



Melatonin and Sleep Problems in Children with Autism Spectrum Disorder

Eun Jin Park and Young-Min Park

Department of Psychiatry, Inje University Ilsan Paik Hospital, Goyang, Korea

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that develops during early childhood. It is characterized by social communication deficits, restricted interests, and repetitive behaviors. The various comorbid problems affect the daily functioning and quality of life of patients and their families. In particular, sleep problems, including insomnia, negatively affect the children's social interactions, emotions, and behavior. Melatonin is the most commonly prescribed drug for sleep problems related to ASD during childhood and adolescence, and the link between decreased melatonin concentration and the pathogenesis of sleep disturbances in ASD has been focused on recently. It is essential to evaluate sleep problems in children with ASD and to make appropriate therapeutic interventions. This article reviews the findings on the sleep-melatonin relationship in patients with ASD.

Key Words: Sleep; Melatonin; Autism spectrum disorder

Received: April 26, 2020 **Accepted:** May 8, 2020

Corresponding author: Young-Min Park, MD, PhD, Department of Psychiatry, Ilsan Paik Hospital, Inje University, 170 Juwaha-Ro, Ilsanseo-gu, Goyang 10380, Korea. Tel: 82-31-910-7260, Fax: 82-31-910-7268, E-mail: medipark@hanmail.net

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by repetitive and restricted behavioral patterns and persistent deficits in social communication. The prevalence of ASD is estimated to be 1.7–1.85% of children and adolescents [1-3]. Children with ASD have a variety of comorbidities that affect their functioning during their daily lives [4]. Especially, sleep disturbances are relatively common and affect not only the daily functioning and quality of life of children but also the quality of life of their family [5-8].

It has been recognized that children with ASD and sleep problems have more emotional and behavioral difficulties than children without sleep problems [9]. Episodes of violent behavior, as well as emotional problems such as depression and anxiety, are significantly increased [10]. Additionally, cognitive tests show they tend to have a worse performance [11], and their daily life functioning is relatively low [10]. It has also been reported that severe sleep disturbances are associated with severe daytime behavior problems [10]. In addition to behavioral problems, ASD children with sleeping disorders have more problems with socialization, attention, self-stimulation, and self-inflicted behavior

[10]. One research has shown that reduced sleeping time at night predicts the severity of social interaction disturbances, one of the core symptoms of ASD [12]. The sleeping disorders of the children also adversely affect their parents' mental health. Parenting stress increases when a child has trouble falling asleep at night or wakes up frequently during sleep [13]. As a consequence, the parents can also end up suffering from poor sleep quality. In particular, sleeping problems of children affect the mother's sleep and stress, and if these difficulties become chronic, it has been reported that the overall health of the mother also worsens [9].

Sleep is essential for brain development in childhood [14]. In a recent review of animal model studies, it was suggested that in the case of ASD, chronic insomnia could have an impact on brain development [14]. Considering the many adverse effects of sleep problems, assessing and treating sleep problems in children with ASD is very important for improving the health of the children and the quality of life of their families [15].

Behavioral therapy, such as sleep hygiene, is currently the primary approach to reduce sleep problems, but the use of medication is steadily increasing [16,17]. The most widely-studied pharmacological agent used for the treatment of sleeping disorders in children with ASD is supplemental melatonin [18-20]. Melato-

nin functions in many ways to treat sleep problems in ASD, and the number of studies of the relationship between melatonin and sleep in patients with ASD is steadily growing [21]. This review will discuss the findings on the sleep-melatonin relationship in patients with ASD.

SLEEP PROBLEMS AND ASD

The rate of sleep problems in children and adolescents with ASD is high. More than 60% of ASD children and adolescents are known to suffer from sleep problems [22]. The sleep disturbances include a variety of problems such as poor quality of sleep, difficulty in falling asleep, and waking up early [20,22]. When a child with ASD is affected by a sleeping disorder, the child's behavioral problems worsen and it affects their daytime functioning.

Many studies have found that children who have ASD have considerably longer sleep latencies than children who develop typically [23,24]. Up to 60% of children with ASD have trouble falling asleep [25]. Miano et al. [24] estimated that 25.8% of children with ASD take 30 minutes to fall asleep relative to 6.6% of typically developing children. There are also studies showing an increased number and duration of night awakenings in children with ASD [26,27]. Prolonged sleep latency and nighttime awakenings contribute to reduced overall sleep time in children with ASD [25]. Children with ASD also have a short overall sleep time. Miano et al. [24] found that 22.6% of children with ASDs slept for less than 8 hours at night relative to just 9.6% of children typically developing. This can explain the high rates of daytime drowsiness experienced by children with ASD [28].

Children and adolescents with ASD are also likely to suffer from parasomnias, such as sleepwalking, night terrors, and restless leg syndrome [28,29]. Children with ASD can show odd bedtime routines and a bedtime resistance [30]. Even very young children with ASD have serious sleep problems. In a recent study conducted in India, sleep problems in preschool children with ASD were severe [31]. This study targeted preschool children between the ages of 2 and 6. The overall prevalence of sleep disturbances was 93% and the prevalent symptoms were bedtime resistance (95%), sleep anxiety (85%), and sleep duration (81%) [31]. The most common sleep problems may differ at different ages [32].

In children with ASD, multiple factors have been correlated with sleep disturbances. Sleep problems in children with ASD are positively associated with autism severity [33]. Mazurek and Sohl [34] studied 81 adolescents with ASD regarding specific types of sleep and behavioral problems. Sleep problems were significantly correlated with physical aggression, inattention, irritability, and hyperactivity. In multivariate analyses, sleep problems accounted for approximately 22–32% of the differences between models of behavioral problems. Notably, night awakenings had the strongest association with daytime behavior, even after adjusting for sex and age [34].

In Western Australia, researchers investigated the child and family characteristics associated with sleep disturbances [35].

Their results suggested that severe ASD symptoms, child epilepsy, maternal autism traits, depression, anxiety, lower family income, and lower paternal education were associated with increased severity of sleep problems. Thus, it is necessary to consider various aspects, including factors of the children and family members, when evaluating sleep problems in children with ASD.

CORE SYMPTOMS AND SLEEP DISTURBANCE IN ASD

The main symptoms of ASD include social communication deficits, restricted/repetitive behaviors (RRB), and sensory abnormalities. Specifically, communication difficulties in children with ASD have been linked to a shorter sleep duration [36]. Deficiencies in interpersonal social communication were correlated with bedtime resistance [32].

A total of 57 children were surveyed for the link between RRB, one of the key ASD symptoms, and sleep. Thirty-eight children with ASD and nineteen developmentally delayed children participated [37]. Sleep problems were assessed at age four and higher-order RRBs (sameness/ritualistic/compulsive behaviors) were investigated from age 2–6 in the ASD group. The researchers found that sleep problems were associated with the trajectories of higher-order RRBs [37].

Sensory sensitivities and sleep disturbances are also associated. In a recent study, 69 autism children and 62 age-matched controls were examined for sleep habits and sensory abnormalities [38]. They found children with ASD displayed more severe sleep disturbances and sensory abnormalities than controls. The sleep disturbances in the autism group were associated with touch and oral sensitivities. Specifically, hypersensitivity towards touch showed the strongest association with sleep disturbances, and explained 24% of the variance in total sleep disturbance scores. Moreover, sensitivity to sensory stimuli is associated with sleep anxiety [39].

On the other hand, studies of ASD children at younger ages showed different results. A study of 281 preschool ASD children aged between 4 and 5 showed that sleep conditions were generally not correlated with the core autism symptoms and were more related to various emotional and behavior problems [40]. Sleep disturbances were associated with aggression, anxiety, depression, and attention problems.

Recent studies have also shown that an ASD diagnosis itself increases the risk of sleep problems [41]. Besides, in cases of hyperactivity, emotional, and behavioral problems in ASD, the prevalence of sleeping disorders is increased, indicating that sleep and behavioral problems are related to each other.

MELATONIN AND AUTISM SPECTRUM DISORDER

Melatonin is a hormone synthesized by the pineal gland that has a number of functions, including the regulation of sleep-

wake cycles [42]. Among patients with ASD, there have been many findings of an association between sleep problems and melatonin abnormalities [43-45]. Many results have shown that the level of melatonin in the blood and urine are decreased significantly in individuals with ASD [46,47]. Additionally, there have been studies showed that melatonin is not only linked to regulating sleep-wake cycles but also to reducing anxiety [48,49].

The serum melatonin level has been negatively correlated with autism severity, suggesting a higher risk for children with more severe ASD to experience insomnia [50]. A recent study measured urine melatonin levels and compared the mothers of ASD children with the mothers of typically developing children. The results showed that the concentration of melatonin in urine from mothers of ASD children was significantly lower. This result suggests a genetic link between ASD and melatonin [51]. A study that examined heritability by surveying children with ASD, healthy siblings, and parents by measuring plasma melatonin levels also showed differences in melatonin synthesis [52]. Pagan et al. [53] examined gut samples from 9 ASD patients and 22 healthy people, and measured the melatonin concentration in blood platelets in 239 ASD patients and their first-degree relatives. The results showed that ASD patients have melatonin production problems and that they had reduced activity of enzymes involved in melatonin synthesis.

Besides, Pagan et al. [54] have suggested that dysfunction of the serotonin-N-acetylserotonin-melatonin system is a biomarker of ASD. There is growing evidence that melatonin synthesis and metabolism differ in patients with ASD [55-57]. Recent studies have shown that reductions of melatonin synthesis are related to a lower melatonin concentration in patients with ASD, and eventually this negatively affects sleep and the circadian rhythm in ASD patients [58]. Additional studies have shown that genetic factors may affect the sleep patterns in ASD. Veatch et al. [57] studied a group of ASD children with sleep onset delay. They tested the genes associated with two melatonin pathways, acetylserotonin O-methyltransferase (ASMT) and cytochrome P450 1A2 (CYP1A2). Higher frequencies of variants found to decrease ASMT expression were related to decreased CYP1A2 enzyme activity. These results indicate that the expression of sleep onset delay is related to melatonin synthesis genes.

Some studies also attempted to find a link between melatonin level and pineal gland volume [59]. Maruani et al. [59] evaluated 215 participants, including 78 children with ASD, 90 unaffected relatives, and 47 healthy controls. They found that both early morning melatonin levels and pineal gland volume were lower in patients compared to controls. However, the effect of pineal gland volume was normalized when analyzed in relation to melatonin levels. Thus, melatonin variations in ASD might be driven mainly by dysregulation of the melatonin synthesis pathway [59]. The role of the pineal gland volume differences has not yet been clarified.

EFFECT OF SUPPLEMENTAL MELATONIN FOR SLEEP PROBLEMS IN PATIENTS WITH ASD

When ASD patients suffer from sleep disturbances, the first-line treatment for children and adolescents with ASD is parent-directed behavioral treatments for sleeping disorders [60]. Treatment should be based primarily on practicing sleep hygiene and behavioral interventions. If sleep problems persist even after behavioral therapy, then drug administration is considered. Medication for sleeping disorders is common in children with ASD [61]. Studies have shown that melatonin has effects on sleep problems in both children and adults [43,62].

Systematic reviews have shown that supplemental melatonin decreases symptoms of insomnia, and significantly improves sleep duration and sleep quality [63,64]. However, studies comparing the effectiveness of melatonin and other sleeping pills in patients with ASD are limited. Future studies, therefore, need to compare the effects of various drugs [43].

Cortesi et al. [65] investigated the efficacy of therapy for sleep disturbances using melatonin, cognitive-behavioral therapy, and combining the two approaches. The best results were observed in patients undergoing combined intervention, then in those taking melatonin. The lowest efficacy was found in patients receiving only cognitive-behavioral treatment [65]. Multiple studies, including meta-analyses, have demonstrated that supplemental fast-release melatonin significantly improved ASD children's sleep, including improved sleep duration, better regular sleep periods, and increased overall sleep time [63]. Also, prolonged-release melatonin significantly reduced nighttime waking and improved sleep duration and sleep time [60]. Melatonin supplementation improved sleep latency, as measured by actigraphy, at 1 mg or 3 mg dosages in most children. It was beneficial in the first week of medication, with effects maintained for several months [66].

Melatonin not only improves sleep but also has additional effects. Melatonin intake in children with ASD has been shown to enhance daytime activity by increasing the total night sleep period [16]. Melatonin has been shown to reduce disruptive behavior and improve communication [66]. Furthermore, treatment with melatonin also reduced children's anxiety and stereotypic behaviors [10,43]. Besides, melatonin supplementation reduced parental stress [66]. In an animal study, melatonin supplementation significantly improved social and behavioral deficits in rats with autistic features. The investigators proposed that melatonin reverses the declines in serine/threonine hippocampal protein kinases in this animal model of autism [67].

THE SIDE EFFECTS OF MELATONIN

Melatonin is well tolerated and has minimal adverse effects [16,66]. It is generally safe for children and adolescents to take daily melatonin for up to 104 weeks [68]. The most frequent adverse events are fatigue (6.3%), drowsiness (6.3%), and mood swings

(4.2%). The changes in mean height, weight, body mass index, and pubertal status are within normal ranges for age [68].

CONCLUSION

ASD is a neurodevelopmental disorder with an onset in early childhood. Sleep problems, including insomnia, are common as various comorbid symptoms and affect the child's daily function and quality of life. The sleep problems can also adversely affect the quality of life of the child's parents. ASD patients differ from healthy individuals in melatonin synthesis and metabolism, and their serum and urine concentrations of melatonin are lower than normal controls. Research has shown that providing supplemental melatonin is effective and relatively safe for treating sleep problems in ASD children and adolescents. Evaluation of sleep problems is essential when treating ASD patients, and proper therapeutic intervention is required.

Acknowledgments

None

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Eun Jin Park, Young-Min Park. Data curation: Eun Jin Park, Young-Min Park. Project administration: Young-Min Park. Resources: Eun Jin Park, Young-Min Park. Supervision: Young-Min Park. Writing—original draft: Eun Jin Park. Writing—review & editing: Eun Jin Park, Young-Min Park.

ORCID iDs

Young-Min Park 

<https://orcid.org/0000-0002-4993-1426>

Eun Jin Park 

<https://orcid.org/0000-0003-4046-1517>

REFERENCES

- May T, Brignell A, Williams K. Autism spectrum disorder prevalence in children aged 12-13 years from the longitudinal study of Australian children. *Autism Res* 2020;13:821-827.
- Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveill Summ* 2020;69:1-12.
- Al-Mamri W, Idris AB, Dakak S, Al-Shekaili M, Al-Harathi Z, Alnaamani AM, et al. Revisiting the prevalence of autism spectrum disorder among Omani children: a multicentre study. *Sultan Qaboos Univ Med J* 2019;19:e305-e309.
- Dizitser Y, Meiri G, Flusser H, Michaelovski A, Dinstein I, Menashe I. Comorbidity and health services' usage in children with autism spectrum disorder: a nested case-control study. *Epidemiol Psychiatr Sci* 2020;29:e95.
- Goldman SE, Alder ML, Burgess HJ, Corbett BA, Hundley R, Wofford D, et al. Characterizing sleep in adolescents and adults with autism spectrum disorders. *J Autism Dev Disord* 2017;47:1682-1695.
- Wang G, Liu Z, Xu G, Jiang F, Lu N, Baylor A, et al. Sleep disturbances and associated factors in Chinese children with autism spectrum disorder: a retrospective and cross-sectional study. *Child Psychiatry Hum Dev* 2016;47:248-258.
- Nadeau JM, Arnold EB, Keene AC, Collier AB, Lewin AB, Murphy TK, et al. Frequency and clinical correlates of sleep-related problems among anxious youth with autism spectrum disorders. *Child Psychiatry Hum Dev* 2015;46:558-566.
- Devnani PA, Hegde AU. Autism and sleep disorders. *J Pediatr Neurosci* 2015;10:304-307.
- Hodge D, Hoffman CD, Sweeney DP, Riggs ML. Relationship between children's sleep and mental health in mothers of children with and without autism. *J Autism Dev Disord* 2013;43:956-963.
- Sikora DM, Johnson K, Clemons T, Katz T. The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. *Pediatrics* 2012;130 Suppl 2:S83-S90.
- Limoges E, Bolduc C, Berthiaume C, Mottron L, Godbout R. Relationship between poor sleep and daytime cognitive performance in young adults with autism. *Res Dev Disabil* 2013;34:1322-1335.
- Schreck KA, Mulick JA, Smith AF. Sleep problems as possible predictors of intensified symptoms of autism. *Res Dev Disabil* 2004;25:57-66.
- Schreck KA, Mulick JA. Parental report of sleep problems in children with autism. *J Autism Dev Disord* 2000;30:127-135.
- Wintler T, Schoch H, Frank MG, Peixoto L. Sleep, brain development, and autism spectrum disorders: insights from animal models. *J Neurosci Res* 2020;98:1137-1149.
- Richdale AL, Baker E, Short M, Gradisar M. The role of insomnia, pre-sleep arousal and psychopathology symptoms in daytime impairment in adolescents with high-functioning autism spectrum disorder. *Sleep Med* 2014;15:1082-1088.
- Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *J Autism Dev Disord* 2011;41:175-184.
- Schwichtenberg AJ, Iosif AM, Goodlin-Jones B, Tang K, Anders T. Daytime sleep patterns in preschool children with autism, developmental delay, and typical development. *Am J Intellect Dev Disabil* 2011;116:142-152.
- Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol* 2011;53:783-792.
- Herrmann S. Counting sheep: sleep disorders in children with autism spectrum disorders. *J Pediatr Health Care* 2016;30:143-154.
- Veatch OJ, Goldman SE, Adkins KW, Malow BA. Melatonin in children with autism spectrum disorders: how does the evidence fit together? *J Nat Sci* 2015;1:e125.
- Rossignol DA, Frye RE. Melatonin in autism spectrum disorders. *Curr Clin Pharmacol* 2014;9:326-334.
- Souders MC, Zavodny S, Eriksen W, Sinko R, Connell J, Kerns C, et al. Sleep in children with autism spectrum disorder. *Curr Psychiatry Rep* 2017;19:34.
- Allik H, Larsson JO, Smedje H. Sleep patterns of school-age children with Asperger syndrome or high-functioning autism. *J Autism Dev Disord* 2006;36:585-595.
- Miano S, Bruni O, Elia M, Trovato A, Smerieri A, Verrillo E, et al. Sleep in children with autistic spectrum disorder: a questionnaire and polysomnographic study. *Sleep Med* 2007;9:64-70.
- Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. *Sleep Med Rev* 2009;13:403-411.
- Giannotti F, Cortesi F, Cerquiglini A, Bernabei P. An open-label study of controlled-release melatonin in treatment of sleep disorders in children with autism. *J Autism Dev Disord* 2006;36:741-752.
- Limoges E, Mottron L, Bolduc C, Berthiaume C, Godbout R. Atypical sleep architecture and the autism phenotype. *Brain* 2005;128(Pt 5):1049-1061.
- Giannotti F, Cortesi F, Cerquiglini A, Miraglia D, Vagnoni C, Sebastiani T, et al. An investigation of sleep characteristics, EEG abnormalities and epilepsy in developmentally regressed and non-regressed children with autism. *J Autism Dev Disord* 2008;38:1888-1897.
- Hirata I, Mohri I, Kato N, Nishimura K, Tachibana M, Kuwada A, Kagitani-Shimono K, et al. Sleep problems are more frequent and associated with problematic behaviors in preschoolers with autism spectrum disorder. *Res Dev Disabil* 2016;49-50:86-99.

30. Giannotti F, Cortesi F, Cerquiglini A, Vagnoni C, Valente D. Sleep in children with autism with and without autistic regression. *J Sleep Res* 2011;20:338-347.
31. Samanta P, Mishra DP, Panigrahi A, Mishra J, Senapati LK, Ravan JR. Sleep disturbances and associated factors among 2-6-year-old male children with autism in Bhubaneswar, India. *Sleep Med* 2020;67:77-82.
32. Goldman SE, Richdale AL, Clemons T, Malow BA. Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. *J Autism Dev Disord* 2012;42:531-538.
33. Mayes SD, Calhoun SL, Murray MJ, Morrow JD, Yurich KK, Mahr F, et al. Comparison of scores on the Checklist for Autism Spectrum Disorder, Childhood Autism Rating Scale, and Gilliam Asperger's Disorder Scale for children with low functioning autism, high functioning autism, Asperger's disorder, ADHD, and typical development. *J Autism Dev Disord* 2009;39:1682-1693.
34. Mazurek MO, Sohl K. Sleep and behavioral problems in children with autism spectrum disorder. *J Autism Dev Disord* 2016;46:1906-1915.
35. Waddington H, McLay L, Woods L, Whitehouse AJO. Child and family characteristics associated with sleep disturbance in children with autism spectrum disorder. *J Autism Dev Disord* 2020 Mar 31 [Epub]. Available at: <https://doi.org/10.1007/s10803-020-04475-7>.
36. Hollway JA, Aman MG, Butter E. Correlates and risk markers for sleep disturbance in participants of the Autism Treatment Network. *J Autism Dev Disord* 2013;43:2830-2843.
37. MacDuffie KE, Munson J, Greenson J, Ward TM, Rogers SJ, Dawson G, et al. Sleep problems and trajectories of restricted and repetitive behaviors in children with neurodevelopmental disabilities. *J Autism Dev Disord* 2020 Mar 5 [Epub]. Available at: <https://doi.org/10.1007/s10803-020-04438-y>.
38. Tzischinsky O, Meiri G, Manelis L, Bar-Sinai A, Flusser H, Michaelovski A, et al. Sleep disturbances are associated with specific sensory sensitivities in children with autism. *Mol Autism* 2018;9:22.
39. Hollway JA, Aman MG, Butter E. Correlates and risk markers for sleep disturbance in participants of the Autism Treatment Network. *J Autism Dev Disord* 2013;43:2830-2843.
40. Zaidman-Zait A, Zwaigenbaum L, Duku E, Bennett T, Szatmari P, Miranda P, et al. Factor analysis of the children's sleep habits questionnaire among preschool children with autism spectrum disorder. *Res Dev Disabil* 2020;97:103548.
41. Sivertsen B, Posserud MB, Gillberg C, Lundervold AJ, Hysing M. Sleep problems in children with autism spectrum problems: a longitudinal population-based study. *Autism* 2012;16:139-150.
42. Wirojanan J, Jacquemont S, Diaz R, Bacalman S, Anders TF, Hagerman RJ, et al. The efficacy of melatonin for sleep problems in children with autism, fragile X syndrome, or autism and fragile X syndrome. *J Clin Sleep Med* 2009;5:145-150.
43. Yan T, Goldman RD. Melatonin for children with autism spectrum disorder. *Can Fam Physician* 2020;66:183-185.
44. Guérolé F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte JM. Melatonin for disordered sleep in individuals with autism spectrum disorders: systematic review and discussion. *Sleep Med Rev* 2011;15:379-387.
45. Goldman SE, Adkins KW, Calcutt MW, Carter MD, Goodpaster RL, Wang L, et al. Melatonin in children with autism spectrum disorders: endogenous and pharmacokinetic profiles in relation to sleep. *J Autism Dev Disord* 2014;44:2525-2535.
46. Leu RM, Beyderman L, Botzolakis EJ, Surdyka K, Wang L, Malow BA. Relation of melatonin to sleep architecture in children with autism. *J Autism Dev Disord* 2011;41:427-433.
47. Guérolé F, Baleyte JM. Meta-analysing the effectiveness of melatonin for sleep-disturbed individuals with autism spectrum conditions: should Rett syndrome be included? *Dev Med Child Neurol* 2011;53:1063-1064.
48. Marseglia L, Manti S, D'Angelo G, Arrigo T, Cuppari C, Salpietro C, et al. Potential use of melatonin in procedural anxiety and pain in children undergoing blood withdrawal. *J Biol Regul Homeost Agents* 2015;29:509-514.
49. Hansen MV, Andersen LT, Madsen MT, Hageman I, Rasmussen LS, Bokmand S, et al. Effect of melatonin on depressive symptoms and anxiety in patients undergoing breast cancer surgery: a randomized, double-blind, placebo-controlled trial. *Breast Cancer Res Treat* 2014;145:683-695.
50. Tordjman S, Najjar I, Bellissant E, Anderson GM, Barbueroth M, Cohen D, et al. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. *Int J Mol Sci* 2013;14:20508-20542.
51. Braam W, Ehrhart F, Maas APHM, Smits MG, Curfs L. Low maternal melatonin level increases autism spectrum disorder risk in children. *Res Dev Disabil* 2018;82:79-89.
52. Benabou M, Rolland T, Leblond CS, Millot GA, Huguet G, Delorme R, et al. Heritability of the melatonin synthesis variability in autism spectrum disorders. *Sci Rep* 2017;7:17746.
53. Pagan C, Goubran-Botros H, Delorme R, Benabou M, Lemièrre N, Murray K, et al. Disruption of melatonin synthesis is associated with impaired 14-3-3 and miR-451 levels in patients with autism spectrum disorders. *Sci Rep* 2017;7:2096.
54. Pagan C, Delorme R, Callebert J, Goubran-Botros H, Amsellem F, Drouot X, et al. The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders. *Transl Psychiatry* 2014;4:e479.
55. Braam W, Keijzer H, Struijker Boudier H, Didden R, Smits M, Curfs L. CYP1A2 polymorphisms in slow melatonin metabolisers: a possible relationship with autism spectrum disorder? *J Intellect Disabil* 2013;57:993-1000.
56. Chaste P, Clement N, Mercati O, Guillaume JL, Delorme R, Botros HG, et al. Identification of pathway-biased and deleterious melatonin receptor mutants in autism spectrum disorders and in the general population. *PLoS One* 2010;5:e11495.
57. Veatch OJ, Pendergast JS, Allen MJ, Leu RM, Johnson CH, Elsea SH, et al. Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. *J Autism Dev Disord* 2015;45:100-110.
58. Melke J, Goubran Botros H, Chaste P, Betancur C, Nygren G, Anckarsäter H, et al. Abnormal melatonin synthesis in autism spectrum disorders. *Mol Psychiatry* 2008;13:90-98.
59. Maruani A, Dumas G, Beggato A, Traut N, Peyre H, Cohen-Freoua A, et al. Morning plasma melatonin differences in autism: beyond the impact of pineal gland volume. *Front Psychiatry* 2019;10:11.
60. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 2017;56:948-957.
61. Malow BA, Katz T, Reynolds AM, Shui A, Carno M, Connolly HV, et al. Sleep difficulties and medications in children with autism spectrum disorders: a registry study. *Pediatrics* 2016;137 Suppl 2:S98-S104.
62. Galli-Carminati G, Deriaz N, Bertschy G. Melatonin in treatment of chronic sleep disorders in adults with autism: a retrospective study. *Swiss Med Wkly* 2009;139:293-296.
63. Jenabi E, Ataei S, Bashirian S. Evaluation of drug interventions for the treatment of sleep disorders in children with autism spectrum disorders: a systematic review. *Korean J Pediatr* 2019;62:405-409.
64. Damiani JM, Sweet BV, Sohoni P. Melatonin: an option for managing sleep disorders in children with autism spectrum disorder. *Am J Health Syst Pharm* 2014;71:95-101.
65. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res* 2012;21:700-709.
66. Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord* 2012;42:1729-1737.
67. Tian Y, Yabuki Y, Moriguchi S, Fukunaga K, Mao PJ, Hong LJ, et al. Melatonin reverses the decreases in hippocampal protein serine/threonine kinases observed in an animal model of autism. *J Pineal Res* 2014;56:1-11.
68. Malow BA, Findling RL, Schroder CM, Maras A, Breddy J, Nir T, et al. Sleep, growth, and puberty after 2 years of prolonged-release melatonin in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 2020 Jan 23 [Epub]. Available at: <https://doi.org/10.1016/j.jaac.2019.12.007>.