20 Sleep in Children with Neurodevelopmental Disorders

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In general, poor sleep is common in children with a neurodevelopmental disorder [1, 2] and is related to additional difficulties for these children, such as increased daytime behaviour problems, poorer adaptive behaviour, and worsened academic functioning. Furthermore, sleep problems in children with neurodevelopmental disorders have a negative impact on families, particularly parents including increased parenting stress and poorer parent mental health [3–5]. This chapter examines sleep problems in the two most common neurodevelopmental disorders, Autism Spectrum Disorder (autism) and Attention-Deficit/Hyperactivity Disorder (ADHD). Additionally, as examples of sleep difficulties that commonly co-occur in a range of genetically determined neurodevelopmental disorders associated with developmental delay and intellectual disability (ID), we describe sleep in the X-linked disorders (Fragile X syndrome [FXS] and Rett syndrome), and the chromosome 15 imprinting disorders (Prader-Willi syndrome [PWS] and Angelman syndrome [AS]).

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20.1 Autism Spectrum Disorder

Autism Spectrum Disorder is characterised by social-communicative difficulties and repetitive and stereotyped behaviours and sensory sensitivities; more boys than girls are diagnosed [6]. Reported prevalence varies according to country, site, and ascertainment methods but, autism affects around 2% of the population [7]. Poor sleep in autism begins in early childhood [8]. Research over the last three decades has established that significant and often severe sleep difficulties, associated with a range of behavioural difficulties, are common in autism [9, 10], with reported prevalence as high as 86% for autistic children [10]. Sleep problems are likely to be chronic in autism and other developmental disorders [11] and occur at all levels of intellectual ability [12], though cognitive functioning or IQ can have some impact on reported sleep issues [13]; poor sleep quality continues to be reported in adulthood [14].

Long sleep onset latency, increased wake after sleep onset, reduced total sleep time and poor

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sleep efficiency are the most often reported sleep difficulties [2] in autistic children. Other sleep issues include sleep fragmentation [15]; bedtime struggles, which are common in younger children; and sluggishness, difficulty waking and daytime sleepiness or fatigue particularly in older children or adolescents [16, 17]. Epilepsy is also more common in autism than in the general population and may be a consideration when sleeping problems are present [18, 19], while gastrointestinal symptoms, which are very common in autism, are associated with increased risk for sleep difficulties [20].

Based on reported sleep symptoms many autistic children are likely to meet criteria for an Insomnia Disorder, while in adolescents Delayed Sleep-Wake Phase Disorder (DSWPD) [21] should also be considered. Restless legs syndrome [18], and sleep apnoea [22, 23] are also reported (Table 20.1). While little attention is generally paid to classifying sleep symptoms into specific sleep disorders in autistic children at least two relatively comprehensive sleep studies have done so with a Behavioral Insomnia of Childhood being the most common diagnosis [24, 25], though these authors also reported that some children's sleep could not be classified and was due to the autism itself. Thus, there are a range of diagnostic possibilities that may explain a child's presentation. The cause of high rates of sleep problems in autism remains unknown and may be multi-factorial, including circadian rhythm dysfunction and melatonin abnormalities, and hyperarousal. Core autistic traits, behavioural difficulties and other co-occurring conditions such as anxiety and ADHD are also associated with sleep difficulties, as are alterations in the sleep EEG [9, 12, 26, 27].

Table 20.1 Sleep symptoms in autism and their relationship with ICSD-3 sleep disorders

ICSD-3 sleep disorder category	Reported symptoms/behaviours or sleep disorder
Insomnia	Settling difficulties, co-sleeping, night waking, sleep efficiency <85%, long sleep onset latency, early waking, problematic bedtime routines, daytime sleepiness, short sleep
Sleep related movement disorders	Restless sleep; restless legs syndrome, periodic limb movements disorder
Sleep related breathing disorders	Sleep apnoea, sleep disordered breathing
Central disorders of hypersomnolence	Kleine-Levin syndrome, hypersomnia, daytime sleepiness
Circadian rhythm sleep-wake disorders	Delayed sleep-wake phase syndrome, late sleep onset, irregular sleep-wake patterns, free-running sleep patterns
Parasomnias	Nightmares, wakes screaming, enuresis
Sleep related epilepsy	Increased risk for epilepsy in autism

Melatonin is a photosensitive neurohormone, produced in the pineal gland, and acts as a marker synchronising circadian rhythms, including the sleep-wake rhythm. It is light sensitive, particularly to blue light; levels are very low during the day and begin to rise at night prior to sleep onset peaking in the first half of sleep [28, 29]. It has been hypothesised that an abnormality in melatonin production may underly sleep difficulties in autism (e.g., [12]). Some studies have shown reduced plasma melatonin or its urinary metabolite, 6-sulphatoxy-melatonin in autism (see [30] for a review). In contrast, a study examining the melatonin circadian rhythm in a small sample of nine autistic children aged 3- to 8-years found it was similar to non-autistic children [31]. Examining dim light melatonin onset (DLMO) in autistic adolescents and young adults the same group also found no difference from non-autistic individuals [32], while in young autistic adults DLMO was consistent with individuals' sleep-wake patterns and increased melatonin prior to sleep was associated with better sleep efficiency [28].

There is some evidence for altered melatonin synthesis in autism. Increased NAS (N-acetylserotonin; [33]) and decreased ASMT (converts NAS to melatonin) gene expression are reported in autistic children [34, 35] and ASMT genotypes have been related to sleep in autistic individuals [35, 36]. Investigation of the heritability of the melatonin synthesis pathway showed that (NAS) and the enzyme ASMT were highly heritable but autistic children tended to have lower heritability

for ASMT than unaffected family members; heritability for serotonin and melatonin was not significant in the autistic group [37]. Relatedly, clock genes, which control circadian rhythms, may be impaired or different in autism, resulting in disruption of the sleep-wake rhythm [36, 38]. Much remains to be understood about the role of melatonin and clock genes in sleep in autism and altered melatonin synthesis likely does not apply to all autistic individuals.

Poor sleep is generally associated with increased overall autism trait severity [39]. However, directionality remains speculative as poor sleep may exacerbate these behaviours or vice versa. One longitudinal study examining sleep and autistic traits from 1.5- to 9-years found that while autistic traits and poor sleep were associated at all ages, sleep problems did not worsen autistic traits, but autistic traits were associated with poorer sleep over time [40]. Social and/or communication difficulties [13], repetitive and stereotyped behaviours [39] and sensory sensitivities [41, 42] are also associated with poor sleep. Sensory sensitivities and repetitive behaviours may be indicators of increased anxiety and arousal. Path analysis has shown that sensory over-responsivity and anxiety predict sleep difficulties in autistic children supporting an association between hyperarousal, anxiety, and poor sleep [41]. Hyperarousal is thought to play a prominent role in insomnia and may underpin the development of anxiety [43], and there is evidence that hyperarousal is related to insomnia in autistic adults [44].

About 70% of autistic individuals have a co-occurring psychiatric disorder, including anxiety and ADHD [6]. Autistic children are at higher risk for an anxiety disorder compared to children in general [45]; anxiety in the general population is associated with poor sleep quality or insomnia [46]. Anxiety in autistic children is associated with poor sleep [47, 48], while examination of sleep and anxiety from 2- and 8-years and autistic traits at 2-years in a large, general population sample showed that autistic traits, anxiety and sleep were related at age 2, but at 8-years the best predictor of anxiety was sleep at 8-years and vice versa [49]. There are also consistent reports of an association between poor sleep and behavioural difficulties, particularly aggression, and neurodevelopmental disorders such as ADHD [2]. For example, aggressive behaviour significantly increased the odds of having poor sleep over time in autistic children [50]. Children with ADHD and co-occurring autism have similar levels of sleep problems as children with ADHD alone, with both internalising and externalising behaviours being associated with their poor sleep [51].

20.2 Attention Deficit Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) affects approximately 5% of children and adolescents worldwide [6]. The core symptoms of ADHD are inattention, hyperactivity and/or impulsivity and to meet criteria for a diagnosis, symptoms need to be frequent, commence before the age of 12 years, occur across settings (e.g., home and school), and contribute to significant impairment in daily life [6]. ADHD is more prevalent in males compared to females [52] and is on average, associated with poorer outcomes across the lifespan [53]. It is understood that ADHD results from a combination of genetic and environmental risk factors, each having a small effect [52]. Co-occurring conditions are the rule rather than the exception in ADHD [52], with sleep problems being amongst the most common co-occurring conditions experienced by children with ADHD [54]. Given the similarity in behaviours that can result from sleep deprivation and the symptoms and consequences of ADHD, there is increasing interest in whether better assessment and treatment of sleep problems in children with ADHD can lead to improved functional outcomes [55].

The last decade has seen a surge in research publications on the topic of ADHD and sleep [54]. Up to 70% of children and adolescents with ADHD experience sleep problems according to parent report, comprising difficulties with both initiating and maintaining sleep [56]. Studies using objective measures (e.g., actigraphy, polysomnography (PSG)) to assess sleep problems in

children with ADHD also point to increased evidence for sleep disturbances in children with ADHD, although this evidence is less consistent than studies using subjective measures of sleep [57].

There is a great deal of variation in the types of sleep problems experienced by children with ADHD. Insomnia, circadian rhythm disorders (e.g., Delayed Sleep Phase Disorder) and parasomnias are all more common in children with ADHD compared to children without ADHD [58]. Additionally, more biological or medically-based sleep problems are also seen at increased rates in children with ADHD including narcolepsy, sleep breathing disorders and restless legs syndrome [59]. There is increased interest in whether variability in sleep parameters are increased in children with ADHD relative to controls with some studies supporting this notion [60], while others do not [61]. Furthermore, daytime sleepiness also appears to be more common in children with ADHD irrespective of night-time sleep problems [62].

The cause of sleep problems in children with ADHD is likely to be multi-factorial. For example, research suggests that higher levels of unhealthy sleep habits (e.g., screen time before bed, caffeine use etc.) in children and adolescents with ADHD is associated with increased sleep problems [63, 64]. Parenting factors such as increased parenting consistency have also been found to be associated with better sleep in children with ADHD [64]. Evening circadian preference is also associated with elevated sleep problems in this population [65]. There is some evidence that individuals with ADHD may experience a delay in DLMO [66], which may also explain the elevation of sleep problems in individuals with ADHD. Additionally, there is evidence of an association between circadian gene single nucleotide polymorphisms and ADHD symptoms [67].

A recent study points to the biological overlap between ADHD and sleep problems. This study found that there were three overlapping areas of association between sleep problems and grey matter volume, and ADHD symptoms and grey matter volume, largely in areas of the brain important for cognitive control and attention [68]. This study also found evidence that ADHD symptoms mediated the association between sleep problems and grey matter volume, and that areas where there were a higher proportion of the association between sleep and grey matter volume mediated by ADHD symptoms had higher gene expression including those important for dopamine [68]. The authors concluded that these complex findings support the notion that changes in grey matter volume and gene expression increase ADHD risk and that ADHD in turn, increases risk for sleep problems [68].

ADHD often co-occurs with other conditions such as internalising disorders (e.g., anxiety and depression) and externalising disorders (e.g., oppositional defiant disorder, conduct disorder [69]), with these additional co-occurring conditions conferring risk for sleep problems. For example, one study of 392 children with ADHD found that children with co-occurring internalising and externalising disorders had the highest risk for sleep problems [70]. In terms of other clinical factors that may be contributing to sleep problems in children with ADHD, the main treatment for ADHD, stimulant medication, has been associated with increases in insomnia [71]. However, research in this area is conflicting [72].

A number of studies now point to the increased burden that sleep problems have on children with ADHD. A recent study by Craig and colleagues found sleep problems in children with ADHD were associated with poorer quality of life and social functioning [73]. Additionally, sleep difficulties in children with ADHD have been associated with poorer cognitive functioning (e.g., executive function, delay aversion and working memory), although the strength of associations is generally small [74, 75]. Most of the research examining the connection between sleep problems and broader functioning in children with ADHD has been cross-sectional with few published longitudinal studies.

Of the small body of longitudinal research in this area, one study found that sleep problems were associated with greater behavioural and emotional problems in children with ADHD over a 12-month period [76]. Similar findings have been reported in young adolescents with ADHD, with one study finding that sleep problems were

predictive of greater behavioural difficulties and depression symptoms 1 year later even when accounting for initial ADHD severity and co-occurring conditions [77]. One recent large-scale study found some evidence to support bi-directional relationships between sleep problems and ADHD symptoms over time, however, there was evidence of a stronger association in the direction of ADHD symptoms predicting later sleep problems compared to vice versa [68].

The strongest evidence to date demonstrating the impact of sleep problems on the daily functioning of children with ADHD comes from sleep restriction studies, where researchers experimentally manipulate sleep times and then assess impact on functioning during normal or extended versus reduced sleep conditions. For example, a large study by Becker and colleagues found that sleep restriction in adolescents with ADHD was associated with increased inattention, oppositional symptoms and greater daytime sleepiness [78] and poorer affective functioning [79].

20.3 Neurodevelopmental Disorders with a Known Genetic Origin

In comparison to autism and ADHD, much less is known about the types of sleep problems and their causes in individuals with X-linked and chromosome 15 imprinting disorders.

20.3.1 X Linked Disorders

Fragile X syndrome (FXS) affects 1 in 4000 males and 1 in 6000 females [80] and is the most common inherited cause of ID and autism. FXS is caused by hypermethylation of the *FMR1* gene, resulting in silencing of *FMR1* mRNA and its protein (FMRP), which is essential for normal neurodevelopment [81]. The behavioural phenotype comprises speech delay, motor and language perseveration, abnormal sensory reactivity, sleep problems, aggression, anxiety, and hyperactivity and short attention [82]. Shyness and social anxiety interfere with social interaction and predispose to autistic features. In fact, ~75% of males and 25% of female patients with FXS also meet criteria for autism [83]). In a large survey study, 32% of children with FXS were reported to have sleep problems with 84% having ≥2 current sleep problems [84].

Most studies examining sleep in FXS have been by parent report. These studies have indicated insomnia symptoms are the most frequently reported problems [84]. Tolerability to objective measures of sleep in FXS and other neurodevelopmental disorders associated with ID can be poor, making objective assessment of sleep difficult. Nonetheless, a study [85] found good adherence to actigraphy and PSG in a small sample of children with FXS (n = 9). This study also demonstrated instability of circadian rhythms and variability in sleep patterns. While there has been a growing amount of work on circadian rhythm dysregulation in autistic adults, there is limited research examining circadian rhythmicity in autistic children and individuals with FXS. Nonetheless, *FMR1* knockout animal studies have demonstrated that both FMRP and FXR2P (a protein family member of FMRP with similar function), play a role in the regulation of sleep physiology [86]. In experimental studies, mice lacking *FMR1* exhibit abnormal circadian behavioural rhythms including loss of rhythmic activity in a 12:12 light-dark cycle and a free running period (<24 h) in constant darkness [86, 87]. Additionally, altered expression of the clock component of circadian rhythm genetic control has been observed in FXS animal models. The overexpression of FMRP via transfection assays increases the transcriptional activity of several key clock genes [86], suggesting that FMRP is essential for the regulation of rhythmic circadian behaviours. Moreover, Drosophila lacking FMRP exhibit altered circadian rhythmicity [87]. Together, these results indicate that FXS-related proteins might be associated with abnormal sleep patterns in FXS, due to alterations in circadian genes.

Rett syndrome (RTT) is a severe neurodevelopmental disorder associated with ID. RTT occurs predominantly in females with a prevalence of 1 in 9000 [88]. The disorder is associated with a mutation within the *MECP2* gene which is located on the long arm of the X chromosome

[89]. Individuals with RTT have an apparent early period of typical development, followed by a regression in communication skills. Co-occurring conditions experienced by individuals with RTT include epilepsy, sleep problems, and scoliosis. In a large questionnaire study of children and adults (median age 14 years, 4 months) with a *MECP2* mutation, 93.4% were reported to have either difficulties falling asleep or night waking [90]. In the same study, 38% of parents reported that the sleep problem had a moderate or major impact on the child, and 44% reported a moderate or major impact on the family unit.

The cause of sleep problems in RTT is not well understood. Nonetheless, research has shown that the severity of the sleep problem is dependent on the type of genetic change that has caused RTT [91]. Specifically, those with large deletions in the *MECP2* gene have the most severe sleep problems. The differences in severity of sleep problems based on the genetic subtypes of RTT, is suggestive of genetic factors contributing to sleep problems in this condition.

20.3.2 Chromosome 15 Imprinting Disorders

Chromosome 15 imprinting disorders including Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are associated with varying degrees of ID and social communication deficits [92]. The chromosome 15 imprinting disorders arise from different deletions or duplications at the 15q11-q13 imprinted region, located on chromosome 15 [93]. These deletions or duplications affect expression of genes located in this region. PWS results from the loss of function of paternal genes from chromosome 15q11.2-q13, while AS from the absence of function of the maternal genes in the same region [93]. Chromosome 15 imprinting disorders affect approximately 1:15,000 individuals [94], with no sex bias.

The most common sleep problems for persons with PWS are excessive daytime sleepiness, sleep disordered breathing (SDB), reduced sleep quality, and early morning waking [95]. Cataplexy and narcolepsy are also commonly experienced by individuals with PWS [96]. PWS is the most common genetic cause of life-threatening obesity, due to an increased appetite and hyperphagia. Thus, obesity is thought to contribute towards the presence of SDB and hypersomnolence in those with PWS; however, oxygen desaturation has been shown to occur during rapid eye movement (REM) sleep even in the absence of obesity [97]. SDB in PWS includes central sleep apnoea (CSA), obstructive sleep apnoea (OSA), and sleep-related hypoventilation disorder [95]. SDB (including OSA and CSA) is reported to affect 53% of children with PWS, while up to 80% of children are reported to have OSA [98].

In AS the most common sleep problems reported are insomnia symptoms, including increased sleep onset latency, frequent and prolonged night wakings, and reduced total sleep time [99]. Interestingly, the diagnostic criteria for AS reports abnormal sleep-wake cycles and a diminished need for sleep as associated features of the disorder [100]. The latter feature was included as individuals with AS do not appear to experience negative consequences of sleep deprivation. However, this may be attributed to an inability to accurately measure the negative consequences of poor sleep in AS, given nearly all individuals with AS have no verbal communication and moderate to severe ID. Using PSG individuals with AS have been shown to have an increased number of transitions between sleep states, increased frequency of awakenings indicating fragmented sleep, and a reduction in the time spent in REM sleep—all suggestive of reduced sleep [101, 102]. The sleep problems have been shown to emerge during infancy in both AS and PWS [103]. Using the Brief Infant Sleep Questionnaire (BSIQ) children with AS had atypical sleep patterns including shorter and more variable sleep duration and longer and more variable periods of night waking. Infants and toddlers with PWS had significantly longer sleep duration over 24 h than those with other neurodevelopmental disorders, suggesting an early emergence of hypersomnolence.

UBE3A is the imprinted gene most likely responsible for maternal-specific effects of

15q11.2-q13 in PWS and AS [104]. In most peripheral tissues, *UBE3A* is biallelically expressed; however, in mature neurons in some areas of the brain, *UBE3A* is expressed off the maternal allele only. Thus, in those with AS there is a loss of *UBE3A,* while in those with PWS there is overexpression of *UBE3A*. In addition to having a critical role in the normal development and regulation of the nervous system, *UBE3A* also plays a significant role in the regulation of sleep homeostasis in animal models [105, 106]. More specifically, in a mouse model of AS with a maternal deficit of *UBE3A*, significant sleep-wake disturbances were observed [105] indicative of circadian dysregulation. Thus, one hypothesis for the cause of the sleep problems in AS is an inability to synchronize the sleep-wake cycle with the light-dark cycle, resulting in atypical melatonin secretion and consequently CRSWDs [107]. Few studies have examined the melatonin profile in AS. However, from the limited number of studies, AS individuals have a tendency towards reduced night-time levels of melatonin and/or altered timing of melatonin secretion [107].

Epilepsy is one of the most common medical co-occurring conditions in AS with approximately 70% of those with AS experiencing seizures which may also contribute towards sleep problems. Specifically, seizures may interfere with night-time sleep structure. Moreover, antiepileptic drugs may also influence sleep. Behavioural symptoms such as anxiety, hyperactivity, and autism traits may also contribute towards the presence of sleep problems in AS.

20.4 Assessment and Treatment of Sleep Difficulties in Children with Neurodevelopmental Disorders

Given the high prevalence and impact of sleep problems in children with neurodevelopmental disorders, it is important that consideration of sleep is given during clinical consultations. Recent research points to the under-identification of sleep difficulties in children with ADHD and autism [108], and both sleep itself and treatment approaches in PWS, AS, FXS and RTT are under researched, with sleep problems remaining ineffectively managed. Little has changed since earlier overviews of approaches to assessment and treatment in autism and other developmental disabilities [109], and ADHD [110].

Clinicians are advised to enquire in more detail about children's sleep patterns and behaviours and not to rely on parents spontaneously reporting poor sleep. While single questions such as such as "Does your child have a sleep problem?" may have good correspondence with sleep diaries and lengthier sleep measures [111], and have been shown to be associated with greater levels of functional impairment in children [56], parents may lack knowledge about normal sleep development in childhood or childhood sleep problems [112, 113]. Parents of children with and without an ID or developmental disorder (DD) scored well below chance on knowledge about childhood sleep and sleep problems [113], and while 63% of parents of children with an ID or DD reported one or more child sleep problems only 27% checked "yes" when asked if their child had a sleep problem [11].

In assessing children's sleep problems screening questionnaires are useful and there are many to choose from [114], though they are not generally developed with children with a neurodevelopmental disorder in mind. Sleep diaries and actigraphy will provide additional information if a sleep problem is indicated and of course PSG will be indicated in some circumstances, for example when sleep apnoea is suspected (e.g., in PWS). A range of factors including co-occurring medical conditions, behavioural difficulties, co-occurring anxiety or other mental health diagnoses, the presence and/or severity of autistic or ADHD traits, and the presence and degree of ID also need to be considered. Furthermore, broader family factors such as organisation and structure in the family environment and parent stress and mental health should be ascertained. These factors can all impact on treatment choice and treatment effectiveness. Behavioural approaches are recommended as the first line of treatment [115,

116]. A useful practice pathway to guide assessment and intervention for poor sleep in autistic children is provided by Malow et al. [116] and these guidelines may be usefully adapted to other developmental conditions.

20.5 Behavioural Interventions

One of the first considerations in treating children's sleep problems is implementing healthy sleep habits, particularly bedtime routines and the elimination of screens from the bedroom [117–119]. For example, in RTT healthy sleep practices were associated with reduced impact of the sleep problem on the family [90]. There is a growing body of research supporting the usefulness of behavioural treatments, generally implemented by parents for insomnia symptoms in autism and other neurodevelopmental disorders [120–122]. Behavioural approaches, including implementing healthy sleep habits, are recommended as part of a treatment plan, even when a pharmacological intervention is used [115] and can also improve child behaviour [121, 123].

There is a range of behavioural interventions for sleep problems in children with neurodevelopmental disorders including education about healthy sleep habits [124], extinction [125], bedtime fading with response cost [126], and graduated extinction procedures [127]. A functional assessment should be conducted prior to implementing a behavioural sleep intervention to determine antecedent and maintenance factors of the presenting sleep problem [128]. For example: (1) functional assessment of the child's sleep problems together with a behavioural sleep training program educating parents about children's sleep development, healthy sleep practices, and extinction procedures to address sleep onset, co-sleeping and night waking in five autistic children and six children with FXS was both successful and acceptable to parents [125]; and (2) individualised behavioural treatments based on functional assessment of each child's sleep difficulties in six boys with neurodevelopmental disorders, including one with PWS and one with ADHD, were reported to lead to significant sleep improvements [129]. While individualised behavioural sleep interventions are often necessary and can take many weeks to be successful, brief behavioural interventions, conducted in small groups or individually have also been reported to be efficacious in treating sleep problems in children with developmental disorders [121, 130].

There is a lack of studies examining the usefulness of cognitive behavioural therapy for insomnia (CBT-I) and acceptance and commitment therapy (ACT) approaches for helping with sleep in the context of children with neurodevelopmental disorders. CBT-I is considered the recommended approach to sleep intervention [131] and ACT is also an effective sleep intervention [132]; both approaches may have utility in addressing insomnia in older children with neurodevelopmental disorders, particularly adolescents. For example, following CBT for anxiety, sleep was reported to improve in autistic children [48]. However, adaptations may be needed to suit these intervention approaches to adolescents with neurodevelopmental disorders [133].

20.6 Pharmacological Interventions

While research on pharmacological intervention is lacking, there are recent reviews on these approaches to treating sleep problems in autism [36] and children with neurodevelopmental disorders [115], with a growing number of studies supporting pharmacological approaches to managing sleep problems in children with ADHD [134]. Nevertheless, with the exception perhaps of melatonin clinical data on management are lacking as is approval by agencies such as the FDA (USA) [115, 135].

Melatonin is the most prescribed pharmacological treatment for paediatric sleep problems and is reported to be an efficacious short-term treatment for sleep onset insomnia [136] and DSWPD in children [137]. Nevertheless, the action of melatonin in sleep in children with neurodevelopmental disorders remains unclear as it

has circadian, soporific [138] and anxiolytic effects [139] and is often prescribed without obtaining clear evidence that a circadian rhythm sleep disorder is present or that there is any abnormality in the child's melatonin rhythm. Melatonin's long-term safety in children requires further investigation [136, 137, 140] and it is recommended that behavioural treatments be tried first [135, 137]. One study demonstrated that a combination of controlled release melatonin with behavioural treatment was superior to melatonin alone in a group of autistic children [141].

Randomised placebo-controlled trials have demonstrated that immediate release [142] and controlled release melatonin [143] can improve sleep latency and total sleep in children with a neurodevelopmental disorder. Using a randomised double-blind, placebo-controlled, multi-national trial the Gringras group later showed that autistic children with and without ADHD, or Smith-Magenis Syndrome (3.2% of group) who had not responded to behavioural treatment had decreased sleep latency, improved total sleep and improvement in parent-reported sleep following prolonged release melatonin treatment [144]. Follow-up, open label trials provided evidence of melatonin efficacy and safety for children from Gringras et al. [144] for up to 2-years with no significant adverse, long-term effects of melatonin and continued improvement in sleep latency, night waking and total sleep, as well as parent-reports of sleep problems [145, 146]. In ADHD, a naturalistic trial of melatonin was largely successful in treating sleep onset delay that developed in 74 children following methylphenidate treatment [147].

Treatment options for sleep problems in AS are usually pharmacological. In a systematic review of 10 studies that investigated interventions to improve sleep in AS, weak evidence for the effectiveness of behavioural interventions and mixed outcomes for the effectiveness of pharmacological treatments were shown [148]. Although one study demonstrated treatment fidelity for a behavioural intervention there was no direct measurement of sleep with all treatment outcomes being subjectively reported by parents [149]. Most studies examining pharmacological interventions included mixed samples of individuals with various neurodevelopmental disorders and results were not reported separately for AS individuals. Nonetheless, in one randomised placebo-controlled efficacy study in eight children with AS and chronic insomnia [150], melatonin significantly advanced sleep onset time, reduced sleep onset latency and the number of nights with wakes per week, and increased total sleep time. However, of the four children who received melatonin, three were reported to have a return of increased night waking at the cessation of the open label period or at the 1-month follow-up. For RTT, pharmacological treatments, including melatonin, have not been shown to improve the sleep problem. In a study of 364 individuals with RTT, those taking medication remained more likely to have more difficulty falling and staying asleep, with greater impacts from the sleep problem still reported [90]. Thus, while melatonin remains one of the most prescribed pharmacological treatments, with some promising results for those with autism, ADHD and FXS, treatment effects in RTT and AS are less promising.

Other common pharmaceuticals that may be efficacious for various neurodevelopmental disorders include gabapentin, clonidine, trazodone, and mirtazapine [115]. Gabapentin, an anticonvulsant, has been shown to have beneficial effects on sleep in a variety of clinical conditions [115]. Moreover, in a case series in 23 children (87% with a neurodevelopmental disorder), gabapentin was shown to be safe and well-tolerated, with 78% of children showing parent-reported improvements in sleep [151]. Clonidine, an α_2-adrenergic agonist, has sedative effects and is commonly prescribed as a sleep aid in paediatric samples [152]. There is also research indicating efficacy of clonidine for sleep problems in ADHD [153, 154], autism [155], and children with neurodevelopmental disorders [156]. There is some support for mirtazapine and trazadone, antidepressant medications with hypnotic effects, for the treatment of sleep disorders in autism and other neurodevelopmental disorders, respectively. However, the evidence for these pharmaceuticals

is preliminary with further research needed. Moreover, trazadone is not recommended for RTT. Clinicians should always consider the severity and type of sleep problem, the associated neurological pathology, and polypharmacy, when considering pharmaceutical intervention.

20.7 Other Treatments

Children with a neurodevelopmental disorder diagnosed with SDB problems are usually treated with oxygen or continuous positive airway pressure (CPAP) [157] and a behavioural intervention may assist compliance to CPAP. Adenotonsillectomy is also used to treat OSA in neurodevelopmental disorders [157, 158]; in an autistic girl both sleep and behaviour improved after adenotonsillectomy for obstructive OSA [22]. A meta-analysis of six studies with 41 PWS patients, showed OSA symptoms significantly improved after surgery. Nonetheless, residual OSA was still frequently observed postoperatively [159], suggesting other factors contribute towards SDB in PWS. Readers should refer to relevant chapters in this textbook on OSA and central sleep apnoea syndromes for further information.

20.7.1 Summary and Research Gaps

While there is a vast amount of research exploring sleep problems, their causes and correlates in autism and ADHD, research in the genetically determined neurodevelopmental disorders is more limited. This is likely due to the rare nature of these conditions inhibiting researchers' ability to examine large samples of affected individuals and reach conclusive findings. Nonetheless, it is evident that sleep is disrupted with impacts on daytime functioning of both parents and children [101, 160, 161]. Further research is needed to delineate the type of sleep problems and their causes in these rarer conditions. Determining the nature of specific sleep problems and correctly diagnosing a sleep disorder has significant implications for the management and treatment of sleep problems in rarer neurodevelopmental disorders. Moreover, for all neurodevelopmental disorders, treatment options remain limited. Further research is needed to explore both behavioural interventions and pharmacological treatments. Individualised treatment plans based on the nature and cause of the sleep problem, as well as other co-occurring conditions experienced by these individuals is required.

20.8 Vignette

Jessica is a 12-year-old child who has been diagnosed with ADHD and autism. She takes long-acting stimulant medication to manage her ADHD symptoms. Jessica has a bedtime of 8 pm and generally needs to be out of bed at 7 am to get ready for school. She has a television in her bedroom and watches television in bed from 8 to 9 pm each night. After lights out at 9 pm she lies in bed awake for many hours and often doesn't fall asleep until 11 pm each night. Her parents then find it hard to wake her in the morning. She generally sleeps well overnight once she falls asleep. On weekends Jessica doesn't follow a set bedtime or waketime and generally falls asleep at 11 pm–12 am and sleeps until about 9 am. A diagnosis of Delayed Sleep Phase Disorder was made.

A number of strategies were suggested to improve her sleep including increased alignment between weeknight and weekend bedtimes and waketimes, removing the television from the bedroom and replacing TV time before bed with reading (in an area of interest). Bedtime fading was also used whereby Jessica's bedtime was temporarily set closer to her approximate sleep time and then the bedtime was brought forward by 15 min once she was able to fall asleep within about 20 min of getting into bed. This fading approach was coupled with a set wake time and early morning light exposure e.g., eating her breakfast in a sunny part of the house. This plan was developed with Jessica in collaboration with her parents. Overall, Jessica's sleep improved with her shifting to fall asleep by 9.30 pm and waking more easily at 7 am.

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