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Autism spectrum disorder and sleep problems: A critical review of literature

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Abstract
Objective: Autism spectrum disorder can range from very mild to severe. The aim of this narrative revision is to discuss about the sleep problems in children with autism spectrum disorder.
Data source: This narrative review considered publications between 2014 and 2018, related to autism and sleep disorders.
Data synthesis: Several studies consider that treating sleep problems on autism spectrum disorder has great potential to improve daytime behavior and family functioning in this vulnerable population. Families of children with autism spectrum disorder should be encouraged to regulate and monitor the timing and content of television and video game use, whether or not such devices are physically present in the child's bedroom. There were identified risk factors for sleep problems in children with autism spectrum disorder such as stereotypies, self-mutilation, hyperactivity, and social withdrawal.
Results: Findings indicated that individuals with autism spectrum disorder presented sleep problems including low sleep efficiency, prolonged sleep latency and increased number and length of night awakenings, together with daily sedentary behavior, and increased nocturnal activity.
Conclusions: Considering that there is an important relationship between sleep problems and autism spectrum disorder, we strongly believe that the desirable path in the fight against negative behaviors/symptoms and the repercussions of this pandemic on health in general, could be the creation of accessible and effective therapeutic strategies. simple, aiming at the management and control of these symptoms, especially among children with autism spectrum disorder.

Keywords: Autism spectrum disorder, sleep disorders, behavioral symptoms, quality of life

Introduction

The autism spectrum disorder (ASD) is a set of neurodevelopmental disorders characterized by a deficit in social behaviors and nonverbal interactions such as (i) reduced eye contact, (ii) facial expression, and (iii) body gestures in the first 3 years of life. It is not a single disorder, and it is broadly considered to be a multi-factorial disorder resulting from genetic and non-genetic risk factors and their interaction [1].

Lord et al., 2018 [2] reported that, along of the time, ASD has gone from a narrowly defined, rare disorder of childhood onset to a well-publicized, advocated, and researched lifelong condition, recognized as fairly common and very heterogeneous. The description of the core features of ASD as being social communication deficits and repetitive and unusual sensory–motor behaviors has not changed substantially since its original delineation. However, ASD is now seen as a spectrum that can range from very mild to severe. Nevertheless, many (but not all) individuals with ASD require lifelong support.

The sleep problems (SPs) are common in children with ASD, and a poor sleep exacerbates a problematic daytime behavior. However, such relationships have received extraordinarily little attention in research and clinical practice. Moreover, intervention recommendations to aid in managing challenging behaviors in ASD, in general, fail to mention conveniently the sleep disorder. Furthermore, limited attention is given to children with low-functioning autism, those individuals who often experience the most severe sleep disruption and behavioral problems [3]. Mutluer *et al*, 2016 [4] consider that SPs are common and difficult to manage in children with ASD, and a major adverse impact of SP is that they exacerbate behavioral impairment. Shui *et al*., 2018 [5] reported that SPs in children with ASD have been well-established.

Moreover, Ballester *et al*., 2018 [6] described that SPs are recognized as a common comorbid condition in ASD and can influence core autism symptoms and mental and physical health. SPs can be lifelong and have been reported that adults on the autistic spectrum with and without intellectual disability (ID) present SPs, such as longer sleep latency, frequent night awakenings, and circadian rhythm sleep-wake disorders. Verhoeff *et al*., 2018 [7] also described that SP is prevalent in children with ASD. The temporal nature of the association between SPs and ASD is unclear because longitudinal studies are lacking.

Grau and Plener, 2018 [8] pointed out that SP are a relevant symptom in childhood and adolescence with a prevalence of approximately 20%. Because of the reduced psychosocial functioning and the burden of suffering associated with insomnia, effective treatment strategies are needed. If interventions such as the implementation of an adequate sleep hygiene and other non-drug treatment approaches are not sufficient, pharmacotherapeutic treatment is often considered.

Methodology

The purpose of this work was to present a critical review of the literature, addressing the factors that contribute to SPs presented by individuals with ASD. In this scenario, it was also possible to consider relevant aspects contextualizing the pandemic caused by COVID-19, which, according to the literature, has been causing, among other damages, an alteration in the quality of sleep.

As a search strategy, it was determined for the inclusion of this review, original articles that addressed the ASD and SPs, between the years 2014 and 2019. Reviews or articles that were not available in the full text version were excluded.

Autism and sleep problems

Cohen et al., 2014 [3] described the nature of SP in ASD and highlights the complexities of sleep disruption in individuals with low-functioning autism. It is proposed that profiling ASD children based on the nature of their sleep disruption might help to understand symptom and behavioral profiles (or vice versa) and therefore lead to better-targeted interventions. It was concluded with a discussion of the limitations of current knowledge and proposes areas that are important for future research. Treating disordered sleep in ASD has great potential to improve daytime behavior and family functioning in this vulnerable population.

Zuckerman *et al*., 2014 [9] have suggested that ASD and childhood obesity (OBY) are rising public health concerns. They evaluated the prevalence of overweight (OWT) and OBY in a sample of 376 Oregon children with ASD and assessed correlation of OWT and OBY in this sample. They used descriptive statistics, bivariate, and focused multivariate analyses to determine whether socio-demographic characteristics, ASD symptoms, ASD cognitive and adaptive functioning, behavioral problems, and treatments for ASD were associated with OWT and OBY in ASD. Overall, 18.1% of children met criteria for OWT and 17.0% met criteria for OBY. OBY was associated with SPs, melatonin use, and affective problems. It was concluded that interventions that consider unique needs of children with ASD may hold promise for improving weight status among children with ASD.

Valicenti-McDermott *et al*., 2015 [10] studied the level of parental stress in families of children with ASD and other developmental disabilities and its association with child comorbid symptoms in an ethnically diverse population, in a cross-sectional study with structured interview. The sample included 50 families of children with ASD and 50 families of children with other developmental disabilities, matched by age/gender. Interview included Parenting Stress Index-Short Form, Gastrointestinal Questionnaire, Child Sleep Habits Questionnaire, and Aberrant Behavior Checklist. Parental stress was significantly higher for the ASD group and for non-Hispanic and US-born mothers. In both study groups, parental stress was related to child irritability. Parental stress was also related to gastrointestinal problems in the ASD group and to SPs in the developmental disabilities group. The authors concluded that targeting child irritability may be particularly important in reducing parental stress for families of children with ASD and other developmental disabilities.

Mazurek *et al*., 2016 [11] proposed a study to try to better understand the use of screen-based media at bedtime among children with ASD. The work specifically examined whether the presence of media devices in the child's bedroom, the use of media as part of the bedtime routine, and exposure to media with violent content just before bedtime were associated with sleep difficulties. Parents of 101 children with ASD completed questionnaires assessing their children's sleep habits, bedroom media access (including television, video game devices, and computers), and patterns of nighttime media use (including timing of media exposure and violent media content). Children with ASD who used media as part of the bedtime routine showed significantly greater sleep onset latency than those who did not (39.8 vs 16.0 minutes). Similarly, children who were exposed to media with violent content within the 30-minute period before bedtime experienced significantly greater sleep onset delays and shorter overall sleep duration. In contrast, the mere presence of bedroom media was not associated with either sleep onset latency or sleep duration. It was concluded that these findings indicate that incorporating television and video games into the bedtime routine is associated with sleep onset difficulties among children with ASD. Exposure to violent media before bed is also associated with poor sleep. Families of children with ASD should be encouraged to regulate and monitor the timing and content of television and video game use, whether or not such devices are physically present in the child's bedroom.

Malow *et al*., 2016 [12] pointed out that SPs are common in children with ASD, with wide-ranging effects on the child's daytime behavior. They reviewed data within their Autism Speaks Autism Treatment Network Registry to determine the prevalence of sleep difficulties and patterns of medication use. Data from 1518 children ages 4 to 10 years were analyzed to determine the number of children documented to have sleep difficulties by parent-completed questionnaires and clinician-completed forms and how these findings related to the use of sleep medications. The Children's Sleep Habits Questionnaire total score was ≥41 (associated with clinically significant SPs in past research) in 71% of children. The prevalence of sleep diagnoses was less frequent (30% of children aged 4-10 years; $P < .0001$). Medications for sleep were prescribed in 46% of 4- to 10-year-olds given a sleep diagnosis. The most common medication used for sleep was melatonin followed by α-agonists, with a variety of other medications taken for sleep (anticonvulsants, antidepressants, atypical antipsychotics, and benzodiazepines). Children taking medications for sleep had

worse daytime behavior and pediatric quality of life than children not taking sleep medications. It was concluded that parent concerns about sleep may not be reflected in the information gathered during a clinic visit, supporting the need to develop screening practice pathways for sleep in ASD disorders. Furthermore, many medications taken for sleep have adverse effects, supporting the need for evidence-based interventions in this population.

Mutluer *et al*., 2016 [4] to assess SPs and possible behavioral risk factors in detail, they compared sleep habits of children with ASD, with healthy children. The relationship between SPs and concomitant behavioral problems such as repetitive behaviors, hyperactivity, and social withdrawal were also examined. Hundred and seventeen children and adolescents including 64 with the diagnosis of ASD and 53 healthy subjects were enrolled in the study. Diagnostic Interview for ASD was performed according to DSM-IV-TR. Socio-demographical data form and childhood autism rating scale were filled by researchers. Aberrant behavior checklist (ABC), child behavior checklist and pediatric sleep questionnaire (PSQ) were completed by the parents of the children. Children with ASD had higher frequency of SPs, snoring, breathing problems, behavioral problems compared with healthy children (for all parameters; $P < 0.001$). A positive correlation was identified between the total score of PSQ and the total score of ABC ($P < 0.05$, Spearman correlation coefficient: 0.347). Sleep latency was prolonged in children with ASD compared with healthy subjects ($P < 0.001$). In accordance with the current literature, children with ASD were subject to SPs significantly more than the control group. Identified risk factors for SPs in ASD children were behavioral factors such as stereotypies, self-mutilation, hyperactivity, and social withdrawal.

Frazier *et al*., 2017 [13], in a preliminary study, have investigated the tolerability and efficacy of a novel mattress technology-the Sound-To-Sleep (STS) system-in the treatment of SPs in children with autism. After screening, 45 children, ages 2.5 to 12.9 years, were randomized to order of mattress technology use (On-Off vs. Off-On). Treatment conditions (On vs. Off) lasted two weeks with immediate crossover. Tolerability, including study discontinuation and parent-report of mattress tolerance and ease of use, was tracked throughout the study. Efficacy assessments were obtained at baseline, prior to crossover, and end of study and included measures of autism traits, other psychopathology symptoms, sensory abnormalities, communication difficulties, quality of life, sleep diary parameters, and single-blinded actigraphy-derived sleep parameters. Statistical analyses evaluated differences in tolerability and efficacy when the STS system was on versus off. STS system use was well tolerated (n = 2, 4.4% dropout) and resulted in parent-reported sleep quality improvements (STS off mean = 4.3, 95% CI = 4.05-4.54 vs. on mean = 4.9, 95%CI = 4.67-5.14). The technology was described by parents as very easy to use and child tolerance was rated as good. Parent-diary outcomes indicated improvements in falling asleep and reduced daytime challenging behavior. Actigraphy-derived sleep parameters indicated improved sleep duration and sleep efficiency. Improvements in child and family quality of life were identified on parent questionnaires. The authors have concluded that future large sample phase 2 trial of the STS system is warranted and would benefit from extended study duration, an objective primary efficacy outcome, and careful attention to methodological issues that promote compliance with the intervention and study procedures.

Shui *et al*., 2018 [5] developed a model to predict SPs in children with ASD. A sample of children in the Autism Speaks-Autism Treatment Network (ATN) registry without parent-reported SPs at baseline and with SPs (yes/no) data at first annual follow up was randomly split into training ($n = 527$) and test ($n = 518$) samples. Model predictors were selected using the training sample, and a threshold for classifying children at risk was determined. Comparison of the predicted and true SPs status of the test sample yielded model performance measures. In a multivariable model aggressive behavior among children with no sleep problems reported at baseline was associated with having more SPs at the first annual follow-up visit. This model performed in the test sample with high sensitivity and accurate prediction of low risk. It was concluded that among children with ASD aggressive behavior independently predicts SPs. The model's high sensitivity for identifying children at risk and its accurate prediction of low risk can help with treatment and prevention of SPs. It is suggested that further data collection may provide better prediction through methods requiring larger samples.

Ballester *et al*., 2018 [6] have conducted a prospective, objective sleep study in 41 adults with ASD (33±6 years old) and ID and 51 typically developing adults (33±5 years old) using ambulatory circadian monitoring (ACM) recording wrist temperature, motor activity, body position, sleep, and light intensity. The findings indicated that individuals with ASD presented SPs including low sleep efficiency, prolonged sleep latency and increased number and length of night awakenings, together with daily sedentary behavior, and increased nocturnal activity. Furthermore, indications of an advanced sleep-wake phase disorder were found in these autistic adults. Examining sleep and markers of the circadian system showed significant differences between adults with ASD and ID and an age-matched, healthy adult population. The sleep disturbances described for this sample of adults with ASD and ID are similar to those of already described for adults with ASD without ID; their relationship with intellectual ability should be further studied. Improving knowledge of sleep patterns in ASD adults with ID might help to designed targeted interventions to improve their functioning and reduce family stress.

Gittins *et al*., 2018 [14] have reported that Sturge-Weber syndrome (SWS) is a neurocutaneous disorder characterized by the combination of a facial naevus flammeus and pial angioma, often associated with learning difficulties and/or epilepsy. The authors reported on the neuropsychological characteristics of a cohort of 92 children with SWS seen at a national referral center between 2002 and 2015. Almost a quarter (24%) had a diagnosis of ASD, with 45% overall having evidence of social communication difficulties (SCD). ASD was more commonly seen in those individuals with bilateral angioma ($p = 0.021$). Significant behavioral difficulties were reported in 50% while 26% had difficulties with sleep. Difficulties with social communication, behavior, and sleep were closely associated with one another. They were not, however, significantly associated with markers of epilepsy severity and were noted to occur even in children without epilepsy. The prevalence of ASD/SCD, sleep difficulties, and behavioral disorders seen in SWS is high and reflects the complex needs of this group.

Verhoeff *et al*., 2018 [7] have tried to clarify whether SPs precede and worsen autistic traits and ASD or occur because

of the disorder. Repeated sleep measures were available at 1.5, 3, 6, and 9 years of age in 5151 children participating in the Generation R Study, a large prospective birth cohort in the Netherlands. Autistic traits were determined with the Pervasive Developmental Problems score (PDP) of the Child Behavior Checklist (CBCL) at 1.5 and 3 years and the Social Responsiveness Scale (SRS) at 6 years. This cohort included 81 children diagnosed with ASD. SPs in early childhood were prospectively associated with a higher SRS score, but not when correcting for baseline PDP score. By contrast, a higher SRS score and an ASD diagnosis were associated with more SPs at later ages, even when adjusting for baseline SPs. Likewise, a trajectory of increasing SPs was associated with ASD. It was concluded that SPs and ASD are not bi directionally associated. SPs do not precede and worsen autistic behavior but rather co-occur with autistic traits in early childhood. Over time, children with ASD have an increase in SPs, whereas typically developing children have a decrease in SPs.

Discussion

In the current narrative revision, several authors have described the relation between SPs and ASD. Cohen *et al*., 2014 [3] have considered that treating disordered sleep in ASD has great potential to improve daytime behavior and family functioning in this vulnerable population. Valicenti-McDermott *et al*., 2015 [10] have verified that parental stress was also related to gastrointestinal problems in the ASD group and to SPs in the developmental disabilities group. Mutluer *et al*., 2016 [4] reported that, in accordance with the current literature, children with ASD were subject to SPs significantly more than the control group. Shui *et al*., 2018 [5] have reported that among children with ASD aggressive behavior independently predicts SPs.

The model's high sensitivity for identifying children at risk and its accurate prediction of low risk can help with treatment and prevention of SPs. Ballester *et al*., 2018 [6] have verified that individuals with ASD presented SPs including low sleep efficiency, prolonged sleep latency and increased number and length of night awakenings, together with daily sedentary behavior, and increased nocturnal activity. Nevertheless, Mazurek *et al*., 2016 [11] have concluded that that incorporating television and video games into the bedtime routine is associated with sleep onset difficulties among children with ASD. Exposure to violent media before bed is also associated with poor sleep. Malow *et al*., 2016 [12] have pointed out that SPs are common in children with ASD, with wide-ranging effects on the child's daytime behavior. Furthermore, many medications taken for sleep have adverse effects, supporting the need for evidence-based interventions in this population. Verhoeff *et al*., 2018 [7] have concluded that SPs and ASD are not directionally associated. SPs do not precede and worsen autistic behavior but rather co-occur with autistic traits in early childhood. Over time, children with ASD have an increase in SPs, whereas typically developing children have a decrease in SPs.

In a review, Ameis *et al*., 2018 [15] have evaluated the treatment evidence for six common symptom targets in children/adolescents with ASD and provides a resource to facilitate application of the evidence to clinical practice. A systematic search identified randomized controlled trials (RCTs) and high-quality systematic reviews published between 2007 and 2016, focused on: social interaction/communication impairment, stereotypic/repetitive behaviors, irritability/agitation, attention-deficit/hyperactivity disorder symptoms, mood or anxiety symptoms, and SPs. The authors then completed qualitative evaluation of high-quality systematic reviews/meta-analyses and quantitative evaluation of recently published RCTs not covered by prior comprehensive systematic reviews. It was found that published RCTs focused on social interaction and communication impairment (trials = 32) using psychosocial interventions. Interventions for irritability/agitation (trials = 16) were mainly pharmacological. Few RCTs focused on other symptom targets (trials = 2-5/target). Integration of these results with our qualitative review indicated that few established treatment modalities exist, and available evidence is limited by small studies with high risk of bias. It was concluded that given the current evidence-base, treatment targets must be clearly defined, and a systematic approach to intervention trials in children/adolescents with ASD must be undertaken with careful consideration of the limitations of safety/efficacy data.

Grau and Plener, 2018 [8] published a literature overview on the use of different substance classes in hypnotic indications. The use of melatonin in children and adolescents with ASD has been well studied and is associated with a positive effect on sleep in this patient group. To date, there is little evidence regarding the efficacy and tolerability of other medication in primary insomnia or sleep disorders in the context of other psychiatric disorders in minors. For this reason, non-drug treatment strategies are preferred, and pharmacotherapy is only to be considered secondarily after critical examination.

Gagnon and Godbout, 2018 [16] in a revision, have reported that melatonin is used to treat SPs associated with (ASD); and that there are growing evidence that melatonin could influence other symptoms than sleep, such as anxiety, depression, pain, and gastrointestinal dysfunctions. Interestingly, these symptoms frequently are found as comorbid conditions in individuals with ASD. In the revision, it was aimed to highlight the potential effect of melatonin on these symptoms. Animal and human studies show that melatonin reduces anxiety. Regarding the effect of melatonin on pain, animal studies are promising, but results remain heterogeneous in humans. Both animal and human studies have found that melatonin can have a positive effect on gastrointestinal dysfunction. It was concluded that melatonin has the potential to act on a wide variety of symptoms associated with ASD. However, other than SPs, no studies exist on melatonin as a treatment for ASD comorbid conditions. Such investigations should be on the research agenda because melatonin could improve a multitude of ASD comorbidities and, consequently, improve well-being.

Curiously, Zuckerman *et al*., 2014 [9] have evaluated the prevalence of OWT and OBY in a sample of children with ASD and assessed correlation of OWT and OBY. OBY was associated with SPs, melatonin use, and affective problems.

It is important consider that a limitation of this current revision was related to the revision only the publication from 2014. However, this critical review of literature leads us to a great reflection on the importance of sleep quality, considering the current days. We have been facing the pandemic caused by COVID-19 for more than 1 year [17]. There are millions of infected individuals worldwide, who have numerous symptoms such as dyspnea, fatigue [18], musculoskeletal pain [19], fever cough and asthenia [20], neurological manifestations [21] and/or severe discomfort in

the respiratory condition, culminating in pulmonary insufficiency [22], hospitalization, use of mechanical ventilatory support, and may progress to death.

However, as worrisome as investigating and paying attention to the health repercussions of thousands of infected individuals, it is also necessary to pay attention to the effects of confinement and social detachment [23, 24], which everyone is required to comply with, recommended by the World Health Organization [25] and health agencies. national and international health, focused on studies to control and cope with COVID-19.

Many studies have sought to map the negative effects of this confinement, in different populations, especially children without and with ASD [26, 27]. Türkoğlu *et al*., 2020 [27], investigate the relationship between chronotype preference/sleep problems and symptom severity of children with ASD during the confinement and social isolation of the COVID-19 outbreak. Children with ASD during the home confinement reported higher chronotype scores, i.e., eveningness chronotype, sleep problems, and autism symptom scores compared to the normal non-hone confinement state. The authors pointed that if sleep problems can be controlled with parental education, pharmacotherapy, and psychotherapeutic interventions, the impact on children with ASD of home confinement can be reduced.

In an intense wave of investigation, scientific production and dissemination of relevant findings on social confinement and distance, we find recommendations that aim to minimize damage to health, the manifestation of symptoms that affect the physical, mental, social and economic condition of the world population [18, 22, 23, 24, 26, 27]. There are studies suggesting the use of technological supports [28], guiding the execution of physical activities [29, 30] and evaluating the nutritional and behavioral status during the confinement period [28].

But the literature has also pointed out the concern of scientists and health professionals with a population that has clearly shown, in addition to the negative effects mentioned above, negative psychological/emotional effects, such as anxiety, depression, mental disorders (or their exacerbation) [28], the decrease in the quality of sleep [31, 32] and, consequently, in the quality of life [33].

Considering that children with ASD demonstrated sleep problems are associated with internalizing behaviors, including lashing out at one's self, such as social withdrawal and anxiety depression, and externalizing behavior problems, including hyperactivity, aggression, and high daytime irritability [34], control of symptoms of children with ASD experiencing negative life events, such as those consequent to the COVID-19 pandemic and associated home confinement, is especially related to the control of sleep problems [27].

The strength

The strength of this work is reflected in the authors' ability to gather studies that ensure the relationship between the ASD and the SPs. In addition, we show the relevance of the discussion of this subject today, in which we face confinement and social distance due to the pandemic caused by COVID-19. This reinforces the need to pay attention to patients affected by the virus in the same way that we need to be concerned with the non-infected population, but who are also sick, losing their quality of life.

Conclusion

Considering that there is an important relationship between PSs and ASDs, we strongly believe that the desirable path in the fight against negative behaviors/symptoms and the repercussions of this pandemic on health in general, could be the creation of accessible and effective therapeutic strategies. simple, aiming at the management and control of these symptoms, especially among children with ASD.

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