Circadian Rhythm Sleep Disorders

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Abbreviations

AASM	American Academy of Sleep Medicine
AS	Angelman syndrome
ASD	Autism spectrum disorder
ASWPD	Advanced sleep-wake phase disorder
CRSWD	Circadian rhythm sleep-wake disorder
CRSWD-NOS	Circadian rhythm sleep-wake disorder—not otherwise specified
DD	Developmental disability
DLMO	Dim light melatonin onset
DS	Down syndrome
DSWPD	Delayed sleep-wake phase disorder
ICSD	International classification of sleep disorders
ID	Intellectual disability
ISWRD	Irregular sleep-wake rhythm disorder
N24SWD	Non-24-h sleep-wake disorder
NDD	Neurodevelopmental disability
PWS	Prader-Willi syndrome
RS	Rett syndrome
SCN	Suprachiasmatic nucleus
SMS	Smith-Magenis syndrome
WS	Williams syndrome

Introduction

As will be described in this chapter, circadian sleep-wake disorders are sleep disturbances that relate to the timing of sleep and wake across the 24-h day. They include phase-delayed sleep, where sleep onset and wake are significantly later than typical or desired, and also phase-advanced sleep, where sleep onset and wake are significantly earlier than typical or desired, considering the individual's age. Also included are those cases where sleep is interspersed irregularly across 24 h or where the sleep-wake rhythm follows a period that is longer than a standard 24-h day. As we will discuss, the literature on circadian sleep-wake disorders in children with neurodevelopmental disabilities (NDD) is sparse.

Many children with NDD exhibit consistently late sleep onset, night waking, early waking, and/or inappropriate napping, which may be indicative of a circadian sleep-wake disturbance. A case example, which we describe in more detail later, was reported by Piazza and colleagues [1] who described an 8-year-old girl with autism, severe intellectual disability, and severe sleep problems. She had not slept more than 3 h per night from age 5 years and had not responded to regular routines or sleep medications. Irregular sleep onset, night waking, shortened night sleep, some nights without sleep, and daytime napping were all reported, indicative of an irregular sleep-wake pattern. Chronotherapy, a sleep scheduling therapy manipulating bedtimes and wake times over time, was used to correct her sleep-wake cycle, resulting in significant improvement in her sleep. She subsequently averaged 7.9 h of sleep at night, which was maintained at a 4-month follow-up.

The Sleep-Wake Cycle Is a Circadian Rhythm

Sleep and wake are governed by two processes, the homeostatic drive for sleep (process S) and the circadian system (process C) [2]. The circadian system regulates sleep timing, with the master "clock" or pacemaker being in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The circadian system organises the daily rhythms of physiology and behaviour, of which sleep and wake are one component, via the synchronisation of internal physiological rhythms, so that their timing relative to each other remains constant [3, 4]. This is

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accomplished via light-sensitive SCN cells that respond to bright light, the primary zeitgeber, or external time cue. Light arrives at the SCN from the eyes via the retinohypothalamic tract [5]. On average, the endogenous circadian period (tau) in humans is just over 24 h [3], ranging from 23.5 to 24.9 h [5]. Thus, the sleep-wake rhythm typically becomes synchronised to a period of 24 h by being reset each day under the influence of the natural light-dark cycle. Under constant conditions where there are no external zeitgebers, a person's sleep-wake rhythm free-runs at its endogenous period, which generally means that the individual falls asleep at a progressively later time each night, with time of sleep onset gradually moving across the 24-h day [5]. The resetting of the circadian clock is thought to involve the neurohormone, melatonin, which is secreted by the pineal gland. Melatonin levels rise each evening near one's usual bedtime, signalling sleep onset, and decrease as usual wake time approaches. Melatonin is suppressed by bright light, and levels are very low during the day. The night-time rise in melatonin, also called dim light melatonin onset (DLMO), is a good estimate of the degree of circadian advance or delay [5, 6]. The sleep-wake cycle is also tightly aligned with the circadian temperature rhythm, with sleep onset occurring on the falling phase of the daily core body temperature rhythm. Core body temperature drops, and peripheral temperature rises around sleep onset [7].

During the first few months of life, an infant's sleep-wake rhythm becomes synchronised by the light-dark cycle and regular social cues such as feeding [8]. The infant develops a 24-h sleep-wake rhythm, with one consolidated and longer night-time sleep period interspersed with usually two, then one, regular daytime naps. By age 3–5 years, the daytime nap is dropped, and the child exhibits a typical pattern of night sleep and daytime wakefulness [9]. Nevertheless, individuals vary in propensity for the circadian onset of sleep and morning wake times, with morning, intermediate, and evening patterns evident. These patterns or preferences are referred to as an individual's circadian chronotype. Morning chronotypes have a natural preference for early rise times and sleep onset; conversely, evening chronotypes prefer to rise later than average with corresponding late sleep onset. This may result in the morning or evening chronotype's sleep-wake patterns being out of synchronisation with typical societal patterns of school, work, or leisure and may adversely affect the individual's education or employment and socialisation with family and peers [10].

Defining Circadian Sleep-Wake Disorders

As has been outlined in other chapters of this book, sleep difficulties including insomnia, excessive daytime sleepiness, and difficulties with napping are common complaints in children with developmental disorders. These symptoms may also be indicative of a circadian sleep-wake disturbance [3]. Okawa and Sasaki [11] reviewed sleep difficulties associated with developmental disability (DD) and intellectual disability (ID), including circadian sleep-wake rhythm disorders, both with respect to children with more severe ID and known brain impairment (acerebrate children), blind children with moderate to severe ID, and children with ID associated with specific DDs. They reported the presence of sleep electroencephalography (EEG) abnormalities associated with ID and specific DDs, as well as free-running or irregular sleep-wake rhythms in children with severe delay, vision loss and delay, and autism. They concluded that "an understanding of the mechanisms of the human biological clock is indispensable for the treatment of mentally retarded or brain-impaired children" [11, p., 286].

This chapter examines circadian sleep-wake rhythm disorders in children with an NDD. In doing so, we use definitions from the *International Classification of Sleep Disorders*, third edition (ICSD-3) [3], and summarise information about circadian sleep-wake rhythm disorders from ICSD-3 and the *Diagnostic and Statistical Manual of Mental Disorders*—fifth edition (DSM-5) [12]. The ICSD-3 defines a circadian rhythm sleep-wake disorder (CRSWD) as follows:

> The disorder is caused by alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment. (p. 189)

The American Academy of Sleep Medicine (AASM) [3] describes seven CRSWDs, while DSM-5 [12] describes six CRSWDs. Shift work disorder and jet lag disorder (ICSD-3) and shift work type (DSM-5) will not be considered further, as they do not typically affect children with NDDs. The five AASM [3] disorders are summarised in Table 9.1 and are similar to those described in DSM-5 [12]. A sleep diary should confirm the abnormal patterns described, and presentation of these sleep schedules should not be better explained by a different current sleep disorder or other medical, developmental, or psychiatric disorder. In all but CRSWD-NOS, symptoms must be present for at least 3 months. In addition, in all CRSWDs, the sleep-wake disturbances involved cause clinically significant distress or impairment in important areas of functioning [3].

Parents' complaints about settling problems and night wakings are common during childhood [13, 14] including in children with an NDD [15] and are generally attributed to environmental or behavioural issues such as poor sleep hygiene and limit setting, lack of appropriate bedtime routines, or, alternately, night-time fears, anxiety, depression, and behavioural problems [16, 17]. Sleep problems are among the most common comorbid issues reported for children with an NDD [18–20]. For some NDDs including autism spectrum disorder (ASD), Rett syndrome (RS), Smith-Magenis syndrome (SMS), and Angelman syndrome

Table 9.1 AASM CRSWDs

CRSWD	AASM brief description
Delayed sleep-wake phase disorder (DSWPD)	A. Phase of the major sleep episode is significantly delayed (late) in relation to desired or required sleep and wake times
	B. Preferred sleep-wake schedule leads to improved sleep, with a advanced phase maintained
Advanced sleep-wake phase disorder (ASWPD)	A. Phase of the major sleep episode is significantly advanced (early) in relation to desired or required sleep and wake times
	B. Preferred sleep-wake schedule leads to improved sleep, with a advanced phase maintained
Irregular sleep-wake rhythm disorder (ISWRD)	Pattern of irregular sleep and wake across 24 h, usually with night insomnia and excessive daytime sleepiness
Non-24-h sleep-wake rhythm disorder (N24SWRD)	History of insomnia and/or excessive daytime sleepiness; asymptomatic episodes due to the 24-h light-dark cycle and the rhythm for sleep-wake propensity being misaligned
Circadian rhythm sleep-wake disorder—not otherwise specified (CRSWD-NOS)	Meets general diagnostic criteria for CRSWD, but not one of the specific subtypes. CRSWD primarily precipitated by medical, neurologic, or psychiatric disorder

Data from the American Academy of Sleep Medicine [3]

(AS), parents also report irregular sleep patterns. These can vary with children sometimes falling asleep relatively quickly but taking hours to fall asleep on other nights, or having shortened night sleep, very early waking (prior to 5 AM), and lengthy periods of night waking during which the child engages in undesirable behaviours [21–24]. Excessive daytime sleepiness is frequently reported in association with Down syndrome (DS) and Prader-Willi syndrome (PWS) [25, 26]. While sleep difficulties in children with an NDD may have similar environmental and behavioural causes to those for other children, they may also be due to conditions associated with the specific developmental disorder (e.g. sleep apnoea associated with DS and PWS) or may be indicative of circadian sleep-wake disturbances. However, the possibility of a CRSWD as the primary reason underlying disturbed sleep in children with an NDD has not often been considered in the peer-reviewed literature. Indeed, other than in ASD, where there has been a burgeoning interest in comorbid sleep difficulties in the past 5–10 years, there is a general lack of literature concerning common sleep difficulties such as insomnia symptoms and their treatment in children with an NDD [15].

Insomnia is a common complaint in individuals with DSWPD. In DSWPD, insomnia typically develops in response to attempts to deal with sleep onset difficulties and societal requirements to wake earlier than desired. Daytime sleepiness is common. Lack of motivation to follow a more "normal" lifestyle may also be present, particularly in adolescents, with resulting treatment resistance [3]. In general, about 10% of patients who complain of insomnia may have DSWPD, and it is most common in adolescents and young adults [3, 12]. Genetic factors may also be involved [12]. Activities that delay bedtime, psychiatric conditions such as mood disorders, familial patterns of late sleep onset, and family dysfunction have been associated with the onset and maintenance of DSWPD. In children, the presence of bedtime resistance may not simply be behavioural but may be an indicator of an evening chronotype and a consequent lack of sleep readiness at the time parents set for bed. AASM notes that among the NDDs, children with ADHD or ASD may be vulnerable to DSWPD and that *little is known about the natural history of the clinical entity of DSWPD in the paediatric population* (p. 195) [3]. Indeed, several authors have suggested that DSWPD may explain susceptibility to sleep disturbances in children with ASD [27–30].

Individuals with ASWPD wake earlier than desired and are sleepy in the evening. They may experience partial sleep loss if they do not go to bed at their desired early evening bedtime. The disorder is thought to be much less common than DSWPD and also more common in older adults [12], with research in adults with autism suggesting it becomes prevalent after age 30 [31]. The suggested prevalence in adults is 1% [11]; familial patterns are reported [2], with possible *PER2* and *CK1* clock gene involvement [11]. ASWPD has also been reported in ASD [31, 32] and SMS [33]. Typical sleep patterns are often advanced anyway in young children, making ASWPD more difficult to discern. Chronic insomnia, poor sleep hygiene, and lack of appropriate and regular bedtime routines are more likely to underlie an apparent ASWPD, and psychiatric disorders such as depression should be considered [3]. Overall, stringent cases of ASWPD may be rare, though advance-related sleep complaints may be more common [3].

Individuals with ISWRD lack a well-defined circadian rhythm of sleep and wakefulness; instead, their fragmented sleep and wake periods occur variably across the 24-h day, along with frequent napping. Insomnia symptoms or excessive daytime sleepiness is likely to be present depending on

the individual's sleep-wake patterns. According to AASM [3], ISWRD is more likely to be seen in adults with dementia and in children with NDD, but prevalence remains unknown [12, 34]. Factors that may contribute to ISWRD include a lack of exposure to external zeitgebers such as light and dark or regular socialisation patterns [3], and it is associated with neurodegenerative and neurodevelopmental disorders [12]. A key factor in ISWRD is the lack of a predictable, single, long consolidated period of sleep as would typically be expected to occur each night. Among children, a chaotic home life resulting in poor sleep hygiene and irregular sleep schedules may also contribute to the development of ISWRD. Children with ASD, AS, Williams syndrome (WS), RS, and SMS may be at an increased risk for ISWRD. However, little is known clinically about the course and impact of ISWRD in children [3].

In N24SWRD, sleep and wake times are not entrained to the 24-h day and appear to free-run. The individual has a circadian period which is generally greater than 24 h, which may fall outside the range in which the circadian pacemaker can be reliably entrained. Such individuals typically report insomnia and daytime sleepiness, interspersed with asymptomatic periods when their sleep-wake periods happen to cycle around to coincide with those of their social surroundings [3]. The most commonly recognised cause of N24SWD is total blindness where photic cues for light and dark cannot reach the circadian pacemaker [3, 12]; psychiatric disorders associated with social isolation are also a risk factor [12]. Children with severe intellectual disability and blindness are also at risk. Some cases have been reported in specific NDDs including RS [35], ASD [36], and AS [37], possibly due to failure to entrain to social and environmental zeitgebers. According to ICSD-3 [3], N24SWRD is rare in typically developing children and may be associated with an endogenous circadian period closer to 25 h than 24 or inadequate daytime light exposure, excessive evening light exposure, or reduced exposure to other environmental cues. These latter factors may be associated with psychiatric conditions like social anxiety or medical conditions associated with long periods of inactivity. DSWPD is also a risk factor for the development of N24SWRD and may also be confused with N24SWRD. Like ISWRD, little is known clinically about the course and impact of N24SWRD in children [3].

Finally, CRSWD-NOS is used to describe disturbed sleep in an individual with a circadian sleep-wake rhythm that does not meet full criteria for a specific CRSWD. CRWSD-NOS is typically associated with medical conditions, psychiatric conditions, medication, or substance abuse. Individuals with neurodegenerative disorders and children with NDDs are also at risk of CRSWD-NOS. The specific manifestations of the disrupted sleep-wake patterns vary across individuals [3].

Given the frequency of reported sleep problems in children with an NDD and that sleep difficulties such as delayed sleep onset, night waking, early waking, and daytime napping in these children may be indicative of a circadian sleep disturbance, it is surprising that little attention has been paid to whether or not a CRSWD is present. Consideration of CRSWDs may help inform treatment, which is likely to be different from that indicated for sleep onset and night-waking difficulties associated with a more typical insomnia diagnosis. The following section describes reports of the presentation of CRSWDs in children with an NDD or sleep difficulties that may fit criteria for a CRSWD.

Intellectual Disability

In 1981, Okawa, Sasaki, Nakajima, and Takahashi [38] reported on a 12-year-old boy with a developmental age of no more than 7 months with low muscle tone and enlarged lateral ventricles, who could not stand and was largely bedridden. He had no obvious aetiology that would account for his delay. The boy showed *prolonged wakefulness for 2–6 days (p. 65)*, followed by similar periods of several days of sleep. The rhythm *repeated every 10–15 days for several months*, and he *then switched into an irregular sleep-wake pattern (p. 65)*; his sleep was independent of seasonal influences. On PSG, the boy had distinct sleep and wake EEG patterns. His body temperature rhythm was greater than 24 h but was stable despite his sleep-wake patterns. Thus, this boy appeared to be internally desynchronised, and his pattern of sleep was not influenced by external environmental factors; his sleep-wake pattern may best be classified as CRSWD-NOS.

In a later paper, Okawa, Takahashi, and Sasaki [39] described sleep-wake patterns in a group of 12 children with severe brain damage experienced perinatally (six cases) or between 6 months and 3 years of age. The children were now aged 3–14 years and presented with a range of circadian sleep-wake disturbances. Nine children were reported to experience seizures; all were bedridden and with vegetative disturbances, and thus, they appeared profoundly delayed. All the children showed REM sleep on PSG, but in seven cases, NREM sleep was monostage (e.g., difficult to distinguish normal NREM sleep stages), and only one child showed normal NREM sleep stages. In these profound cases of brain dysfunction, two types of circadian sleep-wake rhythm patterns were described: consolidated sleep and dispersed sleep. Consolidated children showed a distinct circadian sleep-wake pattern with a night-time sleep period and an afternoon nap, but their total sleep was generally reduced. However, two of these five children showed phase shifts indicative of a free-running rhythm and thus possible N24SWRD. Children with a dispersed pattern had no

optimal sleep time across 24 h and could not stay awake for 6 h at a time; they also had a tendency to hypersomnia, and six showed monostage NREM sleep. Thus these seven children appeared to fit criteria for ISWRD.

A group of 14 young children aged 9 months to 4 years with moderate to severe ID and a lack of consolidated, daily sleep were described by Guilleminault et al. [40]. Nine of the children had seizures, seven had cerebral palsy, and one had macrogyria; none had a known metabolic disorder. All children had adequate vision and were responsive to light. Sleep problems were reported from birth, with up to 3 h of noncontinuous night quiet periods and 30 min periods of quiet and sleep during the day. At the time of evaluation, all children were medicated (sleep medications and/or anti-epileptics), their sleep problems were very disturbing to their families, and treatment, including behavioural approaches, had not been successful. Based on sleep logs, these children slept for an average of 6 h in 24, with an average of only 3.2 h nocturnal sleep, and were not responding to sleep medications. Night behaviours included screaming, yelling, and periods of activity. The dominant pattern of sleep was fragmentation, with the longest sleep period between 8 PM and midnight and scattered periods of sleep varying from 15 to 80 min tending to cluster between 8 PM and 8 AM. Thus, these children all appeared to exhibit an ISWRD associated with their ID. The 12 children on a hypnotic medication were switched to chloral hydrate, and treatment with light therapy with a behavioural programme was attempted, with gradual withdrawal of chloral hydrate when an appropriate sleep pattern was apparent. This was successful for 5 of the 14 children, with a consolidated period of night-time sleep. At a 2–5-year follow-up, sleep improvements were maintained [40].

From this small number of studies, children with moderate to profound ID, often with comorbid seizures, may present with disorganisation of the circadian system resulting in irregular sleep patterns. These disorganised sleep patterns may or may not be amenable to typical sleep treatments.

Intellectual Disability and Blindness

Four girls aged 4–12 years with moderate to severe ID and congenital blindness were reported to have a CRSWD; all girls showed various EEG abnormalities on sleep PSG [41]. Three children had N24SWRD and the fourth had an ISWRD. One 10-year-old girl with seizures and moderate ID showed a free-running rhythm with a 24.8-h period, as well as apnoeic episodes during waking. Her epilepsy was successfully controlled, and attempts were made to entrain her sleep-wake rhythm with both light therapy and strict scheduling but were ineffective. A second girl, aged 12 years with severe ID and seizures and no response to light had a free-running sleep-wake rhythm with a 24.3-h period. Control of her seizures with an evening dose of nitrazepam (a nitrobenzodiazepine) together with forced daytime activities resulted in entrainment to a 24-h cycle. The third case was a 7-year-old girl with seizures, very enlarged ventricles, and light and dark recognition only who was extremely impaired. She had a sleep-wake rhythm with a period that varied from 25 to 30 h. Forced awakening resulted in entrainment to a 24-h period, but when active treatment was stopped, her entrainment drifted. The last girl was 4 years old with moderate ID and an ISWRD. She had one extended sleep period at sometime between midnight and midday, as well as naps between midday and midnight, and showed a rhythm period of 24.5 h. Forced awakening together with appropriate daytime activities eventually resulted in her rhythm becoming entrained to a 24-h period. Thus, strict scheduling activities were able to resynchronise the girls' sleep-wake cycles to a 24-h period in two of the four cases. It is unclear whether brain damage affecting circadian pacemakers or an inability to synchronise to weaker zeitgebers such as social cues due to their significant ID prevented the other two girls' entrainment.

A case study report by Sadeh and colleagues [42] of a blind adolescent with profound ID and severe behavioural problems including self-injurious behaviours as well as sleep problems concluded that the boy had a concomitant sleep-wake schedule disorder. A subsequent letter to the editor [43] expressed disagreement and suggested that bipolar disorder better met the described presentation. In their reply, Sadeh and Anders [44] defended the diagnosis of sleep-wake schedule disorder. They also noted that bipolar disorder and sleep schedule disorders could be related and that pharmacological treatment for the former may also affect the circadian pacemaker. This case illustrates the relationship between blindness, ID and mood disorders, the difficulties associated with differential diagnosis, and the potential for medication to affect the circadian system.

Smith-Magenis Syndrome (SMS)

While research on sleep in this syndrome remains sparse, individuals with SMS have chronic sleep difficulties, which usually begin early in life and are a significant predictor of behavioural problems. Early bedtime, night waking, early morning waking, shortened sleep, and daytime sleepiness [45, 46] suggest that sleep is phase advanced [45] or has an irregular rhythm [46]. These sleep problems are thought to be due to an inverted melatonin rhythm [45, 47, 48], though this is not found in all individuals [48]. Thus the reported melatonin rhythm abnormality in SMS may not be due to an intrinsic dysfunction in the circadian clock but rather may be related to genetic variation in melatonin regulation [48].

One of the genes included in the interstitial deletion at 17p11.2 associated with SMS is the *RAI1* (retinoic acid

induced 1) gene, or a heterozygous mutation of *RAI1*. *RAI1* has been implicated in altered melatonin secretion [46], and mice with *RAI1* deletion show altered circadian rhythmicity. Williams et al. [46] have shown that *RAI1* is a regulator of *CLOCK* (master regulator of the circadian clock) whose protein product heterodimerises with BMAL1. The CLOCK/BMAL1 complex regulates a range of downstream genes that modulate circadian rhythms. Thus, Williams et al. believe that the deletion or mutation of *RAI1* with consequent dysregulation of the expression of circadian genes leads to the inverted melatonin rhythm thought to be responsible for the sleep-wake rhythm abnormalities found in SMS. A combination of treatment with controlled-release melatonin at bedtime and using a beta-adrenergic antagonist to block melatonin in the morning has been effective in phase delaying both sleep onset and morning wake time in children with SMS to a more typical sleep schedule [49].

Autism Spectrum Disorder (ASD)

Inanuma [50] reported that compared to age controls, 33 children with ASD aged 1–8 years had irregular sleep-wake patterns, with highly variable sleep onset and wake times, night waking, significant daytime napping, and shortened night sleep, particularly children less than 4 years. However, perusal of the monthly sleep plots provided suggests that these children did have a longer, consolidated night sleep period; thus, they did not appear to meet criteria for ISWRD and may best be described as having CRSWD-NOS. Similarly, Segawa [36] plotted the sleep-wake rhythm of 63 children aged 1–12 years, compared with their siblings over a 6-month period. Irregular sleep-wake rhythms were reported with late sleep onset and morning waking, daytime naps, and short nighttime sleep in the children with ASD, suggesting DSWPD or CRSWD-NOS, with one case of a free-running rhythm (N24SWRD). Segawa [36] reported that regular play therapy and/or 5-hydroxytryptophan (5-HTP) administration improved or alleviated the children's sleep patterns. As 5-HTP is a precursor to both serotonin and melatonin syntheses, this suggests either serotonin neurotransmitter system involvement in these circadian sleep-wake anomalies or melatonin phase delay.

Later researchers have continued to report irregular sleep-wake patterns in children with ASD. Wiggs and Stores [30] examined sleep in 64 children with ASD using actigraphy and concluded that at least some of their children met criteria for DSWPD. Souders et al. [29] described the sleep of 59 children with ASD with intellectual abilities ranging from severe intellectual disability to average intellect. Children with autism had longer sleep latency, longer night wakings, and shorter total night sleep than controls. They concluded that 18% of children had ICSD-2 Insomnia due to Pervasive Developmental Disorder (PDD), that is, they could find no explanation for the children's sleep problems other than that they had an autism spectrum disorder [51]. They speculated that this may be due to a delayed or reduced-amplitude melatonin rhythm or clock gene abnormalities. These research reports suggest increased CRSWDs and, given the increased sleep latency, most probably DSWPD. Nevertheless, although some children have a significantly delayed bedtime suggestive of DSWPD, they may wake at an acceptable time. This is consistent with individuals on the autism spectrum, on average having reduced total sleep [15, 21]. Reasons for reduced total sleep are unknown, and it is possible that shifting sleep onset to an earlier time may then result in early morning waking. Some children with ASD are also early wakers. It is not always clear whether children with ASD and reduced total sleep are sleep deprived. Sleep timing and quantity often vary in ASD children from what is considered typical, and it is difficult to know whether or not some of these children meet the criteria for a CRSWD. However, addressing these sleep issues is paramount for families.

A case study described an 8-year-old girl with autism, severe intellectual disability, omphalocele, feeding problems, aggressive and self-injurious behaviours, and severe sleep problems [1]. She had stopped sleeping more than 3 h per night at age 5 years, even though she was on both clonidine and chloral hydrate for sleeping and kept a regular daily routine. Prior to inpatient treatment, the child had irregular sleep onset, night waking, shortened night sleep including some nights without sleep, and daytime napping. Inspection of the sleep data provided suggested ISWRD. Her medications were withdrawn. The girl underwent chronotherapy, a sleep scheduling therapy manipulating bedtimes and wake times over time to correct her sleep-wake cycle. She was placed in bed beginning at 3.30 AM, when she was most likely to be asleep, and left in bed for 10 h. Her bedtime was first successively delayed by 2 h and then 1 h per night until 9:00 PM bedtime was reached. No daytime naps were permitted, and her normal daily routine was maintained during her wake period. The child then maintained a regular bedtime routine for sleep at 9:00 PM and was woken at 7:00 AM each morning. There was significant improvement in both sleep and behaviour, and by completion she averaged 7.9 h of sleep during her scheduled night sleep time. Improvements were maintained 4 months later.

Thus there is good evidence that at least some children with ASD may be at an increased risk for CRSWDs possibly due to a phase-advanced or phase-delayed melatonin rhythm, reduced amplitude melatonin rhythm, or clock gene abnormalities. Bourgeron [52] provide a review and theoretical account of this, and several authors have reported abnormalities in melatonin [53–56]. This has led to the use of bedtime melatonin which can successfully improve sleep onset latency and in some cases night waking in children with ASD

(for reviews, see Guénolé et al. [57] and Rossignol and Frye [58]). However, a recent paper by Goldman et al. [59] reported that while melatonin successfully treated sleep onset latency difficulties in nine high-functioning boys with ASD, there was no evidence of abnormality in the melatonin rhythm that might account for their sleep problems. This group has since published a second paper showing that DLMO in 7 of 28 individuals with ASD and normal cognitive functioning aged 11–26 years (M = 15.6 years) did not differ from 7 controls [60]. The authors suggested that the success of melatonin in treating these children may be due to its soporific and anti-anxiolytic effects [59]. This is particularly pertinent as anxiety symptoms as well as diagnosed anxiety disorders are significantly elevated in individuals with ASD. Abnormal circadian sleep-wake patterns in children with ASD and more severe intellectual disability may be due to associated brain damage, an abnormality in the melatonin rhythm, and failure to pick up on social and environmental zeitgebers that assist with rhythm synchronisation, anxiety, or some combination of these factors.

Williams Syndrome (WS)

WS is a deletion syndrome involving chromosome 7q11.23 [61] and is generally associated with mild to moderate ID. While there are a few studies of sleep in WS, disturbed sleep including long sleep latency, night waking, reduced total sleep, and poor sleep efficiency, as well as restless sleep and periodic limb movements, has been reported [61–63].

Sniecinska-Cooper et al. [64] measured sleep using actigraphy and a sleep questionnaire and salivary melatonin and cortisol at 4:00–6:00 PM, bedtime, and wake time (afternoon and bedtime values were normalised against morning values) in 25 children aged 4–11 years with WS. The children with WS showed increased sleep latency, increased time awake at night, increased sleep fragmentation, increased movement, and a tendency to lower sleep efficiency; total sleep time was not reported. While the ratio calculated from bedtime to afternoon melatonin samples increased in the control group, this was not seen in WS children; at bedtime the WS children also showed a higher level of cortisol than controls, with the drop in cortisol from afternoon to bedtime being less pronounced in WS, suggestive of higher arousal. Overall, higher bedtime melatonin levels in the control group were related to better sleep parameters, but no similar relationships were found in the WS group. Lower cortisol was associated with shorter actigraphic sleep latency in both groups. Both reduced melatonin and increased cortisol at bedtime may account for long sleep latency in WS.

A sample of 25 children with WS (6–17 years) was assessed using the Sleep Disturbance Scale for Children (SDSC) and melatonin as measured by day and overnight urinary 6-sulfatoxymelatonin (6-SM), as well as measures of behaviour and memory [65]. On the SDSC, 65% of the children had disturbed sleep, while 6-SM did not show the expected day-night change with no increase in 6-SM in the overnight void. The authors reported that based on 6-SM excretion, 26% of children had a normal melatonin rhythm, 21% had a delayed rhythm, and the remaining 53% had an absent melatonin rhythm. Insomnia symptoms (sleep onset and maintenance) were significantly correlated with 6-SM levels, and the authors suggested that abnormality in the melatonin synthesis pathway with subsequent low melatonin levels may account for disturbed sleep in WS.

Thus, melatonin and cortisol rhythms may be delayed or absent in WS [64, 65], or as suggested by Sniecinska-Cooper et al. [64], cortisol and melatonin rhythms may be desynchronised. These recent findings suggest that children with WS are at risk for CRSWD, but they require replication.

Fragile X Syndrome (FXS)

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, with full mutation prevalence being about 1:2500 [66]. There is a higher prevalence of FXS in males, and FXS carries an increased risk for anxiety disorders and ASD. Affected individuals have an expansion of the CGG trinucleotide repeat on their X chromosomes, with full mutations involving >200 CGG repeats and pre-mutation ≥55 repeats [67]. Parent-reported sleep problems occur in 30% or more of children [68–70], primarily delayed sleep onset and night-waking difficulties; irregular bedtimes and morning wake times were also common [68]. Variable sleep patterns together with elevated melatonin both overnight and during the day were also reported in a small sample of boys [71]. Moreover, peak melatonin levels occurred later in boys with FXS compared to controls, suggesting a possible delay of melatonin secretion and the sleep-wake rhythm. Thus, both the kinds of sleep behaviours reported and suggested abnormality in melatonin secretion may indicate circadian sleep-wake difficulties in at least some children with FXS, but further research is required.

Angelman Syndrome (AS)

AS is a chromosome 15 disorder involving the *UBE3A* gene; in 70% of cases, there is a deletion of maternally derived genes. The condition has a lifelong impact, and children are severely developmentally delayed; significant sleep problems are one of the associated conditions reported [72]. Parent-reported sleep problems include sleep onset and sleep maintenance difficulties and overall poor sleep quality. Sleep-disordered breathing, excessive daytime sleepiness,

and parasomnias are also reported, and the use of sleep medication is common. Rates for a range of sleep problems vary from around 40% to 70% [73–75]. Sleep difficulties have been documented in a small sample using both actigraphy and PSG, confirming that long sleep onset latency, long periods of night waking, poor sleep efficiency, and increased sleep fragmentation are present [76]. There is limited evidence that sleep onset and night-waking difficulties may be behaviourally maintained, with a report that behavioural interventions are helpful [77].

CRSWDs have also been reported for children with AS, though studies have been limited by small sample sizes. In particular, DSWPD, ISWRD, and N24SWRD have been reported in children with AS [37, 78]. Takaesu and colleagues [37] assessed CRSWDs and the melatonin profile in eight children (6–17 years) and seven adults (20–27 years). All AS participants were confirmed to have 15q11–q13 deletions on a DNA test. A total of eight AS patients (six children) received a diagnosis of a CRSWD. In particular, three children received a diagnosis of ISWRD, two of N24SWRD and one of DSWPD. Melatonin was sampled across a 24-h period, with a 4-hourly sampling rate, and the AS group showed significantly lower melatonin levels at all time points except at 8:00 AM. The amplitude of the 24-h serum melatonin level was dampened in the AS group. In particular, the greatest difference was observed between the peak serum melatonin levels. In comparing those children with AS and a CRSWD to children with AS without a CRSWD, peak melatonin levels were significantly higher in the latter group.

A recent study [79] found that pharmacological reversal of *UBE3A* silencing repaired functional circadian physiology in mouse models of AS. *UBE3A* encodes a HECT domain E3 ubiquitin ligase (E6-AP) [79]. Ubiquitin is a small protein that in a multistep process is added to and thus regulates the action of target substrate proteins [80] including circadian clocks [79, 81]. The clock transcription factor BMAL1 is an ubiquitinylation target of E6-AP, supporting the role of *UBE3A* in the regulation of the circadian clock [79, 81]. In particular, reactivation of paternal *UBE3A* in AS brain slices restored circadian periodicity, specifically in E6-AP-deficient neurons, leading the authors to conclude "that deficiency of neuronal E6-AP activity leads to defective ubiquitinylation of clock proteins that alters circadian-clock-mediated behaviour and metabolism" and that these alterations likely underlie the sleep disorders that are associated with AS [79].

Rett Syndrome (RS)

While RS was classified as a pervasive developmental disorder under earlier editions of the DSM, its cause is now known to be due to mutations in the *MECP2* gene, with specific mutations determining severity of clinical presentation and affecting primarily females [23]. Autistic features are common [82]. Sleep problems were first reported as associated with RS by Glaze and colleagues [83]. Reported difficulties include late sleep onset, night waking, and early morning waking; however, daytime napping is common, resulting in relatively normal total sleep time over a 24-h period [84]. Disturbing night-time behaviours such as laughing, screaming, and teeth grinding, as well as actual seizures, are also reported [23]. Sleep architecture and sleep efficiency appear to be relatively normal on PSG [85] in a group of 30 RS girls recruited into a polysomnography study; however, they were not referred for sleep problems. Given reports elsewhere of frequent poor sleep, it is likely there is considerable interindividual variability.

Night-time sleep problems and increased daytime napping suggest that sleep may not be well consolidated in RS, and two papers from the 1990s reported on melatonin treatment for poor sleep [35, 86]. Using actigraphy to monitor sleep over 10 weeks in nine girls with RS, immediate-release melatonin was administered an hour prior to bedtime using a double-blind, placebo-controlled, crossover protocol. The girls presented with long sleep onset latency, night wakings, reduced total night-time sleep, and reduced sleep efficiency. No free-running or non-24-h sleep-wake patterns were observed. Treatment significantly reduced sleep onset latency and improved total sleep and sleep efficiency in the more severely affected girls. However, there was considerable individual variation in response. The second study [35] examined the effects of melatonin in two children; prior to treatment, the first girl (age 7 years) had a free-running rhythm and 6-h delayed melatonin cycle, and the second girl (13 years) had a fragmented sleep-wake rhythm, with a normally timed but relatively low melatonin peak. Oral melatonin prior to bedtime resulted in a considerable improvement in the sleep-wake cycle in the first girl, while in the second child, the authors believed that melatonin had primarily a soporific effect. Cessation of melatonin resulted in return of sleep difficulties, and melatonin administration was recommenced.

Melatonin Treatment for Sleep Difficulties in Children with an NDD

The administration of exogenous melatonin has been widely reported as a successful approach for treating sleep onset difficulties in children with DD (see Schwichtenberg and Malow [87] for a review). Melatonin has both chronobiotic (phase-shifting) and soporific (sleep-inducing) effects, and it is the latter that is argued to assist in reducing sleep onset difficulties. In particular, sleep onset latency is usually reported to decrease significantly after short-term trials [87]. However,

the findings regarding wake after sleep onset and total sleep time are conflicting [87]. In particular, in a randomised double-blind placebo-controlled trial by Gringras and colleagues [88], it was found that melatonin significantly reduced sleep onset latency in children aged 3–15 years at a 12-week follow-up. However, sleep efficiency did not improve significantly, and although there was a statistically significant increase in total sleep time, the difference was not clinically significant. Moreover, children in the melatonin group woke significantly earlier (29.9 min earlier) at follow-up compared to baseline. Thus the chronobiotic mechanisms of melatonin likely phase-shifted the sleep-wake rhythm rather than acting through soporific effects. Similar results were found in a randomised double-blind placebo-controlled study that assessed the efficacy of 3 mg of melatonin in improving insomnia symptoms in children with ASD and/or FXS. Melatonin not only increased sleep duration but also shifted sleep onset times earlier (42 min) compared to placebo, further suggesting that melatonin acts as a chronobiotic.

In the study by Takaesu and colleagues [37], six AS subjects were treated with 1 mg of melatonin for their CRSWD. Melatonin was taken orally between 6:00 pm and 7:00 pm for 3 months. The results indicated that the free-running rhythm associated with N24SWRD in two AS subjects was completely suppressed after commencing melatonin treatment and two of the three ISWRD subjects decreased the frequency of daytime napping and increased nocturnal sleep duration. These subjects also had significant improvements in their sleep quality. Of note, sleep was assessed via parent-report sleep logs and not via more objective measures of sleep.

Mouse models have suggested that melatonin may exert anxiolytic effects [89]. Thus it is possible that sleep improves in children with NDDs treated with melatonin by reducing anxiety symptoms. Children may then be able to fall asleep and return to sleep after waking without the need to alert their parents. However, further research is required using objective measures of sleep and anxiety.

Currently there is no consensus on the required dosage and type of melatonin (immediate versus controlled release), and this may differ for each child's presenting sleep problem. Moreover, long-term safety outcomes of melatonin have not been rigorously assessed, as fast-release melatonin is not registered for child use, with no long-term safety data for children. Animal studies show melatonin can affect the reproductive system, immune system, and metabolism, and it may interact with other medications prescribed for children [90]. There is some evidence for the safety of prolonged-release melatonin (trade name Circadin) in children [91], though it is not recommended in Australia [92]. Consequently the use of melatonin in paediatric samples should be approached with caution until appropriate safety data become available [92]. However, when a CRSWD has been identified, melatonin may be useful in helping phase-shift sleep to more appropriate times and may also help to improve sleep quality, particularly in children with very disturbed sleep patterns and melatonin atypicalities (e.g. AS, SMS, and WS). Prior to melatonin treatment, a comprehensive sleep assessment including assessment of endogenous melatonin levels, where possible, should be undertaken to determine the most appropriate dosage and timing of administration. Behavioural treatments and chronotherapy in conjunction with melatonin are also likely to be beneficial in improving sleep patterns [93]; the additive effects of behavioural treatments may improve problematic sleep habits which melatonin cannot treat.

Conclusions and Recommendations

Overall, common symptoms of sleep onset delay, night and early morning waking, and daytime sleepiness or increased napping are not only indicators of insomnia, but they may also indicate a CRSWD in children with an NDD or ID. N24SWRD and ISWRD are frequently reported, and DSWPD is reported in children with ASD; however, CRSWDs are not always considered in the interpretation of sleep problems. Prevalence rates and presentations also appear to differ across different NDDs. Those with more severe ID (e.g. AS and RS) may be more prone to the development of CRSWDs as they may not use environmental zeitgebers effectively to entrain their sleep-wake rhythms [94]. Moreover, psychopathology symptoms such as anxiety and depression may also account for CRSWDs in children with an NDD, particularly those who are cognitively able. Supporting the presence of CRSWDs, melatonin rhythm abnormalities have also been reported in some rare chromosomal disorders, and melatonin is used with some success in treating delayed sleep onset, though the mechanism of action is disputed, with chronobiotic effects being most likely.

Future Directions

Overall, further research is required that aims to objectively assess sleep in children with an NDD and to classify these sleep problems based on current diagnostic criteria (e.g., ICSD-3). With the emergence of home DLMO kits [95, 96], assessment of endogenous melatonin levels is more easily accessible and will assist in delineating CRSWDs in NDDs. Assessment of DLMO will also assist in determining whether melatonin levels are deficient around the sleep onset period and whether supplemental melatonin will be efficacious in treating sleep problems. While melatonin is reported to be effective in treating several sleep difficulties, particularly sleep onset delay, the mechanism of action is unclear, and studies assessing the long-term safety of exogenous

melatonin, particularly fast-release preparations, are lacking. Further research is also required to determine the efficacy and long-term safety of melatonin for sleep disturbances in children with NDDs and the types of sleep disturbances which it most successfully treats.

All sleep interventions should include attention to sleep hygiene principles, which are discussed elsewhere in this volume (see also Jan et al. [97]). Melatonin has the advantage of being easy to administer, and its efficacy in a particular case will generally be quickly established. Nevertheless, in view of potential long-term safety concerns, other means of shifting the sleep-wake rhythm should be explored. While there is little research in children, both chronotherapy and light therapy can be used to phase shift the sleep-wake rhythm.

We have detailed Piazza's case study using chronotherapy [1], and it is clear that such an approach requires significant support. Light therapy, in which bright morning light results in phase advance (moving sleep onset to an earlier time) and bright evening light in phase delays (moving sleep onset to a later time), can be applied (see Guilleminault et al. [40]). In typically developing children, mean age 10 years, a recent report [98] comparing melatonin and bright light therapy for chronic sleep onset difficulties showed that 30-min morning exposure to bright light (500 nm peak wavelength, 8000 lux) fixed to a cap, thus allowing movement, was successful in advancing sleep onset time, with modest effects on sleep latency, but that overall, melatonin (3 mg) was a superior treatment. Nevertheless sleep latency still exceeded 30 min in both the melatonin and bright light groups, there were treatment adherence issues in both groups, and the authors noted that research on treatment protocols for light therapy in children is needed. Having a child regularly outdoors in bright morning light (possible in summer months), with strong daily routines, may also assist if the sleep rhythm is delayed or irregular. Indeed, sleep hygiene recommendations include getting sufficient daylight at appropriate times of day [97]. Of course, what is needed is more research into the frequency and presentation of CRSWDs in children with NDDs and research into the efficacy, effectiveness, and acceptability of treatment methods other than melatonin, as well as investigation of optimal melatonin protocols and dosage.

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