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Understanding the role of sleep and its disturbances in autism spectrum disorder

Ramanujam Karthikeyan¹, Daniel P. Cardinali², Venkat Shakunthala³, David Warren Spence⁴, Gregory M. Brown⁵, Seithikurippu R. Pandi-Perumal⁶

¹Department of Animal Behavior & Physiology, School of Biological Sciences, Madurai Kamaraj University, Madurai - 625021, India.

²Faculty of Medical Sciences, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina.

³Department of Zoology, Manasagangotri, University of Mysuru, Karnataka, India

⁴Independent Research Consultant, Dufferin Street, Toronto, ON M6K 2B4, Canada.

⁵Molecular Brain Science, Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, 250 College St, Toronto, ON, Canada

⁶Somnogen Canada Inc., College Street, Toronto, On, Canada

Corresponding author S.R. Pandi-Perumal Somnogen Canada Inc., College Street, Toronto, ON, Canada Pandiperumal2019@gmail.com

Abstract

Sleep difficulties are one of the significant complications associated with autism spectrum disorder (ASD). Despite their possible role as contributors to the overall symptoms of ASD, the symptoms of disturbed sleep experienced by many affected patients have only recently started to receive attention from clinicians, caretakers, and family members. Many types of sleep disorders have been reported in ASD individuals, but these have not been categorized under a common terminology. Nevertheless, several studies have established that a positive relationship exists between the occurrence of sleep difficulties and heightened symptomatology in ASD children. When ASD children show evidence of sleep problems there is also an increased frequency of

behavioral problems such as social impairment, decreased cognitive functioning, aggressiveness, and anxiety. Several hypotheses have been put forward regarding the linkage between disturbed sleep and ASD. These have included suggestions that sleep difficulties and other ASD symptoms are induced by disruption of the circadian clock, the presence of comorbid physical or psychological conditions, elevated anxiety levels, or emotional distress. This article reviews the use of sleep therapies in ASD, among which melatonin has shown promise because of its lack of significant side effects. A better understanding of sleep problems in the etiology of ASD, their impact on the symptoms and behavior of ASD individuals, and their potential use as a secondary aid for treating ASD would represent a significant contribution to develop strategies to manage the disorder.

Keywords ASD, Autism spectrum disorder, Sleep, Sleep problems, treatment of ASD, melatonin

List of abbreviations

ADHD - Attention-Deficit Hyperactivity Disorder

ASD - Autism spectrum disorder

ASPSYN - Asperger's syndrome

DSM 5 - Diagnostic and Statistical Manual of Mental Disorders

GI – Gastro-intestinal

LD - Light/Dark

MDD - Major depressive disorder

OSA - Obstructive sleep apnea

PedPRM-Pediatric prolonged-release melatonin

RBD - Rapid eye movement sleep (REM sleep) behavior disorder

REM - Rapid eye movement (sleep)

Introduction

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that first appears in childhood. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1] affected individuals who have persistent difficulties with social communication and social interaction, frequently co-occurring with significant intellectual deficits and abnormal behavior, including restricted, repetitive activities and interests (Table 1). ASD children are highly sensitive to their environments and exhibit severe resistance to sudden changes in their surroundings or daily routines. Other symptoms of the disorder include developmental delays in cognitive functioning and language processing [2].

In recent decades, a significant increase in the worldwide prevalence of ASD has been reported. In 2010, a survey reported that there was a population of 52 million ASD individuals and the prevalence of ASD was 1 among 132 persons [3]. This sudden upsurge has been associated with a significant burden to the health care system, inasmuch as the cost of treating ASD for any disease is greater than the cost of caring for normal children [4,5]. The estimated cost of treating ASD children in the US alone was estimated to be \$268 billion in 2015 [6]. These data exemplify the significant financial burden that the management of ASD represents and thus underscore the need to reduce the costs of currently used therapies and to seek new treatment strategies.

The onset of ASD is thought to be caused by a genetic susceptibility as well as by fetal exposure to chemicals and environmental factors [7]. Intricate gene-environment interaction contributes to the challenge of understanding how this

complex illness develops and how it may be treated [8]. Abnormalities in ASD children exhibit substantial inter-individual variations which depend on the degree of impairment in brain function. Low-functioning autistic children frequently require permanent support for even their most basic daily needs for life maintenance [9]. It is also the case that low functioning autistic children may demonstrate the most severe behavior disorders and sleep-related complications. The fact that such low-functioning ASD children cannot live without the assistance of others adds further to the socio-economic burden that the most severe form of this disorder represents [9].

Sleep disturbances in ASD are a point of concern in view of the possibility that such difficulties may be associated with overall ASD symptom severity and may potentially represent a causal influence. Interest in the role of sleep difficulties in the prevalence and symptomatic profile of ASD is increasing [9]. The current article will focus on sleep-related studies in ASD with the aim of providing a better understanding of ASD, as well as suggesting possible directions for therapeutic strategies based on improving the sleep quality in affected patients.

Sleep has a significant role in the neural development of the children

Sleep is a vital regulator of many biological processes in children including metabolism, development of neural regulation of mood, learning, and memory [10,11]. The process of sleep architecture and duration alters through the developmental stages of the child in such a way that the length of time between REM and non-REM sleep increases with age [12]. It is now known that processes of the timing, duration, and structure of sleep play a crucial role in the development and function of the infant's brain and neural system [13] (Figure 1). After birth, the infant spends more than two-thirds of its time sleeping [14]. Further, immediately

subsequent to birth, and for some time thereafter, the infant's sleep does not synchronize to the light/dark (LD) cycle, and only following a few years sleep is restricted to the nighttime hours [15]. The basic structure and function of sleep tends to be polyphasic during early infancy, and only gradually becomes monophasic. Between 2 to 5 years of age, sleep in normal infants begins to resemble the typical profiles of adulthood. The consistency of findings in studies of this phenomenon supports the conclusion that the immediate future of neurobehavioral development in infants is closely determined by the history of their sleep/wake processes [16,17].

This inference is further supported by studies showing that a relationship exists between the severity of sleep disturbance and the expression of ASD symptoms [18-21]. Generally, data collected from interviews with parents of ASD children indicate that about 50 to 80% of ASD patients exhibited sleep disruption. Since current evidence suggests that sleep/wake processes determine the functional output of the brain, the dysfunctionalities that occur in the developing brain could in many instances be attributed to disturbed sleep/wake episodes that take place in infancy [11,22]. Sleep promotes the process of neurogenesis, whereas sleep loss interferes with the formation of new neuronal cells [23,24]. Sleep restriction in adolescent mice results in the alteration of the structure of pyramidal neurons suggesting that sleep plays a role in determining the structures of brain anatomy [25]. Evidence favors that sleep is essential for promoting neural connectivity in the brain and such connectivity is adversely affected by the loss of sleep in adolescent mice [26]. A substantial amount of study has now firmly established that sleep plays a predominant role in the regulation of both neurophysiological and neuropsychiatric processes so that its prolonged disruption can lead to abnormal neural development and functioning [9,20,27,28]. An

assessment of the functional correlates of sleep in normal subjects as well as in children with ASD could provide new insights into understanding the association between neural development and social communication.

Sleep difficulties reported in ASD

Numerous studies have documented the various types of sleep difficulties that occur in ASD children [18,19]. An investigation that analyzed sleep differences in high and low-level functioning of ASD children found evidence suggesting that the associated sleep changes were due to the modification of brain structure and its behavioral output [29]. The frequency and severity of sleep complications in ASD children show variations but tend to be proportional to the degree of neurological disturbance which generates ASD symptoms [29].

In a parent-report based questionnaire study comprising 303 ASD children, it was found that 53% of ASD children had at least one sleep-related disturbance [30]. Another investigation documented the presence of sleep problems in up to 64% of a group of 69 ASD children [31]. In a survey study (based on a parental questionnaire) of 167 autistic children, around 86% of the sample were reported to have experienced sleep difficulties [32]. Overall, various studies have reported the prevalence rate of sleep-related complications in ASD children to be around 50% to 80%; this compares to the lower prevalence rate that is typical in developing children [30,33-37]. There is currently no uniformity in the categorization of sleep problems in ASD children, nor does there exist a common terminology for describing these problems[38]. The current preliminary evidence suggests sleep problems manifest from an extremely early age in ASD children and continue to persist throughout the lifespan [37].

Instances of delayed sleep onset, structural changes in sleep architecture, a reduction in total sleep time, resistance to lying in bed, inappropriate arousal, and waking at early hours of the morning have all been observed in ASD children [39,40]. Children diagnosed with ASD who have been shown to suffer from one type of sleep disorder frequently experience other sleep problems as well [32,37]. Generally, ASD children with poor development have been reported to suffer from more severe sleep problems when compared to more highly functioning ASD children [33]. It has thus been suggested that sleep problems are such an integral part of overall ASD symptomatology that they may, in fact, have a reciprocal or even causal relationship with the more overt cognitive and behavioral problems of ASD. While sleep disturbances are certainly a symptom of more fundamental underlying abnormalities in the central nervous system, a considerable amount of evidence now supports the inference that this relationship may be mutually facilitating [41-43].

ASD children with obstructive sleep apnea (OSA) exhibited symptoms such as snoring with loud sounds, sleeping with an open mouth, apnea and leaning of the head backward during sleep [44]. The presence of sleep-disordered breathing has been shown to coincide with stereotyped activity, social impairment and overall severity in autism [45]. The administration of antipsychotic drugs in children can produce excessive body weight and may increase their susceptibility for developing OSA [46]. OSA is not as prevalent as other sleep disorders in ASD, but it definitely merits attention and treatment [46]. In a Japanese study, it was found that the prevalence of OSA was higher in children with ASD than in normally developing children [47].

Sleep problems in ASD children produce secondary effects on the sleep quality of parents, disruptions which will ultimately produce increased stress, both

psychologically and socially among family members [48]. It is often long after the parents have settled into bed at night that sleep disturbances among their ASD children may start to occur. These nightly episodes may become particularly annoying for the parents and may further interfere with their attempts to get back to sleep. The priority of parental concern often focusses on the sleeplessness of the child, and over time it may evolve into a child-driven and child-centric pattern of family dynamics. Thus, what is often overlooked in conventional medical diagnoses is that the sleep disturbances of ASD children are not limited to the physiology of the children, but extend beyond into the child's social world, especially to his/her family [38]. This evidence suggests that both the diagnosis and treatment of ASD should be expanded to include the larger social complications of the disorder for the family and those who are involved in the child's care.

Effect of sleep problems on the behavior of ASD children

Sleep loss has the potential to affect cognitive processes, word formation, creative thinking, and mood. In addition, sleep perturbations can affect learning and memory functions, and, further, may alter the normal physical development of affected children [49,50]. Even a single night of sleep restriction in children (age group 10-14) can impact the higher levels of cognitive function, including verbal proficiency and abstract thought processes [51]. Additionally, abnormalities in sleep/wake episodes may adversely affect the child's circadian rhythms [40], which in turn may have a negative influence on the child's mood and next-day alertness [52].

Reduced sleep quality and sleep disturbances have been linked to aggressive behavior in humans. This has been particularly demonstrated in psychiatric patients who have been shown to be more sensitive to aggressive or threatening behavior

when they experienced impaired sleep quality [53]. Further, studies have indicated that the incidence of aggressive behavior is greater in children diagnosed with ASD than among those with any other developmental disorder [54]. Poor sleep in children with ASD is also associated with impaired social behavior, thus suggesting that quality and duration of sleep may have further effects on the social skills of affected children [55]. A study on 21 ASD children found that, compared to normal subjects and to other ASD children who had only a limited amount of sleep disturbance, the ASD children with the most impaired sleep quality also suffered from a greater amount of affective problems and social impairment [37]. Recently, a study also reported that severe behavioral problems were observed in ASD children with insomnia [47]. The prevalence of insomnia in high functioning autism predicted the overall symptoms of ASD [56]. Also, developmental problems in ASD children were predicted by the severity of parasomnia episodes [45]. One sleep variable that has been found to be relevant is the number of nighttime awakenings, which are correlated with the overall severity of autistic symptoms [9]. Other ASD symptoms, including perceptual or visual difficulties and decreased appetite, have additionally been reported to correlate with the number of nighttime awakenings [57]. In a study of parental reports of 55 autistic children, it was found that disturbed sleep was correlated with deficits in social interaction, enhanced sensitivity to changes in their surroundings, and communication difficulties [55]. A parental questionnaire survey of 1784 ASD children who were either good (n=1200) or poor (n=584) sleepers found that the presence of sleep disturbances tended to be correlated with behavior problems. These included a greater incidence of aggressiveness, anxiety-related problems, mood variation, hyperactivity, heightened sensitivity to changes in the environment, attentional deficits, and reduced social skills

[58]. Among ASD children, those suffering from sleep problems exhibited excessive attention-seeking behavior, more hyperactivity, and a greater incidence of repetitive behavior[59]. Also, fragmented sleep has been associated with increases in restricted or repetitive behavior in ASD children [58]. Severe sleep disturbances in ASD children, such as parasomnias, have shown linkages to gastrointestinal (GI) problems, reduced food intake, and avoidant behavior[60].

Epileptic seizures and sleep processes are interconnected, inasmuch as elevated expression of one problem tends to be positively correlated with increases in the severity of the other [61]. It has been shown for instance that epileptic seizures contribute to serious sleep disturbance while, conversely, a high degree of sleep problems is followed by an increase in seizures [62,63]. Seizure activity in ASD individuals, as shown in EEG measures, have been found to be correlated with abnormal patterns of melatonin [64]. Various studies had shown that the presence of sleep problems in ASD children affected their daytime behavior [36]. At least one animal study is consistent with this generalization, demonstrating that pups born to mothers in which REM sleep had been experimentally restricted appeared to show abnormalities in their vocalization behavior [65]. This finding could be interpreted as evidence that sleep quality may contribute to the regulation of neurobehavioral processes, including social communication. It should be noted that difficulties in getting to sleep with an increased delay in sleep onset are known to further deteriorate the autistic profile [66]. It could be suggested that these sleep problems are unique to ASD children and might predict the behavioral symptoms as observed in ASD individuals (Table 2).

Causal factors behind the origin of sleep disturbances in ASD

The evidence of numerous studies now points to the conclusion that the causes of sleep complications in ASD children are multifactorial, including social factors within the family, the surrounding environment, and psychological or other biological factors [32] (Figure 2). Evidence cited to support the possible influence of psychological factors on sleep in ASD include the observations that affected children typically exhibit abnormally high levels of anxiety and depressed mood, factors which are known to interfere with the sleep process [67,68]. Children with ASD are more sensitive to sounds while asleep and this could also be a factor that disturbs the process of sleep [31]. One of the most commonly observed comorbidities in ASD children is the occurrence of GI problems and often these act to exacerbate the sleep problems in ASD [60,69]. Other studies have found that sleep complications in ASD children are related to coexisting morbidities, such as attention-deficit hyperactivity disorder (ADHD), asthma, epileptic seizures, gut-associated complications, allergic reactions and intake of drugs [32]. There is evidence that pain in the abdominal region of ASD children may induce anxiety and thus may indirectly be a cause of disturbed sleep [60].

Circadian rhythms in children begin to appear at approximately 3-4 months of age, a process that is established with the help of time cues from the environment [70]. The entrainment quality or synchronicity of the circadian rhythms is in turn responsible for regulating the children's sleep/wake cycles. The most prominent environmental cue in humans is the light/dark cycle. This signaling information reaches the suprachiasmatic nucleus through the monosynaptic retinohypothalamic tract. It has been suggested that inasmuch as ASD children have many constraints in getting sufficient exposure to natural light/dark cycles, this fact, combined with their poor

social interaction skills, could affect the entrainment process, an influence which, in turn, could promote sleep disturbances [40]. In addition, there might be other contributors, such as an injury or impairment involved in the brain regions responsible for the entrainment. Some evidence has been interpreted to suggest that in individuals who suffer from circadian clock disruption, the impairment reduces the ability to both initiate and maintain sleep [40]. It is thus worthy of note that all of these symptoms are present in children with ASD. There is evidence that children with ASD may have significant circadian disruptions [71]. It has been reported that ASD children frequently have difficulty waking up in the morning [57]. From this observation, it can be speculated that the difficulties in awakening in the morning are due to a lengthened circadian periodicity or delay in completing the process of sleep, although this point needs to be verified with clinical studies [71]. It has been speculated further that children who suffer from neurodevelopmental disorders do not possess the sense or cues which are needed to synchronize their sleep/wake episodes with that of the signaling of the environment [71,72]. It has also been postulated that the sleep disturbances that occur in ASD may be due to the associated social and behavioral deficits that have been documented to occur in this neurodevelopmental disorder.

Abnormal serotonin levels have been identified in one-fourth of the ASD children [73]. Serotonin influences the process of sleep at the level of regions, such as the brainstem, that are involved in the regulation of REM sleep as well as wakefulness [74]. Many studies have shown that both the synthesis and concentration of serotonin are abnormal in ASD children [73], findings which are relevant inasmuch as insufficient serotonin levels may have additionally affected the neurodevelopmental processes of the brain [75]. Further, deficits in serotonin synthesis or distribution could

be a possible contributor to the sleep disturbances that are seen in ASD children. It is well known that serotonin synthesis is regulated by the circadian clock [76] and abnormalities in serotonin could be caused by the disruption of the circadian clock.

Melatonin, a major neurohormone involved in circadian clock activities, is a factor responsible for the regulation and duration of the sleep process [77]. The phase and amplitude of melatonin secretion in ASD children are abnormally reduced, both during the day and at nighttime [64,78-80]. It has been suggested that the unusual structural and functional modifications that are seen in the sleep profiles of ASD children could be caused by abnormalities in melatonin synthesis. Furthermore, the fact that disturbances in phase alignment and melatonin synthesis [64,78-80] are known to occur in ASD suggests that affected children may additionally have disruptions in the functioning of their circadian clocks. Furthermore, it has been reported that abnormalities in melatonin synthesizing enzymes occur in children with ASD [81]. It is thus possible that misalignment of the circadian clock and impairment of its regulatory action could account for the sleep difficulties experienced by ASD children [71]. Taken together, these findings point to the possibility that therapeutic adjustments of melatonin and/or serotonin deficiencies might represent a means for treating the sleep disorders experienced by ASD children.

Treatment of sleep problems in ASD

Diagnosis of sleep disorders: The first step for developing an understanding of what sleep difficulties the ASD child is experiencing is to obtain the child's comprehensive sleep history [82]. Once this is obtained the objective of therapy is to develop a plan for a behavioral and/or medical intervention. Obtaining this information can be accomplished in various ways, e.g., by asking parents to provide a sleep report of the

child, monitoring the child's sleep by actigraphy, or by measuring the quality and duration of sleep in more detail through the use of overnight testing (polysomnography). This multi-axial assessment approach can provide a thorough basis for carrying out treatment of the sleep disorders that are present in ASD individuals [37,83].

Behavioral medicine: The treatment of sleep disorders often includes non-pharmacological approaches, including prescriptions for sleep hygiene practices and behavioral activities [84-87]. Parents and caretakers should be made aware of the importance of sleep hygiene practices, and, further, should be counseled that parent or caregiver behavior can enhance the success of any recommended program. As a first step in treating sleep behavior problems in ASD, basic principles of proper sleep hygiene practice should be imparted to the parents, and, further, it should be urged that they themselves should adhere to these principles to set an example for their children [85].

Suggestions for sleep hygiene practice: Sleep hygiene involves the principles of behavioral strategies in bringing a good quality of sleep along with appropriate day time and nighttime practices. The main objective is to ensure that the child and parents follow this principle as a regular routine. Specific recommended measures for ensuring that children get the proper sleep quality should include, e.g., setting a regular bedtime schedule, establishing an environment that is conducive to sleep, and not allowing children to do any activity which would hinder the sleep process [88]. The practice starts with having a calm, cool, dark and soothing environment as a sleeping place. Bedtime practices and an appropriate sleep schedule provide clues about sleep time and aid in the mental preparation of the ASD children [89]. Sleep hygiene

principles function by single or groups of activities involving the entrainment of the circadian clock, decreasing anxiety, minimizing the effects of environmental sensitivity, and promoting relaxation of the individual [89].

A few hours before their bedtime, ASD children should be discouraged or prevented from taking stimulating agents such as caffeine and sleep-disrupting food products.

Parents can identify the things which make a wind-down routine of the children and assist in a smooth transition in getting sleep [90]. Many different procedures exist for settling down the children, for instance, having a warm bath before few hours of bedtime, although in some particularly sensitive children this may, in fact, have an undesired or stimulating effect [91]. Lullaby and soft music could be also used as a relaxing option as well as sleep inducer for ASD children [91, 92]. Routines should be individualized for each child, inasmuch as some activities, such as video games or electronic devices, may have divergent effects in different individuals, and may actually be relaxing for some children [89,91]. The brightness of environmental light or blue light should be decreased and appropriate background light should be used to reduce the suppressant effect on melatonin synthesis. Steps should be taken to ensure adequate exposure to sunlight during the morning and the daytime, and avoidance of bright light during nighttime. This will assist in the proper entrainment of the circadian clock, resulting in reductions in sleep onset time and thus an enhanced quality of sleep.

Physical exercise and increases in total sleep duration have been shown to delay REM sleep onset, in addition, these behavioral changes have been shown to enhance SWS and to decrease REM sleep [93]. High-intensity exercise performed 3-4 h before bedtime has been found to enhance SWS and to improve sleep efficiency in school-

aged children [94]. Physical activity patterns have been shown to correlate with the sleep pattern of ASD children, and, further, intense exercise substantially reduced difficulties in sleep onset and quality [95]. In a study of the effect of physical exercise on a group of ten ASD children, it was found that sleep efficiency was enhanced, the timing of sleep onset was reduced, and motor skills were also improved [96]. While doing exercise, care should be taken since high-intensity exercise for long periods of time (more than 2 h) could disturb the process of sleep [93]. Also, other criteria including health status and timing of the exercise should be considered. Physical activity should be carried out at least 4-6 h before bedtime for the best promotion of optimal sleep quality [97]. Also, the results would be better if it is done in the morning and in broad daylight. Various studies have shown that personal characteristics, including age, gender, mood state, and body condition, can influence the benefits of exercise for improving sleep quality, and should be taken into consideration before recommending exercise as a behavioral intervention [93]. In general, however, the difficulties of settling in bed and nighttime arousals are minimized following strategically planned exercise [38]. Positive bedtime practices and sleep strategies have been found to bring more satisfaction to parents by reducing the stress of getting children to conform to a bedtime schedule [98].

Treatment of OSA in ASD children: Tonsillectomy, adenotonsillectomy and continuous positive airway pressure (CPAP) are different lines of treatment for OSA. In one study, adenotonsillectomy in a 5-year-old of ASD child who had OSA was found to enhance the child's social communication, sleep, and attention, and additionally reduced repetitive stereotyped behavior and hypersensitivity [99]. In another study, adenotonsillectomy treatment in ASD children with OSA improved sleep quality which

further reduced the severity of behavioral problems [44]. Adenotonsillectomy in ASD children can stimulate anxiety-related problems, but these can be dealt with by following proper guidelines and procedures before the treatment [100].

Melatonin treatment: In a preliminary study investigators administered 5 mg of melatonin medication to a group of seven ASD children for four weeks and found that the treatment was associated with beneficial reductions in sleep problems, including reduced sleep latency, a reduction in the number of nighttime awakenings, and improved the sleep quality in the treatment group [101]. The same research study additionally found that melatonin reduced behavioral symptom severity and aided in the management of ASD children. In an investigation of 25 ASD children, the effects of 3 mg of melatonin which was given to ASD children at 20.00 h, was studied and measured at 1, 3 and 6 months. The administration of melatonin was found to enhance sleep quality, whereas withdrawal of melatonin treatment triggered the reappearance of ASD symptoms to their original levels [102]. In a group of 17 ASD children, a study investigated the effect of melatonin on dysomnias. ASD children were given up to 10 mg of melatonin for three months and melatonin enhanced sleep latency (47 min) and total sleep length by 52 min [103]. Melatonin administration did not reduce the awakenings at night time and there were no side effects.

Administration of melatonin was tested in a group of children identified with Asperger's syndrome (ASPSYN) (n=15, age range=6-17 years) [104]. A 3mg/day dose of melatonin was given for two weeks and observations were done before the therapy and during the administration and 21 days after the withdrawal of melatonin administration. Actigraphy recording of the children showed that sleep onset was reduced by around 19 min and difficulties in behavior were reduced. When melatonin

treatment was withdrawn however, the pre-treatment levels of sleep and behavioral problems reoccurred in the ASPSYN children [104]. In a study of the efficacy of melatonin in major depressive disorder (MDD), 5 mg of slow-release melatonin was administered to 10 patients for four weeks along with 20 mg fluoxetine, a known SSRI compound. This treatment enhanced both the sleep quality and duration of sleep, but no significant effect was observed on the depressive mood [105]. In another study, 6 mg of slow-release melatonin was given as treatment for MDD for four weeks at bedtime. Objective and subjective measures of sleep showed that the MDD patients exhibited a reduction in sleep difficulties and that their mood was also improved, indicating that the administration of exogenous melatonin may be an effective treatment for depressed mood [106]. The Standards of Practice Committee of the American Academy of Sleep Medicine has recommended melatonin as a therapeutic option for the treatment of REM sleep behavior disorder (RBD) since it has no adverse side effects [107]. With 3-9 mg dose per day, melatonin was found to successfully decrease sleep problems reported in a group of RBD patients [108].

The demonstrated effectiveness of melatonin therapy supports the inference that circadian clock disruption may be closely linked to elevated ASD symptom expression, and, further, that re-establishment of normal circadian rhythmicity may represent an important means for both long- and short-term treatment of symptom severity in ASD. It was noted in a study of controlled-release melatonin in children with ASD that an additional secondary benefit of the treatment was that the sleep quality and mood of the parents also improved as the therapy progressed [102]. Many differences exist in the dosage, time duration and improvements in specific sleep problems following melatonin therapy. The precise effects of exogenous melatonin administration on

sleep duration, sleep quality, and nocturnal awakenings remain under researched. All these parameters warrant long term studies of melatonin as a treatment strategy for ASD children. It has been suggested that prior to the application of melatonin therapy, the timing and dosage of its administration as well as seasonal fluctuations should be noted, since these may influence the therapy's effectiveness. The timing of melatonin administration is critical since it can advance or delay the phase of the sleep, thus underscoring the need for careful planning of the administration schedule. It has been noted that if melatonin is administered early in the evening, i.e., around 21.00 h, the phase of the circadian clock might thereby be advanced, causing early awakenings, and associated reductions in sleep quality and duration. Inasmuch as melatonin therapy comprehensively influences the sleep process, from initiating the onset of sleep and subsequent sleep maintenance throughout the night, as well as having beneficial effects for mood disorders, it has attracted considerable research interest for treatment of these problems in adults. Preliminary studies have now shown that melatonin treatment may be equally valuable for treating insomnia in children with neurodevelopmental disabilities [109-111].

Melatonin agonists such as agomelatine [112] and ramelteon [113] are used as options for the treatment of sleep in ASD children. A three-month administration of agomelatine (25 mg/day) in ASD children significantly lengthened the total duration of their sleep and strengthened the phase and the stability of sleep [112]. Ramelteon, a melatonin agonist (dose- 2-8 mg/day) that was used for the treatment of three ASD children, was found to decrease sleep problems such as insomnia with parallel improvements being shown in behavior [113]. Pediatric prolonged-release melatonin (PedPRM) is an innovative drug which is suggested for children with

neurodevelopmental disabilities and those have problems in swallowing. PedPRM has been formulated in such a way that it would release melatonin slowly as similar to that of melatonin secretion in individuals. In a randomized, double-blind, placebo-controlled, parallel-group multicenter study, the effects of administering PedPRM for up to 52 weeks were investigated in a pediatric group. The study sample consisted of children and adolescents with ASD and with or without ADHD comorbidity, who had not shown improvement after standard sleep behavioral interventions had been attempted [114,115]. PedPRM (2/10 mg) was effective and it enhanced the total sleep duration, maintained un-perturbed sleep with reduced sleep latency. It could be suggested that the administration of melatonin and behavioral interventions are efficient strategies for treating sleep based problems in ASD children [41].

Future approaches

The importance of sleep for sustaining critical biological and psychological processes, including learning and memory, social communication, neural development, neuroendocrine synthesis, and regulation is well documented. The abnormal and pronounced sleep behavior patterns exhibited by ASD patients represent an obvious target for therapy. There continues to remain a lack of clarity concerning how sleep disturbances could impact the social and cognitive deficits shown by ASD patients [22,48]. However, the utility of using polysomnography and actigraphy [82] as an adjunctive test for diagnosing mood disorders suggests that this option may also prove useful for understanding the possible determinants of ASD.

Stakeholders such as the physicians, caretakers, parents and paramedical professionals need to be aware of the severity of sleep problems and their association with ASD. More importantly, they should examine ASD children for sleep difficulties as

a routine measure. An increasing number of studies have noted an association between ASD symptoms and sleep disorders in ASD children, thus emphasizing the importance of including the assessment of sleep problems in developing treatment plans for this patient group. The issue of how aggressive behavior is influenced by sleep disturbances needs to be investigated along with the role of other emotional factors [116]. There are many studies showing associations between ASD symptoms and the disruption of circadian markers, including cortisol, melatonin and the sleep/wake cycle. The close association among sleep difficulties, disturbed behavior, and abnormal brain and nervous system development that has been repeatedly observed in ASD children is unusual to the point of being unique, and thus merits the attention of long-term studies [38]. Among the various sleep difficulties that exist in ASD, sleep-disordered breathing has received less attention and should be investigated further [45].

Although the clinical significance of sleep has been established, the strategic use of sleep therapies is generally absent in medical textbooks and is typically not viewed as a therapeutic option for treating abnormal behavior in ASD [117]. It has been suggested that the neglect of sleep disorders in clinical medicine limits the range of treatment options for dealing with complex neurological or developmental problems, and thus may impede the recovery of many affected patients. Low-cost behavioral interventions may represent a potential means for expanding the range of treatment options for ASD. One area that has shown promise for treating adults with sleep disorders is the use of environmental manipulations for influencing circadian timing mechanisms. It is thus suggested that research be undertaken to investigate

the effect of the strengthening of entrainment as well as social zeitgebers in the treatment of ASD individuals, both children and adults.

Many sleep-related studies remain preliminary [39]. More detailed and extensive studies are required to determine what influence sleep quality may have on social communication processes in ASD. Moreover, the current emphasis given to studies of associational relationships between sleep disorders and abnormal behaviors is necessary but not sufficient for resolving questions of causality. A hypothesis which needs to be studied in animal models is whether experimentally induced sleep disruption may actually cause the worsening of ASD symptoms. These kinds of studies would improve our understanding of the relationship between sleep and symptoms of ASD and further, could be used in the treatment of ASD. Furthermore, elucidating the significance of sleep would alert clinicians, caretakers and family members to the importance of this issue, and may thus lead to exploration, at the very least, of basic therapeutic strategies such as improving sleep hygiene practices in this patient group. Most importantly, efforts should be undertaken to make parents aware of the adverse impact that poor sleep quality and reduced duration of sleep have on daytime behavior in ASD children. In addition, earlier identification of sleep perturbations in ASD children could potentially prevent the development of neurobehavioral difficulties in their later years.

More research is needed to study the conditions which are comorbid with ASD [118]. In view of the findings of surveys showing that the worldwide burden of ASD is growing and, further, because efforts to treat ASD medically have enjoyed only limited success, it is essential that every therapy which may potentially be of benefit for this neurodevelopmental disorder should be considered. The finding of alterations in

melatonin synthesizing enzymes in ASD children with sleep problems must be followed up intensively to determine a) how close the association is with the sleep disorders as well as b) whether that abnormality is predictive of a positive response to melatonin treatment. Such a proven relationship would establish for the first time personalized treatment for this combined disorder.

Conclusion

An understanding of the role of sleep in the development of ASD and the investigation of sleep-related therapies offers the potential for developing treatment strategies for ASD children. The available evidence strongly suggests that improving the sleep quality of ASD children would almost certainly have beneficial effects on their behavior and mood symptoms, or, at the very least, a reduction in sleep difficulties. A reduction in the sleep disturbances in ASD children would also positively influence the sleep of ASD children's parents, and thus further enhance their own personal and psychological health. The possible impact of improvements in the sleep quality of ASD children on their neurological, psychological, and social development continues to remain poorly studied and urgently merits further investigation from a cross-disciplinary perspective.

Many factors act as inducing agents for the development of sleep problems in children with neurodevelopmental disorders. Among these "triggering factors" are infections as well as the disruptive effects of stressful environments, anxiety, emotional stress, and circadian clock abnormalities. Similarly, the issue of whether sleep complications might be a predictor of the disorder needs to be explored further in ASD children. It is evident that future research efforts should focus on understanding and modifying the factors which contribute to sleep problems in ASD, an area where research work is still preliminary. The available findings strongly support the inference

that improving the sleep quality of ASD children has the potential to improve their quality of life as well as that of their family members and caretakers.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests and disclosure statements

All authors report no conflict of interest. All authors have read the journal's policy and would like to report the following statement: SRP is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declared no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, or any other personal interest of any kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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Author Contributions

Conceived and designed the manuscript: RK, GMB, SRP; Wrote the paper: RK, VS; Critically reviewed the manuscript: RK, DPC, GMB, DWS, SRP. All authors met the ICMJE criteria for authorship. All authors approved the final version of the submitted manuscript.

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Table 1. Autism spectrum disorder has been diagnosed based on two core symptoms as suggested by DSM 5, 2013

<p>1. Individuals exhibit persistent behavioral deficits in social communication and socialization processes. This has been observed in various behavioral activities of children including</p> <p>i). Impairment in social-emotional reciprocity – cannot initiate and maintain a conversation, non-sharing of their interest and social skills</p> <p>ii). Non-verbal communication is poor and they have difficulties in forming words and sentences, cannot maintain eye contact and devoid of facial expressions</p>	<p>2. Individuals show unusual repetitive or stereotyped motor activities</p> <p>i) Using repeated things and words – Making a line with playing objects, echolalia, speaking irrelevant and meaningless sentences</p> <p>ii). Rely on the sameness and highly rigid to adapt to normal routine activities –Small changes can induce extreme difficulties, unchangeable pondering processes and sticking to take the same food for eating</p> <p>iii). Concentrating on things, which are not necessary or unusual – having strong bond</p>
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iii). Difficulties in forming and fathoming relationships between people and they do not have enthusiasm in having friends and lack interest with their equal aged children	with unnecessary stuff and display extremely limited, interests iv). Oversensitivity and intense reactivity to the surrounding environment
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Table 2. Prevalence and the intensity of sleep difficulties determine the behavioral problems in ASD

Sleep difficulties reported in ASD children	Behavioral problems associated with the sleep difficulties in ASD children
Insomnia – Difficulties in getting sleep and having sleep onset for long time, complications in settling down in the bed, sleepiness during day time, poor sleep quality, early arousal, night time awakenings	High prevalence of behavioral problems [46], predicted overall severity of ASD symptoms [9,55], visual perception difficulties [56] and decreased appetite [56]
Parasomnia - Nightmares, sleepwalking, restless leg syndrome, REM sleep disorders, enuresis	Predicted the prevalence of developmental problems [44], GI complications [59], reduced food intake [59] and poor social skills [59]
Sleep disordered breathing, OSA – Difficulties in breathing during sleep and in OSA, the airway is partially or completely blocked by throat muscles causing sleep apnea	High occurrence of stereotyped behavior[44], social impairment [44] and severity of ASD [44]
Poor sleep quality having increased sleep disturbances due to disruption of circadian rhythm such as delayed sleep onset, changes in sleep architecture, short sleep duration, bed time resistance and arousals at early morning	Increased social impairment [36,54,57], heightened sensitivity to environment [57], excessive attention seeking behavior [58], increased aggressiveness [57], affective problems [36], anxiety-related problems [57], hyperactivity [57], mood variation [57], repetitive behavior [57,58], epileptic seizures [61] and daytime behavior [35]

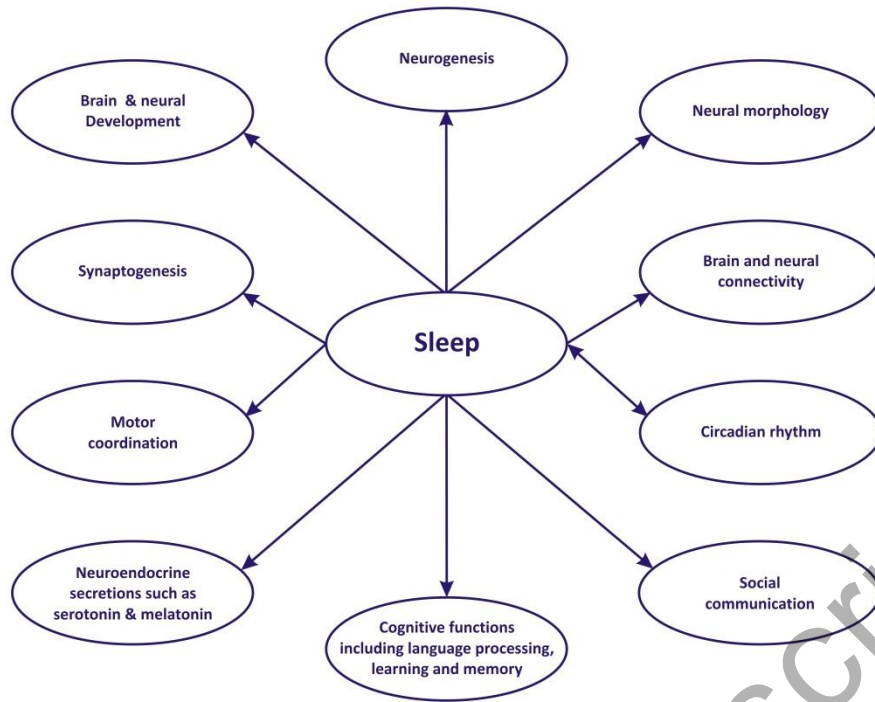


Figure 1. Sleep and its correlation with neural development and processes

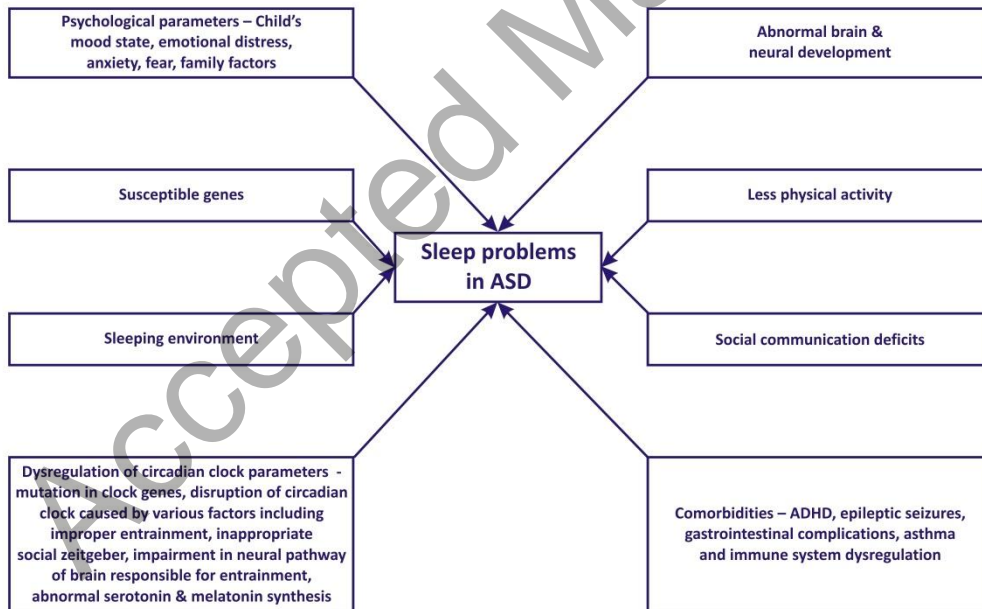


Figure 2. List of biological, social, psychological, and environmental parameters causing sleep problems in ASD.