurol* 2009;51(5):340–349
- 113 Phillips L, Appleton RE. Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment. *Dev Med Child Neurol* 2004;46(11):771–775
- 114 Appleton RE, Jones AP, Gamble C, et al. The use of MELatonin in children with neurodevelopmental disorders and impaired

- sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess* 2012;16(40):i-239
- 115 Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS. Treatment effects of gabapentin for primary insomnia. *Clin Neuropharmacol* 2010; 33(2):84–90
- 116 Robinson AA, Malow BA. Gabapentin shows promise in treating refractory insomnia in children. *J Child Neurol* 2013;28(12): 1618–1621
- 117 Nguyen M, Tharani S, Rahmani M, Shapiro M. A review of the use of clonidine as a sleep aid in the child and adolescent population. *Clin Pediatr (Phila)* 2014;53(3):211–216
- 118 Delbarre B, Schmitt H. Sedative effects of alpha-sympathomimetic drugs and their antagonism by adrenergic and cholinergic blocking drugs. *Eur J Pharmacol* 1971;13(3):356–363
- 119 Ingrassia A, Turk J. The use of clonidine for severe and intractable sleep problems in children with neurodevelopmental disorders—a case series. *Eur Child Adolesc Psychiatry* 2005;14(1):34–40
- 120 Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. *Brain Dev* 2008;30(7):454–460
- 121 Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. *Res Dev Disabil* 2011;32(3):939–962
- 122 Spiller HA, Klein-Schwartz W, Colvin JM, Villalobos D, Johnson PB, Anderson DL. Toxic clonidine ingestion in children. *J Pediatr* 2005;146(2):263–266
- 123 Arens R, Wright B, Elliott J, et al. Periodic limb movement in sleep in children with Williams syndrome. *J Pediatr* 1998;133(5): 670–674
- 124 Goraya JS, Viridi V, Parmar V. Recurrent nocturnal tongue biting in a child with hereditary chin trembling. *J Child Neurol* 2006; 21(11):985–987
- 125 Thirumalai SS, Shubin RA, Robinson R. Rapid eye movement sleep behavior disorder in children with autism. *J Child Neurol* 2002; 17(3):173–178
- 126 Edinger JD, Fins AI, Sullivan RJ, Marsh GR, Dailey DS, Young M. Comparison of cognitive-behavioral therapy and clonazepam for treating periodic limb movement disorder. *Sleep* 1996;19(5): 442–444