Sleep Problems, Behavior, and Psychopathology in Autism:

Inter-relationships across the Lifespan

Kimberly A. Schreck^a

Amanda L. Richdale^b

^aPenn State Harrisburg 777 W. Harrisburg Pike W311 Olmsted Building Middletown, PA 17057 kas24@psu.ed

bOlga Tennison Autism Research Centre, La Trobe University Melbourne Victoria Australia 3086 a.richdale@latrobe.edu.au

Corresponding Author: Kimberly A. Schreck

Penn State Harrisburg 777 W. Harrisburg Pike W311 Olmsted Building Middletown, PA 17057

<u>kas24@psu.edu</u> 717-948-6048

Abstract

Across the lifespan, autistic individuals experience symptomatology concomitant with their diagnosis including increased rates of daytime behavior (e.g., stereotypy, self-injurious behavior, and aggression) and psychopathology (e.g., attention deficit hyperactivity disorder, anxiety, and depression). In addition to this inter-related behavior and psychopathology, autistic children, adolescents, and adults consistently exhibit a wide variety of sleep problems (e.g., insomnia, reduced total sleep time, increased sleep onset latency, night waking, etc.). Early research and current research continue to describe the inter-relatedness among these daytime behaviors, psychopathology, and sleep problems for autistic individuals. Although descriptions of these issues appear in research, only preliminary suggestions exist for the causes and contributors toward the sleep problems or the interactions of sleep problems with psychopathology, although current research suggests a possible biopsychosocial interaction.

Keywords: Sleep, Autism, Psychopathology

Introduction:

The diagnostic criteria for autism have evolved from their original classification as a psychopathology (i.e., childhood schizophrenia) to that of a distinct neurodevelopmental syndrome based on developmental behavioral differences. Nevertheless, the core areas of diagnosis have remained relatively consistent [1]. Autistic individuals exhibit difficulties with social communication and interactions (e.g., eye contact, social initiation and rules, communication, imaginative play), increased rates of restricted, repetitive patterns of behavior (e.g., lining up toys, perseverative motor movements/stereotypies, fixated interests, distress with environmental changes) and sensory sensitivities [2]. A wide range of comorbid developmental, physiological, behavioral, and psychopathological conditions also commonly co-occur in autism, such as intellectual disability (ID), epilepsy, sleep problems, self-injurious behavior (SIB), aggression, attention deficit hyperactivity disorder (ADHD), anxiety, and depression [2,3].

Early research explored the relationships of these comorbid conditions with autism. This research showed that significant sleep problems inter-related with both behavior and psychopathology. These results lead to the proposal of a biopsychosocial model interpreting autism's core symptoms in relationship with commonly co-occurring sleep problems, behavior problems, and psychopathology [3]. Since the publication of this model, research investigating sleep's interconnectedness with behavior and psychopathology has remained relatively consistent in its focus and conclusions. Current research mostly replicates earlier research and continues to describe types of sleep problems and their connections to comorbid behaviors (i.e., stereotypy, restricted and repetitive behavior, self-injurious behavior: SIB, aggression) and psychopathology (i.e., ADHD, anxiety, depression). This paper provides an overview of current research (primarily since 2016) regarding the types of sleep problems in autism, sleep's

relationships to co-morbid behaviors, ADHD, and anxiety, and possible explanations for this inter-relatedness.

1.1 Sleep Problems in Autism

Early research concluded that the majority of autistic individuals experience some type of chronic sleep problem within their lifetime [3]. Consistent with this, current research indicates that autistic children, adolescents, and adults primarily experience symptoms of insomnia and/or circadian sleep-wake rhythm disorders (CSWRDs), including difficulty falling asleep, increased sleep onset latency (SoL), reduced total sleep time (TST), increased wake after sleep onset (WASO), and poor sleep efficiency (SE) [3, 4-7]. Table 1 provides descriptions of these sleep problems in autism.

Specifically for autistic children, sleep problems begin as early as toddlerhood [8]. In addition to insomnia and CSWRDs, autistic children experience parasomnias, obstructive sleep apnea [9], and sleep enuresis [10], the latter possibly due to toilet training difficulties. Current research with autistic children has replicated or extended previous work with some studies using larger samples or longitudinal cohorts [9-13]. Findings continue to support earlier conclusions concerning the types of sleep problems for autistic children [9-13]. While sleep problems often remain chronic [3], some children may improve over time [12, 14], while others develop more severe sleeping problems with age [12].

Both early and current recent research have largely neglected examining sleep in autistic adolescents and adults compared to children. In these age groups, current results indicate a continuation of the sleep problems found in childhood [4], particularly insomnia symptomatology [5-7]. Problematic sleep for adolescents may be exacerbated by biological changes associated with puberty where adolescent sleep patterns naturally shift their circadian phase resulting in later bed and wake times. Shifts in sleep phase and related sleep problems

often associated with early school start times result in insomnia symptoms and related fatigue/daytime sleepiness for about half of adolescents [4, 5]. These changes in circadian phase can continue into early adulthood [6], primarily with delayed sleep wake phase disorder [6,7,15, 10] and insomnia symptoms. Adults with autism and ID may experience higher rates of sleep problems, such as increased SoL, increased WASO, and reduced SE when compared to non-autistic adults [15]. These sleep problems often impair or correlate with daytime functioning [16].

1.2 Sleep Problems & Co-morbid Behaviors

Autistic individuals can exhibit a variety of daytime behaviors, including stereotypy and repetitive and restrictive behaviors, SIB, aggression, and sensory sensitivities [2]. Early research indicated relationships among these behaviors and sleep problems in autism [3]. Current research continues to describe the inter-relatedness of sleep and behaviors, supporting earlier findings which established relationships between sleep problems and comorbid autistic behaviors [17].

Sleep problems and co-morbid behaviors appear to be associated across the lifespan. For example, general and specific sleep problems (e.g., reduced TST, bedtime resistance, CSWRD, WASO with screaming, reduced SE, parasomnias) relate to increased rates of stereotypy and repetitive/restricted behaviors, SIB, and aggression [9, 12, 18-28]. Some research describing behaviors related to or leading to aggression also relate to reduced TST, sleep anxiety, WASO, reduced SE, variable SoL, and parasomnias [20, 22-24, 29].

The etiologies underlying the inter-relatedness of co-morbid behaviors with sleep problems remains primarily unstudied and unclear. For example, for toddlers with autism, sensory over-responsivity predicted late sleep difficulties, but this relationship did not hold for 4- to 10-year-olds [12], indicating the potential complexity and developmental differences of sleep-behavior

relationships in autism. For the association of SIB with sleep for adults the relationship may be influenced by the severity of autism symptoms, rather than the presence of SIB [23]. It remains unclear if the physiological differences underlying autism and its severity or sleep difficulties contributed more to the SIB-sleep problem relationship. The question remains if the relationships exist due more to psychosocial or behavioral impacts of an autism diagnosis or to the sleep difficulties themselves.

1.3 Sleep Problems & ADHD

Autistic individuals also exhibit a variety of symptoms of ADHD (e.g., inattention and hyperactivity) leading to some being co-diagnosed of ADHD and autism [2, 30, 31]. Both past and current research consistently describe the relationship of these autism-ADHD symptom connections with sleep problems [3-17] across the lifespan. For all ages, hyperactivity especially relates to reduced TST, WASO, and parasomnias [22, 23, 27]. However, more specifically for children, the combination of hyperactivity and inattention symptoms correlate with generally poor sleep, including daytime sleepiness, WASO, and reduced TST [12, 20, 21, 27]. Path analysis of longitudinal sleep data indicates that poor sleep predicts later ADHD behaviors in autistic toddlers, but not 4- to 10-year-olds [12]. The known impact of significant sleep difficulties and their individual variability on attention and daytime functioning [32] may result in behavior change consistent with an ADHD diagnosis.

The causal relationships among sleep problems and ADHD in autism have not been studied directly. However, current research of treatments for autistic children's and adolescents' sleep problems indicates that successful behavioral sleep treatment (e.g., sleep hygiene, non-graduated and graduated extinction, bedtime fading, bedtime pass) had a trans-diagnostic effect on ADHD symptoms [33, 34]. Behavioral treatments targeting sleep problems improved ADHD

symptoms without directly treating ADHD. This provides support for a behavioral explanation for the autism-ADHD-sleep problem relationship [33, 34].

Research on the autism-ADHD-sleep problem connection strongly supports their interrelatedness. However, current research suggests that ADHD symptoms may make a smaller contribution to the autism-psychopathology-sleep problems connection than do anxiety or internalizing symptoms. Internalizing or anxiety symptoms may be more predictive of sleep problems in autism than ADHD symptoms [29, 35].

1.4 Sleep Problems & Anxiety/Depression

Symptoms of internalizing disorders (i.e., anxiety and depression), commonly co-occur with autism leading to a co-diagnosis in a third or more of autistic individuals [36-40]. Up to 40% of autistic children and adolescents meet criteria for an anxiety disorder [39]. As anxiety and depression symptoms for autistic children may present as stereotypies, restricted/repetitive behaviors, and sensory arousal (e.g., hypersensitivity to touch), the underlying anxiety may not be recognized [41], suggesting even higher rates. The rates of anxiety and depression in adults remain similar to children's at 42% and 37% respectively [36].

Research shows a relationship among anxiety symptoms and sleep problems across the lifespan of autistic individuals, which appears as early as 2-years and may predict anxiety over time (i.e., at 8 years) [42]. Specifically for children, the combination of autism-specific anxiety symptoms (i.e., sensory arousal and restricted/repetitive behavior) and traditional anxiety diagnoses (e.g., generalized anxiety), or depressive symptoms predict sleep problems [19, 43]. Current research concludes that anxiety/depression/sensory arousal and sleep problems correlate with high rates of insomnia symptomatology including increased SoL, fatigue/daytime

sleepiness, sleep hygiene problems (e.g., nightlights, co-sleeping), nightmares/WASO, reduced TST, and increased TST [9, 11, 14, 21, 44].

The scarce current research on the relationship of anxiety/depression and sleep problems for autistic adolescents and adults provides conflicting results. Some research suggests relationships among poor sleep, anxiety, and depression, which predict poor daytime functioning [45], while another that separately analyzed adolescents and children indicates anxiety and depression do not relate to sleep problems for autistic adolescents [21]. These contradicting results may be due to methodological differences (e.g., parent report versus adolescent self-report); however, they indicate more research describing the relationship among anxiety/depression and sleep problems must be conducted for adolescents.

Although a specific understanding of the inter-relatedness of autism, anxiety, and sleep problems does not exist in children and adolescents, autistic adults appear to have similar sleep issues and relationships. The most current research suggests that hyperarousal, particularly presleep arousal or anxiety, may strongly influence sleep in adults, potentially explaining the relationships of these variables for autistic adults [46, 47]. For adults, higher levels of anxiety, depression, and/or sensory arousal (which has been suggested to be related to anxiety [41]) may relate specifically to insomnia symptomatology, including increased SoL and poor SE [46, 47].

As with co-morbid behavioral difficulties and ADHD, the etiology of the correlation of anxiety/depression, autism, and sleep problems remains understudied and mostly descriptive.

Treatment studies support the conceptualization of an interaction among biological (autism/anxiety traits) and psychosocial (behavioral) variables and poor sleep [3]. Current treatment studies for children and adolescents indicate a similar trans-diagnostic effect as found in ADHD. Behavioral interventions for reducing sleep problems, which also involve modifying

the sleep environment (e.g., remove toys, cool room, remove lights, calming bedtime activities, faded bedtimes, bedtime passes) decreased daytime anxiety [34, 48]. After treatment, children and adolescents no longer met anxiety/depression diagnostic criteria or had reduced anxiety/depression symptoms, and sleep problems (e.g., night time fears, SoL, SE, sleep hygiene problems) decreased [34, 48]. Although these results suggest support for a biopsychosocial explanation for the inter-relatedness of sleep problems, autism, and psychopathology, significantly more research is needed to address the both the description and etiology of these relationship.

1.5 Moving Forward: Inter-Relatedness of Symptoms

As described above, current research mostly replicates earlier research on autism, sleep problems, and their relationships, primarily providing descriptions of sleep problems in autism, especially insomnia, across the lifespan. The status of knowledge of relationships between sleep problems, comorbid behaviors and psychopathology diagnoses in autism also remains highly correlational (with suggested relationships existing for all ages of autistic individuals). Research mostly focuses on the cross-sectional description of sleep and behavior in autism, regardless of age, generally ignoring developmental or longitudinal changes particularly in adolescence and adulthood. To move the field forward, the developmental progression of sleep problems and their correlations with co-morbid behavior and psychopathology across the lifespan must be studied longitudinally with descriptions of the existence and development of symptoms among autistic adolescent and adults.

Further advances to the field also must include investigations into mechanisms contributing to sleep problems and their inter-relatedness to autism symptoms and psychopathology. Current reported relationships among sleep, autism, and psychopathology

continue to support a biopsychosocial model [3]. Since problematic behaviors and psychopathology often co-occur in autism [36-40, 41], sleep disturbances may contribute significantly to prevalence and maintenance of psychopathology and poor behavior regulation. Sleep problems, behavioral issues, and psychopathology also may negatively impact core autism symptomatology and other co-morbid developmental issues (e.g., ID, social communication, learning, ADHD, mood and anxiety disorders [2,3]). These interactions preliminarily appear reciprocal and interactive yet remain mostly unstudied.

To move forward, the field also requires understanding of the interaction of the biological variables within the biopsychosocial model [3]. Future research must investigate interactions between sleep and possible physiological differences for autistic people (e.g., genetic circadian rhythm dysregulation, melatonin, and neurotransmitters [49 -55]. Some of the possible multiple genetic influences on the expression of autism symptoms may contribute to sleep and psychopathology relationships. For example, variation in clock genes (i.e., genes controlling circadian rhythms) in autistic individuals [56] may be etiologically implicated in the expression of sleep difficulties as suggested in the biopsychosocial model [3] and in autism itself [49, 50, 56], but the latter remains speculative. Heritability of melatonin synthesis pathways [52] and alterations in melatonin pathway genes possibly that relate to sleep onset delay [57] also point to the potential role of melatonin. Melatonin's effectiveness for reducing insomnia in autistic children [58] and anxiety in non-autistic populations [59, 60] support this assertion. Investigation of the role of neurotransmitters (e.g., serotonin, GABA) that influence the sleep/wake state [51, 54, 55] differ in autism requiring more research [53, 55].

Despite existing research suggesting possible biological/genetic mechanisms that contribute to a biopsychosocial model, research supporting a purely physiological etiology underlying sleep

difficulties in autism remains mostly conjectural with little empirical data to support proposed biological etiologies. Since it remains probable that many pathways lead to autism, similarly several pathways may lead to co-morbid sleep difficulties and their inter-relationships with psychopathology. Future research into the inter-relationships among autism, sleep problems, behaviors, psychopathology, and underlying physiology will need to investigate these and other potential causal mechanisms. As existing correlational research suggests a possible bio-psychosocial feedback model [3], distinct studies on the relationships among physiological differences must be conducted in coordination with changes in the psychosocial component of the model [3, 49, 50]. The effectiveness of trans-diagnostic treatments [33, 34, 44, 48, 61, 62] suggests that physiology, psychopathology, and behavior cannot be distinctly separated. Thus, it does not appear that physiological mechanisms alone can explain differences in sleep and related daytime problems in autism. To move the field forward, exploring the inter-relatedness of physiological, and behavioral differences appears to be needed.

References

- [1] Richdale A, Schreck KA: **Assessment and intervention in autism: An historical perspective**. In *Clinical Assessment and Intervention for Autism Spectrum Disorders*. Edited by J. Matson. Elsevier; 2008: 3-32.
- [2] American Psychiatric Association: **Diagnostic and statistical manual of mental disorders (DSM-5)**. American Psychiatric Pub, 2013.
- [3] Richdale A, Schreck KA: Sleep problems in autism spectrum disorders: Prevalence, nature, & possible biopsychological aetiologies. Sleep Med Rev 2009, 13: 403-411.
- [4] Baker E, Richdale A, Short M, Gradisar M: **An investigation of sleep patterns in adolescents with high-functioning autism spectrum disorder compared with typically developing adolescents**. *Dev Neurorehabil* 2013, **16**: 155-165. DOI: 10.3109/17518423.2013.765518.
- [5] Montazeri F, de Bildt A, Dekker V, Anderson GM: (2019). **Network analysis of behaviors in the depression and autism realms: Inter-relationships and clinical implications**. *J Autism Dev Disord* 2019: online. Doi 10.1007/s10803-019003914-4.
- [6] Goldman SE, Alder ML, Burgess HJ., Corbett BA, Hundley R, Wofford D, Fawkes DB, Wang L, Laudenslager ML, Malow BA: **Characterizing sleep in adolescents and adults with autism spectrum disorders**. *J Autism Dev Disord* 2017, **47**:1682-1695. DOI 10.1007/s10803-017-3089-1.
- *[7] Baker EK, Richdale AL: **Examining the behavioural sleep-wake rhythm in adults with autism spectrum disorder and no comorbid intellectual disability**. *J Autism Dev Disor* 2017, **47**: 1207-1222. Doi 10.1007/s10803-017-3042-3. This paper showed the prevalence of CSWRDs in autistic adults using a multi-method approach. This has implications for assessment and treatment in adults presenting with insomnia symptomatology and for preventative strategies in younger cohorts.
- [8] Hoshino Y, Watanabe H, Yashima Y, Kaneko, M, Kumashiro H: **An investigation on the sleep disturbance of autistic children.** *Folia Psychiatr Neurol Japn* 1984, **38**:45–51.
- [9] Hirata I, Mohri I, Kato-Nishimura K, Tachibana M, Kuwada A, Kagitani-Shimono K, Ohno Y, Ozono K, Taniike M: **Sleep problems are more frequent and associated with problematic behaviors in preschoolers with autism spectrum disorder**. *Res Dev Disabil* 2016, **49-50**: 86 99. Doi. 10.1016/j.ridd.2015.11.002.
- [10] Malhi P, Kaur A, Singhi P, Sankhyan N: **Sleep dysfunction and behavioral daytime problems in children with autism spectrum disorders: A comparative study**. *Indian J Pediatr* 2019, **86**:12-17. Doi 10.1007/s12098-018-2731-z.
- [11] Lambert A, Tessier S, Rochette A, Scherzer P, Mottron L, Godbout R: **Poor sleep affects** daytime functioning in typically developing and autistic children not complaining of sleep

- problems: A questionnaire-based and polysomnographic study. Res Dev Disabil 2016, 23: 94-106. Doi.org/10.1016/j.rAS .2015.11.010.
- [12] Mazurek MO, Dovgan K, Neumeyer AM, Malow BA: Course and predictors of sleep and co-occurring problems in children with autism spectrum disorder. *J Autism Dev Disord* 2019. Doi 10.1007/s10803-019-03894-5.
- [13] van der Heijden KB, Stoffelsen RJ, Popma A, Swaab H: **Sleep, chronotype, and sleep hygiene in children with attention-deficit/hyperactivity disorder, autism spectrum disorder, and controls.** *Eur Child Adolesc Psychiatry* 2018, **27**: 99-111. Doi 10.1007/s00787-017-1025-8.
- [14] Fletcher FE, Foster-Owens MD, Conduit R, Rinehart NJ, Riby DM, Cornish KM: **The developmental trajectory of parent-report and objective sleep profiles in autism spectrum disorder: Associations with anxiety and bedtime routines.** *Autism* 2017, **21**: 493-503. DOI 10.1080/154002.2016.1180522
- *[15] Ballester P, Martinez JJ, Javaloyes A, Inda M, Fernandez N, Gazquez P, Aguilar VV, Perez A, Hernandez L, Richdale AL, Peiro AM: **Sleep problems in adults with autism spectrum disorder and intellectual disability**. *Autism Res* 2019, **12**: 66-79. doi: 10.1002/aur.2000 This paper comprehensively addresses sleep in a larger sample of adults with autism and ID for the first time using objective measurements. Results indicated the continuity of risk for poor sleep, regardless of age and IQ.
- [16] Hohn VD, deVeld DM, Mataw KJ, van Someren EJ, Begeer S: Insomnia severity in adults with autism spectrum disorder is associated with sensory hyper-reactivity and social skill impairment. *J Dev Disord* 2019, online. Doi.org/10.1007/s10803-019-03891-8.
- [17] Mazzone L, Postorino V, Siracusano M, Riccioni A, Ciratolo P: **The relationship between sleep problems, neurobiological alterations, core symptoms of autism spectrum disorder, and psychiatric comorbidities**. *J Clin Med* 2018, **7**:102-113. doi: 10.3390/jcm7050102.
- [18] Abel EA, Schwichtenberg AJ, Brodhead MT, Christ SL: **Sleep and challenging behaviors** in the context of intensive behavioral intervention for children with autism. *J Autism Dev Disord* 2018, **48**: 3871-3884. Doi 10.1007/s10803-018-3648-0
- [19] Hundley RJ, Shui A, Malow BA: **Relationship between subtypes of restricted and repetitive behaviors and sleep disturbance in autism spectrum disorder**. *J Autism Dev Disord* 2016, **46**:3448-3457. Doi 10.1007/s10803-016-2884-4
- [20] Johnson CR, Smith T, De Mand A, Lecavalier L, Evans V, Gurka M, Swiezy N, Bearss K, Scahill L: **Exploring sleep quality of young children with autism spectrum disorder and disruptive behaviors.** *Sleep Med* 2018, **44**: 61-68. doi.org/10.1016/j.sleep.2018.01.008
- [21] Veatch OJ, Sutcliffe JS, Warren ZE, Keenan BT, Potter MH, Malow BA: **Shorter sleep duration is associated with social impairment and comorbidities in AS**. *Autism Res* 2017, **10**: 1221-1238. Doi 10.1002/aur.1765

- [22] Sannar EM, Palka T, Beresford C, Peura C, Kaplan D, Verdi M, Siegel M, Kaplan S, Grados M: **Sleep problems and their relationships to maladaptive behavior severity in psychiatrically hospitalized children with autism spectrum disorder.** *J Autism Dev Disord* 2018, **48**: 3720-3726. DOI 10.1007/s10803-017-3362-3
- [23] Rattaz C, Michelon C, Munir K, Baghdadli A: Challenging behaviors at early adulthood in autism spectrum disorders: topography, risk factors and evolution. *J Intellect Disabil Res* 2018, **62**: 637-649. Doi 10.1111/jir.12503
- [24] Cohen S, Fulcher BD, Rajaratnam SM, Conduit R, Sullivan JP, St Hilaire MA, Phillips AJK, Loddenkemper T, Kothare SV, McConnell K et al: **Sleep patterns predictive of daytime challenging behavior in individuals with low-functioning autism**. *Autism Res* 2018, **11**: 391-403. Doi 10.1002/aur.1899.
- [25] Soke GN, Rosenberg SA, Hamman RF, Fingerlin T, Rosenberg CR, Carpenter L, Lee LC, Giarelli E, Wiggins LD, Durkin MS, et al: **Factors associated with self-injurious behaviors in children with autism spectrum disorder: Findings from two large national samples**. *J Autism Dev Disord* 2017, **47**: 285-296.
- [26] Smith CE, Carr EG, Moskowitz LJ: (2016). **Fatigue as a biological setting event for severe problem behavior in autism spectrum disorder**. *Res Autism Spectr Disord* 2016, **23**: 131-144. Doi 10.1016/j.rAS .2015.12.003
- [27] Mazurek MO, Sohl K: (2016). **Sleep and behavioral problems in children with autism spectrum disorder.** *J Autism Dev Disord* 2016, **46:** 1906-1915. Doi 10.1007/s10803-016-2723-7.
- *[28] Shui AM, Katz T, Malow BA, Mazurek MO: **Predicting sleep problems in children with autism spectrum disorders**. *Res Dev Disabil* 2018, **83**: 270-279. Doi 10.1016/j.ridd.2018.10.002 This paper examines a model for predictors of the development of sleep problems longitudinally in ASD. It uses an existing data set of training and test samples. Aggression was an important predictor. This has implications for prevention and treatment.
- [29] Thomas S, Lycett K, Papadopoulos N, Sciberras E, Rinehart N: **Exploring behavioral sleep problems in children with ADHD and comorbid autism spectrum disorder.** *J Atten Disord* 2018, **2**: 947-958. DOI: 10.1177/1087054715613439
- [30] Ramtekkar UP: **DSM-5** changes in attention deficit hyperactivity disorder and autism spectrum disorder: Implications for comorbid sleep issues. *Children* 2017, **4**: 62-72. doi:10.3390/children4080062
- [31] Salazar F, Baird G, Chandler S, Tseng E, O'Sullivan T, Holwin P, Pickles A, Simonoff E: Co-occurring psychiatric disorders in preschool and elementary school-aged children with autism spectrum disorder. *J Autism Dev Disord* 2015, **45**: 2283-2294. Doi 10.1007/s10803-015-2361-5

- [32] Becker S, Sidol C, Van Dyk T, Epstein J, Beebe D: **Intraindividual variability of sleep/wake patterns in relation to child and adolescent functioning: A systematic review**. *Sleep Med Rev*, 2017, **34**: 94-121. DOI: 10.1016/j.smrv.2016.07.004
- *[33] Papadopoulos N, Sciberras E, Hiscock H, Mulraney M, McGillivray J, Rinehart N: **The efficacy of a brief behavioral sleep intervention in school-aged children with ADHD and comorbid autism spectrum disorder**. *J Atten Dis* 2019, **23**: 341-350. DOI: 10.1177/1087054714568565. Children on the autism spectrum with comorbid ADHD (n=61) received behavioral treatment or "usual clinical care". Those who received the behavioral intervention improved in sleep and in daytime behaviors.
- *[34] Loring WA, Johnston RL, Shui AM, Malow BA: Impact of a brief behavioral intervention for insomnia on daytime behaviors in adolescents with autism disorders. *J Contemp Psychother* 2018, **48**: 165-177. Doi 10.1007/s10879-018-9381-3. Behavioral interventions for sleep hygiene and sleep onset latency were used with 18 adolescents on the autism spectrum. The interventions resulted in improvements in sleep and in behaviors and psychopathology (e.g., impulsivity, attention, anxiety, depression, hyperactivity).
- [35] Reynold KC, Patriquin M, Alfano CA, Loveland KA, Pearson DA: **Parent-reported problematic sleep behaviors in children with comorbid autism spectrum disorder and attention-deficit/hyperactivity disorder.** *Res Autism Spectr Disord* 2017, **39**: 20-32. doi.org/10.1016/j.rAS .2017.04.003
- [36] Hollocks MJ, Lerh JW, Magiati I, Meiser-Stedman R, Brugha TS: **Anxiety and depression in adults with autism spectrum disorder: A systematic review and meta-analysis**. *Psychological Med* 2019, **49**:559-572. Doi 10.1017/s003329171802283
- [37] Lever AG, Geurts HM: **Psychiatric co-occurring symptoms and disorders in young,** middle-aged, and older adults with autism spectrum disorder. *J Autism Dev Disord* 2016, **46**: 1916-1930.
- [38] Montazeri F, de Bildt A, Dekker V, Anderson G M: **Network analysis of behaviors in the depression and autism realms: Inter-relationships and clinical implications**. *J Autism Dev Disord* 2019: online. Doi.org/10.1007/s10803-019-03914-4
- [39] van Steensel FJA, Bogels SM, Perrin S: **Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis**. *Clin Child Fam Psychol Rev*, 2011, **14**: 302-317. Doi 10.1007/s10567-011-0097-0
- [40] Whitney DG, Shapiro DN, Peterson MD, Warschausky SA: **Factors associated with depression and anxiety in children with intellectual disabilities.** *J Intellect Dis Res* 2018, **63**: 408-417. doi: 10.1111/jir.12583
- [41] Wigham S, Rodgers J, South M, McConachie H, Freeston: **The interplay between sensory processing abnormalities, intolerance of uncertainty, anxiety and restricted repetitive behaviours in autism spectrum disorder**. *J Autism Dev Disord* 2015, **45**: 943-952. Doi 10.1007/s10803-014-2248-x

- [42] Uren J, Richdale AL, Cotton SM, Whitehouse AJ: **Sleep problems and anxiety from 2 to 8 years and the influence of autistic traits: A longitudinal study**. *Eur Child Adolesc Psychiatry*, 2019, online. doi 10.1007/s00787-019-01275-y
- [43] Tzischinsky O, Meiri F, Manelis L, Bar-Sinai A, Flusser H, Michaelovski A, Zivan O, Ilan M, Faory M, Menashe I, et al: **Sleep disturbances are associated with specific sensory sensitivities in children with autism**. *Molecular Autism* 2018, 9:22-31. Doi 10.1186/s13229-018-0206-8
- [44] Nadeau JM, Arnold EB, Keene AC, Cullier AB, Lewin AB, Murphy TK, Storch EA: Frequency and clinical correlates of sleep-related problems among anxious youth with autism spectrum disorders. *Child Psychiatry Hum Dev* 2015, **46**:558-566. Doi: 10.1007/s10578-014-0496-9.
- [45] 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 Medicine*, 2014, **15**:1082-1088. Doi 10.1016/j_sleep.2014.05.005
- [46] Baker EK, Richdale AL, Hazi A, Prendergast LA: **Assessing a hyperarousal hypothesis of insomnia in adults with autism spectrum disorder**. *Autism Res* 2019, **00**:1-14. DOI: 10.1002/aur.2094
- [47] Hohn VD, deVeld DM, Mataw KJ, van Someren EJ, Begeer S: Insomnia severity in adults with autism spectrum disorder is associated with sensory hyper-reactivity and social skill impairment. *J Autism Dev Disord* 2019. Doi 10.1007/s10803-019-03891-8.
- [48] Souders MC, Zavodny S, Eriksen W, Sinko R, Connell J, Kerns C, Schaaf R, Pinto-Martin J: **Sleep in children with autism spectrum disorder**. *Curr Psychiatry Rep* 2017, **19**: 34-50. Doi 10.1007/s11920-017-0782-x
- [49] Carmassi C, Palagini L, Caruso D, Masci I, Nobil L, Vita A, Dell'Osso L: **Systematic review of sleep disturbances and circadian sleep desynchronization in autism spectrum disorder: Toward an integrative model of a self-reinforcing loop**. *Frontiers Psychiatry*, 2019, **10**: 1-18, doi:10.3389/fpsyt.2019.00366.
- [50] Geoffray MM, Nicolas A, Speranza M, Georgieff N: **Are circadian rhythms new pathways to understand autism spectrum disorder?** *J Physiol Paris*, 2016, **110:** 434-438. Doi:10.1016.j.physparis.2017.06.002
- [51] Al-Otaish H, Al-Ayadhi L, Bjørklund G, Chirumbolo S Urbina M, El-Ansary A. **Relationships between absolute and relative ratios of glutamate, glutamine and GABA and severity of autism spectrum disorder**. *Metab Brain Disease*, 2018, **33:** 843-854. Doi: 10.1007/s11011-018-0186-6
- [52] Benabou M, Rolland T, Leblond CS, Millot, GA, Huguet G, Delorme R, Leboyer M, Pagan C, Callebert J, Maronde E, Bourgeron T. **Heritability of the melatonin synthesis variability in**

- **autism spectrum disorders**. *Scientific Reports*, 2017, **7:** 17746. DOI 10.1038/s41598-017-18016-3
- [53] Brondino N, Fusar-Poli L, Panisi C, Damiani S, Barale F, Politi P. **Pharmacological Modulation of GABA function in autism spectrum disorders: A systematic review of human studies**. *J Autism Dev Disord* 2016, **46**: 825-839. Doi /10.1007/s10803-015-2619-y
- [54] Franco-Pérez J, Ballesteros-Zebadúa P, Custodio V, Paz C. **Major neurotransmitters** involved in the regulation of the sleep-wake cycle. *Revista de Investigación Clinica*, 2012, **64:** 182-191.
- [55] Pagan C, Delorme R, Callebert J, et al. **The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectrum disorders**. *Transl Psychiatry*, 2014, **4**: e479. Doi: 10.1038/tp.2014.120
- [56] Yang Z, Matsumoto A, Nakayama K, Jimbo EF, Kojima K, Nagata K, Iwamoto S, Yamagat T. Circadian-relevant genes are highly polymorphic in autism spectrum disorder patients. *Brain Dev*, 2016 **38:** 91-99. Doi: 10.1016/j.braindev.2015.04.006
- [57] Veatch OJ, Pendergast JS, Alen MJ, Leu RM, Johnson CH, Elsea SH, Malow BA. **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. DOI:10.1007/s10803-014-2197-4
- [58] Maras A, Schroder CM, Malow BA, Findling RL, Breddy J, Nir T, Shagmoon S, Zisapel N, Gringras P. **Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder**. *J Child Adolesc Psychopharmacol*, 2018, **28:** 699-710. Doi: 10.1089/cap.2018.0020
- [59] Impellizzeri P, Vinci, E, Gugliandolo MC, Cuzzocrea F, Rosealba L, Russo T, Gravina MR et al. **Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients**. *Eur J Pediatr*, 2017, **176:** 947-953. DOI:10.1007/s00431-017-2933-9
- [60] Hansen MV, Halladin NL, Rosenberg J, Gögenur I, Møller AM. **Melatonin for pre- and postoperative anxiety in adults**. *Cochrane Data Base of Systematic Reviews*, 2015, Issue 4. Art. No.: CD009861. https://doi.org/10.1002/14651858.CD009861.pub2
- [61] Cunningham JEA, Shapiro CM: **Cognitive behavioural therapy for insomnia (CBT-I) to treat depression: A systematic review**. *J Psychosom Res*, 2018, **106**: 1-12. Doi doi.org/10.1016/j.jpsychores.2017.12.012

[62] McGowan SK, Espejo EP, Balliett N, Werdowatz, EA: **The effects of transdiagnostic group CBT for anxiety on insomnia symptoms**. *Cogn Behav Therapy*, 2016, **45**:2, 163-175, DOI: 10.1080/16506073.2015.1134639

External Funding: This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Table 1 Common sleep problems for individuals on the autism spectrum

Sleep Problem (abbreviation)	Description/Summary
Insomnia	Individuals on the AS tend to have trouble with settling at
	bedtime, co-sleeping, bedtime resistance, sleep hygiene
	problems (e.g., poor bedtime routines or sensitivity to
	sleeping environments)
Circadian Sleep-Wake	Individuals on the AS may have advanced (early onset/
Rhythm Disorder (CSWRD)	early waking) or delayed (late sleep, late waking) sleep-
	wake phase. Some may have irregular sleep-wake
	rhythms that are poorly entrained to the 24 hour light-
	dark cycle or even non-24 hour patterns
Increased Sleep Onset	Individuals on the AS tend to take longer than neuro-
Latency (SoL)	typical peers to fall asleep from the time of lights out
Reduced Total Sleep Time	Individuals on the AS may sleep fewer hours per night as
(TST)	compared to similar-age neuro-typical peers
Increased Wake After Sleep	Individuals on the AS may spend longer awake during
Onset (WASO)	the night than neuro-typical peers. This sometimes co-
	occurs with screaming, talking, or playing with toys
Poor Sleep Efficiency (SE)	Individuals on the AS tend to proportionately spend less
	time asleep while in bed compared to awake while in bed
	compared to neuro-typical peers
Parasomnias	Individuals on the AS can experience night waking
	similar to nightmares and night terrors, possibly more
	frequently than neuro-typical peers. They also experience
	higher rates of sleep enuresis (bed wetting)
Sleep-related breathing	Individuals on the AS may have difficulty with breathing
disorders	during sleep. This can include obstructive sleep apnea
	(breathing interruption due to obstructions, such as
	enlarged adenoids or tonsils) or snoring

Note: Representative references [3, 9, 10]