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REVIEW PAPER

Sleep Disturbances in Autism Spectrum Disorders

Gaétane Deliens[1,2] · **Rachel Leproult**[2] · **Rémy Schmitz**[2,3] · **Arnaud Destrebecqz**[1] · **Philippe Peigneux**[2]

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Abstract Sleep problems have been commonly reported in children with autism spectrum disorder (ASD). This review takes a lifespan perspective in discussing recent findings on sleep disturbances in ASD, including sparse but pivotal studies in toddlers and adults. Current evidence shows that more than a mere comorbidity, sleep disturbances can represent a key factor in ASD. Already present before the age of 2, sleep problems are one of the early warning signs of ASD, which persist through lifespan. Genetic, epigenetic, psychological, and social/environmental factors involved in sleep disturbances in ASD contribute to better understand the core symptoms of autism (restricted and repetitive behaviors, communication, and social deficits). Although often considered as secondary by the therapeutic community, behavioral and pharmacological sleep interventions are efficient to reduce symptoms severity in ASD individuals and improve parents' mental health. This review should convince the scientific and medical community to address sleep complaints and autism symptoms together rather than separate entities.

Keywords Sleep problems · Autism spectrum disorders · Cognition · Symptom severity · Lifespan · Nonpharmacological treatment · Pharmacological treatment

✉ Gaétane Deliens
Gaetane.Deliens@ulb.ac.be

✉ Philippe Peigneux
Philippe.Peigneux@ulb.ac.be

[1] CO3 - Consciousness, Cognition & Computation at CRCN - Center for Research in Cognition and Neurosciences and UNI - ULB Neurosciences Institute, Université Libre de Bruxelles (ULB), Avenue F.D. Roosevelt, 50, 1050 Brussels, Belgium

[2] UR2NF - Neuropsychology and Functional Neuroimaging Research Group at CRCN - Center for Research in Cognition and Neurosciences and UNI - ULB Neurosciences Institute, Université Libre de Bruxelles (ULB), Avenue F.D. Roosevelt, 50, 1050 Brussels, Belgium

[3] LABNIC - Laboratory for Neurology and Imaging of Cognition - Department of Neurosciences, University Medical Center - University of Geneva (UNIGE), Rue Michel-Servet, 1, CH-1211 Geneva, Switzerland

Introduction

Autism spectrum disorder (ASD) is a developmental disorder characterized by impairments in social interactions and communication in association with restricted and repetitive behaviors (American Psychiatric Association 2013). Formerly, ASD was subdivided into five distinct disorders, namely Autistic Disorder, Asperger's Syndrome (AS), Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder (PDD)-Not Otherwise Specified. Currently, ASD is viewed as a continuum of psychological conditions necessitating moderate to substantial support to cope with deficits in social communication and restricted, repetitive behaviors (American Psychiatric Association 2013). Sleep difficulties are recognized as comorbidities of ASD (e.g., in the DSM-V). Decreased sleep quality and/or lack of sleep is also known to exert a deleterious impact on emotional processing (Deliens et al. 2014), learning abilities (Astill et al. 2012), and social interactions (Beattie et al. 2014), i.e., in domains associated with ASD symptoms. Therefore, there is a need to better understand how sleep problems interact with autistic symptoms, which might eventually lead to complementary therapeutic interventions targeting sleep symptoms in ASD. Prior literature reviews have focused on the relationships between sleep and ASD in children (Hollway and Aman 2011; Kotagal and Broomall 2012). In this review, we take a

lifespan perspective as the sparse, but insightful studies in toddlers and adults are included. We also emphasize the utmost importance to determine early signs that identify infants (<3 years old) at risk for ASD to further develop earlier interventions (Deconinck et al. 2013).

Prevalence of Sleep Problems in ASD

Large-scale studies (n>1000) published in the past 5 years report sleep problems in 32 to 71.5 % of children and adolescents with ASD (Goldman et al. 2011; Hollway et al. 2013; Sikora et al. 2012). Variable prevalence might be due to different criteria (i.e., different cut-off scores) and assessment methods for sleep problems (hetero-evaluation scales, auto-questionnaires, actimetry, polysomnography, etc.). When prevalence rates are compared to those of typically developed (TD) children (poor sleep being also commonly observed in the general population), sleep problems are more frequent in ASD (81.5 %) than in TD children and adolescents (50 %) (Hodge et al. 2014). Furthermore, ASD children are more likely to exhibit sleep problems (47 %) than their unaffected siblings (16 %) after controlling for family factors such as inadequate child-rearing practices (e.g., no parental supervision of bedtime), stress, or noisy environments (Park et al. 2012). Overall, despite a wide range of reported prevalence of sleep disturbances, there is a growing consensus in the literature that prevalence of sleep problems is increased in ASD children as compared to TD children.

Sleep disturbances have also been found in adults with ASD (Galli-Carminati et al. 2009; Hare et al. 2006a, b; Limoges 2005; Matson et al. 2008; Oyane 2005; Tani et al. 2003, 2005, 2006). However, these studies are less frequent than in ASD children and limited by small sample sizes (n≤20), preventing an accurate estimation of the prevalence of sleep disturbances (Galli-Carminati et al. 2009; Hare et al. 2006a, b; Limoges 2005; Oyane 2005; Tani et al. 2003, 2005, 2006). Intellectual disability (ID) is an additional contributing factor as sleep problems assessed in adults and elderly people with ASD (n =168) are more prevalent in ASD with ID (44.7 %) than without ID (13.7 %; Matson et al. 2008). Unfortunately, there was no healthy control group, and prevalence was not calculated separately for adults and elderly people in this latter study. At present, the prevalence rate for sleep disturbances in young and older adults remains unclear. Further studies on larger samples, comparing separately ASD adults and elderly to a control group matched for age and ID are needed to obtain a lifespan perspective of sleep disturbances in ASD.

Retrospective studies have highlighted the early presence of sleep problems in infants later diagnosed with ASD. These studies are mostly based on screening tools for autistic traits that often include questions on sleep quality. Parents of adolescents and young adults with AS report less daytime sleep and more sleep disturbances in their child before the age of two, as compared to a TD group (Dewrang and Sandberg 2010). Sleep difficulties were one of the warning signs that brought concern on children development in 8.5 % (Guinchat et al. 2012) to 64.7 % (Swinkels et al. 2006) of the parents. The discrepancy between the two studies depended on the time elapsed between the actual assessment and the interview. Furthermore, the presence of sleep disturbances in PDD before the age of two was found as a risk marker for subsequent sleep difficulties in life (Doo and Wing 2006). Given that treatment strategies can be efficient as early as 3 months of age in TD toddlers (Thomas et al. 2014), these findings emphasize the importance to identify sleep problems at an early age.

Although recall biases due to the delayed reminiscence of infancy events by the parents call for caution in the interpretation of retrospective studies, the number of registered consultations for sleep disturbances in Child Health Centers during the first 2 years of age was higher in children later diagnosed with ASD than in TD children (Barnevik Olsson et al. 2013). In addition, interviews of parents about their toddler's sleep difficulties during the course of the 0–2 years developmental period evidenced that children with ASD are more prone to sleep problems than those with TD (Matson et al. 2010), PDD, or atypical development (Kozlowski et al. 2012). Unfortunately, these studies are not conclusive to identify sleep problems as a warning sign for later ASD diagnosis, since the selected patient group is already diagnosed for ASD. Prospective studies are thus needed to investigate sleep problems as a red flag for a later diagnosis of ASD.

Taken together, studies concur to indicate that increased prevalence of sleep problems in ASD is already observed before the age of two and seems to persist across adolescence and even across the lifespan according to the few studies on adulthood. Further studies should investigate sleep problems as a red flag for a later diagnosis of ASD, using prospective designs that include early screening tools to detail sleep disturbances and early sleep interventions.

Risk Markers for Sleep Problems in ASD

The occurrence of sleep problems in ASD is influenced by multiple risk markers summarized in the *Bidirectional Theoretical Framework of Sleep Disturbance* (Hollway and Aman 2011). According to this model, the core symptoms of autism (i.e., restricted and repetitive behaviors, communication, and social deficits) are vulnerability factors to sleep disturbances when associated with environmental stressors such as fear evoking stimuli and unpredictability of the environment. Indeed, severe core symptoms coupled with environmental stressors are associated with maladaptive coping strategies such as internalizing (anxiety, depression, and overcontrolling) and externalizing (aggression, hyperactivity, noncompliance) behaviors eventually leading to

hyperarousal disrupting sleep. Comorbid medical conditions (e.g., epilepsy) are also predictors for sleep problems. In line with this model, a recent study showed that the likelihood of sleep dysfunction in ASD increases in the presence of anxiety, higher symptoms severity, communication and social interaction deficits, sensory sensitivities, developmental regression, and gastrointestinal problems (Hollway et al. 2013). Therefore, the occurrence of sleep problems in ASD involves complex and multiple risk markers.

This model implies that levels of intellectual functioning would not be directly associated with sleep problems but would reduce sleep disturbances by moderating autism symptom severity (Hollway and Aman 2011). Although intelligence level is positively associated with sleep anxiety (Hollway et al. 2013), it does not modulate sleep duration, bedtime resistance, and sleep problems. Discrepancy between studies evidencing (Gail Williams et al. 2004) or not (Krakowiak et al. 2008; Mayes and Calhoun 2009; Sivertsen et al. 2011) that a lower IQ is a risk marker of sleep disturbances in ASD may come from the assessment of the intelligence level using a variety of tests, some being more based on language than others. Interestingly, sleep problems were more prevalent in ASD children with lower language levels (Maskey et al. 2013).

The current literature on age as a risk marker for sleep disturbances in ASD individuals yielded mixed results. Several studies found that sleep problems are more common in older than in younger ASD children (Sivertsen et al. 2011; Honomichl et al. 2002), whereas others found either the inverse association (Hollway et al. 2013; Richdale and Prior 1995) or no age-related changes in the prevalence of sleep disturbances in ASD children (Gail Williams et al. 2004; Goldman et al. 2012; Mayes and Calhoun 2009; Schreck and Mulick 2000; Wiggs and Stores 2004). Inconsistencies in the literature might reflect the use of heterogeneous samples including PDD, Rett's syndrome, Angelman syndrome, etc. (Honomichl et al. 2002; Schreck and Mulick 2000), which precludes clear conclusions about ASD. Moreover linear correlations between age and sleep complaints are generally used whereas nonlinear associations cannot be excluded (Hodge et al. 2014). A recent study conducted across four age groups of children with ASD concludes that sleep disturbances are equally present throughout childhood, but that the types of sleep problems (e.g., bedtime resistance, parasomnia, sleep anxiety) differ by age group (Goldman et al. 2012). Unfortunately, the specificity of age-related changes in sleep problems of children with ASD cannot be ascertained in the absence of a control population of TD children. A study comparing sleep patterns in children with and without ASD subdivided in three age groups confirmed that sleep problems persist within the ASD groups, but that types of sleep problems change across time (detailed in the next section; Hodge et al. 2014). The prevalence of sleep disturbances is higher in the 6–9 and 10–17 years but not in the youngest ASD group, as compared to the age-matched TD groups. An improvement in TD children's sleep pattern through ages is observed, whereas in ASD children, sleep problems reach a peak in the 6–9-year group relative to the 2–5- and 10–17-year groups. In summary, the prevalence of sleep disturbances seems stable from childhood to adolescence, but the types of sleep disturbances change over time. This relevant finding explains the reason why it is not possible to extract a unique sleep profile among ASD individuals who encounter sleep difficulties. Moreover, it highlights the utmost importance of an ongoing adaptation of sleep intervention programs over time by the clinician.

Cross-sectional studies are limited since they cannot evaluate intra-individual changes, leaving the contribution of other factors that might differentiate the studied populations unsolved. Due to their demanding nature in terms of time and resources, longitudinal studies avoiding such caveats are unfortunately scarce and often suffer from a limited sample size (Allik et al. 2008), heterogeneity, and/or a lack of control group (Honomichl et al. 2002). One-week periods of actigraphic data collection in high-functioning children with ASD (HFA, $n=16$) and their age-matched TD children revealed a similar age-related sleep evolution, with a sleep phase delay and a decrease in sleep duration after 2 to 3 years in both groups (Allik et al. 2008). On the other hand, caregiver reports in a longitudinal population-based study yield evidence for an increased incidence rate of sleep problems from 7–9 to 11–13 years in children with Autism Spectrum Problems (ASP) as compared to the TD population (37.5 vs. 8.6 %, respectively; Sivertsen et al. 2011). Remission rate is also lower in children with ASP (8.3 %) than without ASP (52.4 %), suggesting that sleep problems remain stable in ASP children, whereas they improve over time in no-ASP children. Accordingly, sleep problems decrease in TD children after 1 year but persist in children diagnosed with HFA (May et al. 2013).

To summarize, available studies indicate that anxiety, autism symptoms severity, communication and social interaction deficits, sensory sensitivity abnormalities, and developmental regression can predict sleep problems in individuals with ASD. Age also seems to influence sleep problem features, more than being a risk factor of sleep disturbances. The relationships between sleep disturbances and intelligence in ASD need to be explored while controlling for language skills.

Sleep and Sleep Problems Features in ASD

Sleep is not a unitary process but comprises several cycles of alternations between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep can be subdivided into NREM1 (N1), N2, and N3 sleep stages characterized by an increasing slow and ample electroencephalographic activity with diminished muscle tone and with slow

eye movements or no eye movements. By contrast, REM sleep presents with a desynchronized rapid and low-amplitude electroencephalographic activity, muscular atonia, and bursts of rapid eye movements. Since sleep architecture (e.g., sleep stages durations, sleep latency, sleep efficiency, etc.) changes across the development (Ohayon et al. 2004), the investigation of sleep features in children with ASD is needed with respect to age-matched TD individuals. Table 1 lists the polysomnographic studies fulfilling this criterion.

Across reports, the most consistent features of sleep disturbances in ASD children are shorter total sleep time (Buckley et al. 2010; Elia et al. 2000; Goldman et al. 2014a; Miano et al. 2007), prolonged sleep latency (Allik et al. 2006b; Goldman et al. 2009, 2014a; Lázár et al. 2010; Limoges 2005; Limoges et al. 2013; Malow et al. 2006), increased wake time after sleep onset (WASO) (Diomedi et al. 1999; Lázár et al. 2010; Limoges 2005; Limoges et al. 2013), lower sleep efficiency (Allik et al. 2008; Diomedi et al. 1999; Lázár et al. 2010; Limoges 2005; Limoges et al. 2013; Malow et al. 2006), increased time spent in light sleep (Limoges 2005; Limoges et al. 2013), decreased percentage of REM sleep (Buckley et al. 2010; Diomedi et al. 1999; Malow et al. 2006), and reduced spindles density (Godbout et al. 2000; Limoges 2005; Limoges et al. 2013). Results are more controversial regarding the proportion of slow wave sleep (SWS) (Buckley et al. 2010; Lázár et al. 2010; Malow et al. 2006 vs. Limoges 2005; Limoges et al. 2013) and REM sleep latency (Buckley et al. 2010; Miano et al. 2007) (see Table 1).

Spectral analyses of sleep recordings indicate reduced power in the alpha, sigma, beta, and gamma bands in AS versus TD subjects (7 to 21 years old), probably suggesting an altered cortico-cortical and thalamo-cortical resonance (Lázár et al. 2010). Increased delta activity in individuals with ASD may reflect delayed brain maturation and/or the consequence of increased sleep propensity during the experimental night after poor sleep during the adaptation night. Reduced sigma activity may indicate deficits in the thalamo-cortical resonance in frontal regions. Finally, reduced intrahemispheric coherence over the frontal region and the right hemisphere is in line with the "underconnectivity hypothesis," which suggests a fontal dysfunction in AS, a region known to be involved in the mirror neuron system (Hadjikhani et al. 2006).

Table 1 Differences in sleep architecture between ASD and TD individuals reported by polysomnographic and actigraphic studies

	Sample sizes	Age range (years)	TST	SL	WASO	SE	N1	N2	SWS	REM	REML
Polysomnography											
Buckley et al. 2010	60 ASD, 15 TD	2–13	↓	=	=	=	=	=	↑	↓	↑
Diomedi et al. 1999	10 ASD, 10 TD	12–24			↑	↓	=	=	=	↓	
Elia et al. 2000	17 ASD, 5 TD	5–16	↓	=	=	=	=	=	=	=	=
Godbout et al. 2000	8 AS, 8 TD	7–53	=	=		=	=	=	=	=	=
Goldman et al. 2009	27 ASD poor sleeper, 16 TD	4–10	=	↑	=	=					
	15 ASD good sleeper, 16 TD	4–10	=	=	=	=					
Lázár et al. 2010	18 HFA, 14 TD	7–21		↑	↑	↓	=	=	↑*	=	=
Limoges 2005	16 ASD, 16 TD	16–27	=	↑	↑	↓	↑	=	↓	=	=
Limoges et al. 2013	15 ASD, 12 TD	16–27	=	↑	↑*	↓*	↑	=	↓	=	=
Malow et al. 2006 (first night)	11 ASD poor sleepers, 10 TD	4–10	=	↑	=	↓	=	=	↑	↓	=
Malow et al. 2006 (second night)	11 ASD poor sleepers, 10 TD	4–10	=	=	=	=	=	=	=	=	=
Miano et al. 2007	31 ASD, 31 TD	3–19	↓	=	=	=	=	=	=	=	↓
Actigraphy											
Allik et al. 2006a	10 AS/HFA with insomnia, 10 TD	8–12	=	↑	=	↓					
Allik et al. 2006b	32 AS/HFA, 32 TD	8–12	↓*	↑	=	↓					
Allik et al. 2008 (wave 1)	16 AS/HFA, 16 TD	8–12	=	↑	=	↓					
Allik et al. 2008 (wave 2)		11–15	=	=	↑	=					
Baker et al. 2013	15 HFA, 25 TD	15.5±1.3	=	↑							
Goldman et al. 2009	27 ASD poor sleeper, 16 TD	4–10	=	=	=	=					
	15 ASD good sleeper, 16 TD	4–10	=	=	↓	=					
Goldman et al. 2014a	11 ASD, 6 TD	4–10	↓	↑	=	=					
Hare et al. 2006a	10 AS, 19 TD	30.8±6.9	=	↑	↑	↓					
Tani et al. 2005	19 AS, 10 TD	young adults	=	=	=	=					

AS asperger's syndrome, *ASD* autism spectrum disorder, *HFA* high-functioning autism, *N1* nonrapid eye movement sleep stage 1, *N2* nonrapid eye movement sleep stage 2, *REM* rapid eye movement sleep, *REML* REM latency, *SE* sleep efficiency, *SL* sleep latency, *SWS* slow wave sleep, *TD* typically developing, *TST* total sleep time, *WASO* wake after sleep onset, ↑ increase, ↓ decrease, = no difference, not investigated (empty case), * trend

ASD is associated with a higher prevalence of behavioral insomnia syndromes (Allik et al. 2006a; Baker et al. 2013), delayed sleep phase (Baker et al. 2013), obstructive sleep apnea (Hodge et al. 2014), and parasomnias such as bedwetting, disoriented waking, night terrors, rhythmic movements while falling asleep, bruxism, sleep walking, and acting out dreams (Goldman et al. 2011; May et al. 2013; Miano et al. 2007; Schreck and Mulick 2000).

Based on questionnaires, a cross-sectional study across lifespan reports more bedtime resistance, sleep anxiety, parasomnias, and night waking in children with ASD, whereas adolescents with ASD feature more delayed sleep onset, shorter sleep duration, and daytime sleepiness (Goldman et al. 2012). Another cross-sectional study confirmed an improvement of bedtime resistance with age but a worsening of sleep anxiety (Hodge et al. 2014). As compared to controls, actigraphic data also evidence longer sleep latency, lower sleep efficiency during school days, early bedtime and wake-time during weekends in HFA/ASD children, and longer intra-sleep awakenings and lower sleep efficiency during weekends at 2–3-year follow-up (Allik et al. 2008). In this study, the sleep phase delay and the shorter sleep duration are observed in both groups.

In adolescents, actigraphy also indicates longer and more variable sleep latencies in ASD than in TD samples (Baker et al. 2013), whereas ASD adults exhibit poor sleep efficiency and high sleep fragmentation (Hare et al. 2006a). Desynchronization of circadian rhythm is not observed, but its amplitude (i.e., the difference in activity levels between most and least active periods) is lower and more variable, suggesting a lower influence by environmental synchronizers (Hare et al. 2006a). Besides complaints of poor sleep quality, other studies failed to evidence different actigraphic sleep profiles between adults with AS and controls (Tani et al. 2005). Unfortunately, objective measurements of sleep in ASD toddlers are missing as existing studies are exclusively based on questionnaires completed by caregivers that evidenced bedtime resistance, shorter sleep duration, parasomnias, daytime sleepiness (Doo and Wing 2006), night wakings (Doo and Wing 2006; Guinchat et al. 2012), wake up crying (Guinchat et al. 2012), and less daytime sleep (Dewrang and Sandberg 2010) before the age of 2 years. The fact that screening tools only include few questions on sleep prevents a precise delineation of sleep problems in toddlers with or susceptible to develop ASD.

Nevertheless, polysomnography disturbs patients, especially ASD patients who have difficulties with breaking routines. This procedure is relatively invasive and performed in unfamiliar surroundings, rendering data of the first night less representative of typical sleep pattern (Buckley et al. 2013; Malow et al. 2006). Sleep architecture of the second night is also biased because patients compensate the sleep debt from the previous night (Malow et al. 2006). Furthermore, polysomnographic studies select ASD patients who can tolerate this invasive procedure limiting generalizability. Although less invasive, actigraphy underestimates sleep latency and is not tolerated by all individuals with ASD (Adkins et al. 2012; Wiggs and Stores 2004) leading some researchers to settle the actigraph in a hidden pocket of the pajamas (Adkins et al. 2012). Finally, most studies do not specify if studied children with ASD complain about sleep problems or not although no difference of sleep pattern was shown between TD and ASD good sleepers (Malow et al. 2006).

Despite these potential limitations, most studies confirm the presence of sleep features anomalies in ASD, especially prolonged sleep latency, increased WASO, and lower sleep efficiency, taking different forms from childhood to adulthood.

Etiology of Sleep Dysfunction in People with ASD

Sleep disturbances in individuals with ASD can be ascribed to biological, psychological, and/or social/environmental factors. Comorbid medical conditions may also predispose to sleep disturbances in people with ASD such as attention-deficit/hyperactivity disorder (Liu et al. 2006), asthma (Liu et al. 2006), epilepsy (Liu et al. 2006), pain (Tudor et al. 2014), and gastrointestinal problems (Mannion et al. 2013). Most importantly, clinical characteristics and psychiatric comorbidities in ASD, such as pathological anxiety (Mazurek and Petroski 2014; Nadeau et al. 2014) and depression, predispose to sleep disorders (Richdale and Baglin 2015). Indeed, somatic and cognitive hyperarousal states resulting from rumination and negative thoughts prevent sleep to settle. Since ASD individuals have difficulties with breaking routines, ASD children used to fall asleep in their parents' arms are at risk to be unable to fall back to sleep alone after a spontaneous awakening. Similarly, even slight changes in bedtime routine will lead to later sleep onset (Kotagal and Broomall 2012). Finally, the impaired novelty processing (i.e., altered shift of attention from a formerly relevant to an irrelevant attribute) observed in ASD individuals (Maes et al. 2011) is also hypothesized to be linked with longer sleep latency when an arousing event occurs around bedtime (Kotagal and Broomall 2012).

It has been proposed that sleep disorders in people with ASD, and circadian rhythm disturbances in particular, relate to a socialization deficit. Indeed, the entrainment and the synchronization of the circadian clock depend on zeitgebers (i.e., timegivers) such as the natural light–dark cycle, sound, and social cues. Therefore, a deficient perception or interpretation of social cues in ASD individuals may hamper the efficiency of sleep/wake cycle synchronization processes (Richdale and Prior 1995). Alternatively, persons with ASD may experience difficulties to synchronize with their internal and external environments, eventually leading to rhythm and timing problems that impact various fields such as social interaction and circadian rhythms (Amos 2013). In other words, the inability to mirror

the internal clock on environmental and social rhythms would lead to circadian disturbances in ASD individuals.

Low melatonin and clock gene anomalies in people with ASD seem to be involved in social and circadian problems (Bourgeron 2007). Melatonin, a hormone synthesized in the pineal gland from serotonin, exhibits a circadian pattern with low daytime concentrations and elevated overnight levels and mainly contributes to the regulation of circadian rhythms (Zee et al. 2013). Melatonin production appears to be abnormal in individuals with ASD despite inconsistent results [i.e., similar (Ritvo et al. 1993) vs. lower (Kulman et al. 2000; Melke et al. 2008; Nir et al. 1995; Tordjman et al. 2005, 2012) nighttime levels, and elevated (Nir et al. 1995; Ritvo et al. 1993) vs. reduced (Tordjman et al. 2012) daytime levels]. Inconsistencies in research studies could be due to sample sizes, demographics (age, weight, pubertal stage), severity of the disease, medication use, and methodology such as sampling procedure, but more importantly to the lack of control in sleep times, light exposure, and circadian rhythms which could be inverted, delayed, or advanced. However, a study conducted in adolescents and young adults controlling for sleep times and light exposure discloses both lower daytime and nighttime urinary excretions of melatonin primary metabolite in ASD, as compared to controls (Tordjman et al. 2012). Moreover, the nocturnal urinary excretion negatively correlates with the severity of autistic impairments in verbal communication but not with sleep problems (Tordjman et al. 2005, 2012). Interestingly, overnight levels of urinary excretion in ASD appear to be correlated with SWS and inversely correlated with NREM sleep stage 2 and daytime sleepiness (Leu et al. 2011). In a small group study, plasma melatonin profiles are comparable to those reported in the literature for typically developing children, and actigraphic sleep onset occurs when plasma melatonin levels rise (five of six children; Goldman et al. 2014b). To summarize, there is a high interindividual variability in melatonin production indicating that benefits of melatonin administration could be useful to a subgroup of individuals with autism. Moreover, it is noteworthy that deficits of melatonin production in autism seem to be associated with high serotonin levels (Melke et al. 2008; Mulder et al. 2010) and low acetylserotonin methyltransferase activity, an enzyme involved in the last step of melatonin synthesis (Melke et al. 2008). Regarding clock gene anomalies, studies report a reduced gamma-aminobutyric acid (Plante et al. 2012) and mutations in the NLGN/NRXN/SHANK3 (neuroligin/neurexin/synaptic scaffolding protein 3) complex (Bourgeron 2007) in ASD individuals resulting in insomnia and sleep-wake disturbances, respectively. The fact that these mutations trigger different ASD phenotypes suggests the involvement of epigenetic mechanisms (Bourgeron 2012). This hypothesis is reinforced by differences in methylation levels for retinoic acid-related orphan receptor alpha (RORA) (Nguyen et al. 2010) and the abnormal expression in ASD people of two microRNAs involved in circadian rhythms (Sarachana et al. 2010).

As mentioned above, sensory sensitivity abnormalities might also contribute to ASD's sleep problems (Goldman et al. 2011; Liu et al. 2006; Mazurek and Petroski 2014). Underresponsive children with sensory seeking behavior are more likely to miss social zeitgebers needed to synchronize their sleep/wake cycle (Maski et al. 2011). Conversely, patients with ASD displaying hypersensitivity to tastes or textures may feel more anxious at bedtime, when they brush their teeth for instance, resulting in difficulties to fall asleep (Stein et al. 2011). One study confirms that children who are underresponsive, sensory seeking, with auditory filtering dysfunctions, have more trouble sleeping (Hollway et al. 2013). Moreover, higher electrodermal activity in response to sensory stimulation is present in children with ASD, as compared to TD children (Reynolds et al. 2012), and elevated sympathetic arousal predicts sleep disturbances in ASD children with 85.7 % accuracy.

Taken together, complex interactions between biological, genetic, psychological, and environmental factors are implicated in ASD individuals' sleep problems. The emerging field of epigenetic in ASD will allow us to better understand the interfaces between these factors.

Sleep Disturbances and Autism Symptomatology

Increasing evidence demonstrates the compounding effect of sleep problems on autism symptomatology. In toddlers, sleep difficulties are associated with lower developmental functioning (Kozlowski et al. 2012). In children and adolescents, sleep disturbances, particularly reduced sleep duration (Schreck et al. 2004), predict ASD symptom severity (Allik et al. 2006a; Mayes and Calhoun 2009). Poor ASD sleepers have higher problems with social interaction (Goldman et al. 2011; Malow et al. 2006; Schreck et al. 2004; Sikora et al. 2012; Taylor et al. 2012), increased affective problems (Malow et al. 2006; Richdale and Baglin 2015), lower adaptive functioning (Sikora et al. 2012; Taylor et al. 2012), and communication deficits (Hollway et al. 2013; Park et al. 2012; Schreck et al. 2004; Sikora et al. 2012). Shorter sleep duration and night waking are associated with more communication problems (Taylor et al. 2012), whereas bedtime resistance, screaming during the night, and fewer hours of sleep are linked to stereotypic behaviors (Goldman et al. 2009; Park et al. 2012; Schreck et al. 2004). Additionally, sleep problems exacerbate externalizing (aggressive, hyperactive, noncompliant, and undercontrolled) behaviors (Goldman et al. 2009, 2011; Mayes and Calhoun 2009; Park et al. 2012; Sikora et al. 2012) and internalizing (anxious, depressive, and overcontrolled behaviors) problems (Malow et al. 2006; Mayes and Calhoun 2009; Park et al. 2012; Richdale and Baglin 2015; Sikora et al. 2012). Poor sleep also predicts anxiety difficulties 1 year later both in TD and ASD children (May et al. 2013).

Studies on ASD adolescents and adults are scarce (Matson et al. 2008; Richdale et al. 2014). Available information indicates that poor sleep worsens daytime functioning to a larger extent in HFASD than TD adolescents (Richdale et al. 2014). ASD adolescents and adults with moderate to severe sleep dysfunction are more likely to display aggressive behaviors, whereas eccentric types of problem behaviors (unusual play with objects, inappropriate sexual behavior) are more common in ASD adolescents and adults with mild sleep problems (Matson et al. 2008).

Conclusions that can be drawn from these studies are limited by possible biases in the relationships between sleep and symptom severity due to comorbid developmental disabilities. It is noteworthy that sleep onset delay, sleep duration, and parasomnias exacerbate autism severity in ASD children without any comorbid developmental disabilities (Tudor et al. 2012). Night waking is a strong predictor for social interaction deficits, whereas sleep onset delay predicts communication difficulties, stereotyped behavior, and autism severity (Tudor et al. 2012). Altogether, available evidence indicates that sleep problems exacerbate ASD symptom severity. Interestingly, worsened ASD symptomatology appears to increase the risk of sleep problems suggesting that the relationship between sleep and autism severity is bidirectional (Adams et al. 2014).

Relationship Between Sleep Disturbances, Cognition, and Daily Living Skills in ASD

It is now well established that sleep plays an important role in cognition (Astill et al. 2012). Moreover, sleep disturbances in ASD individuals seem to lead to cell signaling, protein synthesis, and cortical connections abnormalities which in turn alter synaptic plasticity (Picchioni et al. 2014). Only few studies investigated the relationships between sleep patterns in ASD and daytime cognition or the ability to function pragmatically in the environment. In ASD children, shorter sleep duration is associated with lower intelligence, verbal and nonverbal abilities, adaptive behavior and motor development (Taylor et al. 2012), and sleep disturbances with poor receptive vocabulary (Malow et al. 2009). In ASD children and adolescents, lower perception skills are associated with prolonged sleep latency, more stage shifts during the night, longer REM sleep latency, and more WASO (Elia et al. 2000). Worse eye-hand coordination correlates with more stage shifts during the night, longer REM sleep latency, more WASO, and a shorter sleep period (Elia et al. 2000). Lastly, lower nonverbal communication skills are associated with shorter total sleep time (Elia et al. 2000).

Language development and sleep architecture seem to be interconnected in TD children. Indeed, poor sleep-dependent consolidation before the age of two predicts long-term language delays (Dionne et al. 2011). In healthy adults, sleep spindles might promote lexical consolidation, as reflected by a higher lexical competition for existing word competitors of recently learned words after a night of sleep (Tamminen et al. 2010). In individuals with ASD featuring reduced spindles activity (Limoges 2005; Limoges et al. 2013), off-line consolidation of vocabulary is intact but exhibits a reverse time course of lexical integration as compared to age- and vocabulary-matched TD children (Henderson et al. 2014). Whereas competition with existing lexical neighbors emerges after sleep in TD children, reflecting the overnight integration of new words in the existing lexical knowledge, competition is observed after the learning phase but not 24 h later in ASD children.

Off-line consolidation in probabilistic implicit sequence learning was also tested in children and adolescents with and without ASD (Nemeth et al. 2010). Despite common sleep disturbances in ASD individuals, sequence-specific and general skill learning were intact during both the learning phase and the delayed recall performed after a night of sleep. Although this result suggests a non-sleep-dependent consolidation of implicit sequence learning in ASD like in TD children and adolescents, the absence of an appropriate control condition with a similar interval of wakefulness makes it premature to conclude that sleep does not play a role in the off-line consolidation of implicit sequence learning in ASD children and adolescents.

In ASD young adults with normal intelligence, sustained attention and working memory deficits as well as impaired performance in sensory motor and cognitive procedural memory are associated with poor sleep quality (i.e., prolonged sleep latency, increased light sleep, and WASO) (Limoges et al. 2013). Individuals with and without ASD who present less SWS during the third part of the night exhibit lower learning performances on the sensory motor procedural memory task, and more sleep spindles are associated with better performances in this task but only in ASD adults (Limoges et al. 2013).

Hence, sleep disturbances seem to modulate verbal and nonverbal abilities in ASD. Since all ASD individuals do not suffer from sleep problems, further studies comparing good and poor ASD sleepers are however needed to disentangle the respective roles of sleep problems and autistic symptomatology in the cognitive profile featuring ASD individuals. Finally, the interplay between sleep problems in ASD and social cognition abilities (e.g., identification of salient affective social cues, perspective-taking abilities) remains an uncharted area of inquiry.

Treatment

ASD children presenting sleep problems are more likely to experience poor health-related quality of life than ASD children who are good sleepers (Delahaye et al. 2014). Besides a detrimental effect on the well-being of ASD children, sleep

disturbances also affect the mental health of family members. Indeed, even after controlling for children behavior, sleep measures in ASD children predict parental depressive symptoms and sleep quality (Goldman et al. 2014a). Unaffected siblings are also more likely to present sleep difficulties than siblings with no family history of autism (Schwichtenberg et al. 2013). Therefore, sleep intervention in people with ASD is an essential component of their treatment which should be embedded into a comprehensive approach of the ASD problematic.

Nonpharmacological Treatment

Although behavioral methods to manage sleep disturbances in autism are numerous (for review, see Turner and Johnson (2012); for a brief overview of the different methods, see Table 2), their efficiency was assessed using objective measures in only a few well-controlled evaluations.

Actigraphic recordings in children indicate that 6-h workshops aimed at helping small groups of parents to establish bedtime routines and strategies to prevent night and early morning awakenings were efficient in decreasing sleep latency 1 month after the final session (Reed et al. 2009), which was not the case when a brochure was simply handed over to parents (Adkins et al. 2012). Likewise, both group and individualized education programs improve sleep latency and sleep efficiency (measured by actigraphy) in ASD children (Malow et al. 2014). Parents report beneficial effects of the program on their children's behavior and quality of life, as well as a better sense of competency in their parents' role. In children and adolescents with ASD who experience sensory integrative difficulties, the efficacy of a weighted-blanket was investigated to reduce the level of arousal and anxiety by the deep pressure it exerts (Gringras et al. 2014). However, actigraphic data failed to disclose sleep differences after 2 weeks of using usual weighted blankets versus a commercial weighted blanket designed specifically for somatosensory stimulation (heavier than usual blanket without being too warm).

Other nontraditional approaches to improve sleep difficulties in children with autism include sensory processing, white noise, bright light therapy, exercise, relaxation, diet, valerian, and aromatherapy (for a review, see McLay and France 2014). Amongst these, only massage therapy and multivitamin supplement are validated by empirical evidence in people with ASD (McLay and France 2014).

Pharmacological Treatment

When behavioral interventions are not effective to treat sleep disorders in ASD children, pharmacological treatments might be considered. However, no medication is currently approved by the Food and Drug Administration (FDA) to treat pediatric insomnia. Melatonin administration is effective to improve sleep in individuals who experience bad sleep quality, especially those with circadian rhythm sleep disorders (Zee et al. 2013). Since irregular sleep/wake cycles and sleep disturbances such as longer sleep latency or sleep-onset insomnia, reduced total sleep time or sleep-maintenance insomnia, and nocturnal and early morning awakenings are frequently reported in ASD (Glickman 2010), administration of melatonin might be beneficial in improving sleep alterations in ASD.

Investigations of melatonin treatment for sleep problems in ASD differ with regard to the sampled populations (sample size, age range, pubertal stage, and clinical heterogeneity), doses (0.5–15 mg), forms (immediate vs. controlled release), and timing (fixed timing or minutes before bedtimes) of administration, sleep measurements (subjective reports, actigraphy, polysomnography), and the severity of autistic behavioral impairments (reported or measured using well-validated tools). Moreover, melatonin is considered a dietary supplement by the FDA and is therefore not regulated like a pharmaceutical drug, resulting in uncontrolled amounts of melatonin in pills. Nevertheless, available evidence suggests a beneficial effect of melatonin administration on sleep problems in ASD.

Table 2 Behavioral sleep interventions

Sleep hygiene	Providing a comfortable sleep environment (dark and quiet bedroom), establishing regular bedtime routine and schedules, teaching children to fall asleep alone, avoiding daytime naps, and stimulating activities around bedtime
Extinction	Ignoring children's cries, tantrums, and calls for the parents from bedtime to wake time (standard extinction) or for specified periods with progressively longer interval between check-ins (graduated extinction)
Scheduled awakenings	Preemptive awakening 30 min before a typical spontaneous awakening
Faded bedtime	Delaying bedtime until falling asleep within 15 min and progressively setting bedtime earlier
Faded bedtime with response cost	Taking children out of bed for prescribed periods of time when they do not fall asleep.
Sleep restriction	Temporally restricting the amount of time slept by 10 % to diminish the time spent awake in bed. After sleep disturbances diminish, the bedtime is faded each week.
Stimulus fading	Progressively eliminating the presence of parents from the children's room
Chronotherapy	Altering sleep timing to reset the circadian clock

Retrospective, open-label and randomized placebo-controlled trials have investigated potential beneficial effects of melatonin administration on sleep problems in ASD (Table 3).

Retrospective studies indicate an improvement in sleep problems when using melatonin administration 30 to 60 min before bedtime in children, adolescents, and in adults.

Table 3 Retrospective, open label, and randomized placebo-controlled trials that have investigated melatonin treatment on sleep problems in ASD

Study	Participants	Melatonin treatment (dose–timing)	Results	Side effects
Retrospective studies				
Gupta and Hutchins 2005	9 children 2–11 years	IR 2.5–5 mg 45 min before bedtime	↓ sleep latency (4) ↑ total sleep duration (5/9) No response (3/9)	–
Andersen et al. 2008	107 children/teens 2–18 years	1 to 6 mg (IR:91 %) 30–60 min before bedtime	No more sleep concerns (25 %) Still some sleep concerns (60 %) Benefits stopped after 3–12 months (6.5 %)	Sleepiness Fogginess Enuresis (3/107)
Galli-Carminati et al. 2009	6 adults 19–52 years	IR 3 to 9 mg 40–50 min before bedtime	↑ total sleep duration (6/6)	–
Open label trials				
Jan et al. 1994	15 children	2 to 10 mg bedtime	Partial sleep benefits Behavioral and social benefits	–
Ishizaki et al. 1999	50 children/adults 3–28 years	bedtime	Sleep benefits (42/50: 39/44 insomniacs and 3/6 circadian sleep disorders) Excitabilities improved	Sleepiness Awakening Excitement (17/50)
Paavonen et al. 2003	15 children/teens 6–17 years	IR 3 mg 30 min before bedtime	↓ sleep latency (11/14) ↓ nocturnal activity Behavioral/emotional benefits	Tiredness (3/15) Headache (1/15) Diarrhea (1/15)
Giannotti et al. 2006	25 children 2.6–9.6 years	IR/CR 3 to 6 mg 8 pm	↓ sleep latency ↑ total sleep duration ↓ nocturnal awakenings Behavioral/emotional benefits	–
De Leersnyder et al. 2011	88 children 7 ASD: 12±4 years	CR 2–6 mg 60 min before bedtime	↓ sleep latency ↑ total sleep duration ↓ nocturnal awakenings	Sleepiness (1) Daytime nap (8) Difficulties to swallow pills (2)
Malow et al. 2012	24 children 3–9 years	CR 1–6 mg 30 min before bedtime	↓ sleep latency (actigraphy) Sleep improvements (reports) Behavioral benefits Same improvements in sleep	Loose stool (1)
Goldman et al. 2014b	Subgroup of (Malow 2012[104]) 9 children (3–8 years)	CR 1–6 mg 30 min before bedtime	↓ sleep latency (actigraphy, PSG) ↓ night wakings (reports)	–
Randomized placebo-controlled trials				
Garstang and Wallis 2006	7 children/teens 5–15 years	IR 5 mg 60 min before bedtime	↓ sleep latency ↑ total sleep duration ↓ nocturnal awakenings Behavioral benefits	–
Wasdell et al. 2008	50 children/teens 16 ASD 2–18 years	IR/CR 5–15 mg 20–30 min before bedtime	↑ total sleep duration ↓ sleep latency ↓ anxiety ↓ family stress	–
Wirojanan et al. 2009	12 children/teens (8 ASD) 2–15 years	IR 3 mg 30 min before bedtime	↓ sleep latency ↑ total sleep duration	–
Wright et al. 2011	17 children/teens 3–16 years	IR 2 to 10 mg 30–40 min before bedtime	↓ sleep latency ↑ total sleep duration Behavioral benefits	–
Cortesi et al. 2012	144 children 4–10 years	CR 3 mg 9 p.m.	↓ sleep latency ↑ total sleep duration ↓ nocturnal awakenings	–
Gringras et al. 2012	136 children 3–15 years	IR 0.5–12 mg 45 min before bedtime	↓ sleep latency slight ↑ total sleep duration	–

IR immediate release, *CR* controlled release, *PSG* polysomnographic

Although daytime sleepiness, enuresis, depression, and increased seizures are possible adverse effects of exogenous melatonin (Andersen et al. 2008), only three individuals out of the 122 experienced side effects in these retrospective studies (Table 3). Similarly, open-label and randomized placebo-controlled trials indicate that melatonin is an effective treatment for sleep problems, especially to reduce sleep latency, without major side effects. Controlled release appears to be more beneficial for sleep maintenance (Table 3). Notably, melatonin treatment works more efficiently in particular in individuals with more severe sleep problems (Giannotti et al. 2006; Jan et al. 1994) and to partially improve behavioral autistic impairments (Table 3). These benefits could disappear after discontinuation of the treatment (Giannotti et al. 2006; Paavonen et al. 2003), especially in individuals with more severe sleep/wake rhythm disturbances, which raises the question of a long-term treatment with melatonin. Instead of continuously increasing the doses to prevent the disappearance of melatonin efficacy, it has been suggested that doses should go back to lower amounts to counteract the slow melatonin metabolism assumed to be due to a single nucleotide polymorphism of CYP1A2 (Braam et al. 2013).

In summary, parent-based sleep education workshops are positive in addressing sleep disturbances in ASD children, but few studies have investigated nonpharmacological treatment of sleep problems in ASD adolescents and adults. Melatonin treatment, the most prescribed pharmacological treatment for sleep disturbances in ASD, is an effective treatment for sleep problems without major side effects.

General Conclusion

Although sleep disturbances are not inherent to the autistic condition, they are clearly more prevalent in ASD than in TD individuals. Considering the available evidence, it is not possible to extract a unique sleep profile among ASD individuals who encounter sleep difficulties. The heterogeneity of sleep problems observed in people with ASD probably mirrors the phenotypic heterogeneity with respect to their autistic symptom profile. However, sleep problems are well known to be comorbid to a large number of pathologies, including in the psychiatric domain. Therefore, investigating and treating sleep problems should be at the forefront of therapeutic interventions, especially in ASD individuals. This review emphasized that sleep disturbances may represent early warning signs of autism, exacerbate autism symptoms severity, significantly decrease the health-related quality of life of individuals with ASD, and affect the mental health of family members. Behavioral and pharmacological interventions yield promising results, which should convince the scientific and medical community to address sleep complaints and autism symptoms together rather than separate entities.

In conclusion, this review aimed at taking a lifespan perspective to discuss sleep disturbances in ASD. Although promising, toddler studies are lacking validated and standardized sleep questionnaires dedicated to children before the age of two, which prevents to draw clear conclusions (Spruyt and Gozal 2011). Moreover, studies on sleep problems in adults with ASD are scarce, and sleep is completely unexplored in elderly with ASD. Addressing sleep problems in these populations should therefore be a priority to extend our understanding of sleep disorders in ASD across lifespan.

Compliance with Ethical Standards

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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