**Sleep Disorders in Children and Adolescents with Autism Spectrum Disorder: Diagnosis, Epidemiology and Management**

Samuele Cortese 1-4 \*, Fang Wang 5,1\*, Marco Angriman 6, Gabriele Masi 7, Oliviero Bruni 8

\*These two authors have contributed equally to the manuscript

1 Centre for Innovation in Mental Health, School of Psychology, Life and Environmental Sciences, University of Southampton, UK; Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, UK

2 Solent NHS Trust, Southampton, UK

3 Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK; National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre; NIHR MindTech MedTech Co-operative, Nottingham, UK

4 New York University Child Study Center, New York, NY, USA

5 School of Social Development, Nanjing Normal University, Nanjing, China

6 Department of Pediatrics, Child Neurology and Neurorehabilitation Unit, Central Hospital of Bolzano, Bolzano, Italy

7 IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Pisa, Italy

8Department of Developmental and Social Psychology, Sapienza University, Rome, Italy

**Address correspondence to:**

Samuele Cortese, M.D., Ph.D.

Centre for Innovation in Mental Health, School of Psychology

Faculty of Environmental and Life Sciences

University of Southampton, Southampton, UK,

Tel: +442380594604; Fax: +44238059500,

E-mail: [samuele.cortese@soton.ac.uk](mailto:samuele.cortese@soton.ac.uk)

**ABSTRACT**

Sleep problems are a common complaint in children/adolescents with Autism Spectrum Disorder (ASD). Correctly diagnosing and treating sleep problems in individuals with ASD is key, as they can add to the psychosocial burden of the disorder and exacerbate associated symptoms, such as inattention or irritability. Here, we provide an overview of the epidemiology, diagnosis and management of sleep problems/disorders in children and adolescents with ASD. This narrative review is mainly informed by a systematic search in Pubmed and PsycInfo (last search: 10 October 2019) of available pertinent meta-analyses. We also searched for randomised controlled trials (RCTs) published after the search date of available meta-analyses. As for the epidemiology of sleep disorders in ASD, recent meta-analytic evidence shows a pooled prevalence of 13% (95% Confidence Interval, CI = 9 to 17) in the ASD population, compared with 3.7 % in the general population. In terms of diagnosis of sleep disorders, it should be based on standardised criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, DSM-5 or International Classification of Sleep Disorders (ICSD)- third edition); clinicians should bear in mind that the communication difficulties presented by individuals with ASD may make the diagnostic process more challenging. Regarding the treatment, a meta-analysis of behavioural interventions, including only 3 RCTs, found significant effects in terms of increase in total sleep time (24.41 min, 95% CI 5.71, 43.11, P = 0.01), decrease in sleep-onset latency (-18.31 min, -30.84, -5.77, P = 0.004), and a significant effect on sleep efficiency (5.59, 0.87, 10.31, P = 0.02), albeit the risk of bias of the included studies was rated “high” in relation to issues with the blinding. The bulk of the evidence for the pharmacological treatment is for melatonin, with a meta-analysis of 5 double-blind RCTs showing large effect size, favouring melatonin, in sleep duration (44 min compared with placebo, Hedge's g 1.07 [95% CI: 0.49-1.65]) and sleep-onset latency (39 min compared with placebo, Hedge's g-2.46 [95% CI: -1.96 to -2.98]). We conclude that additional RCTs are desperately needed to support the management of sleep disorders in ASD with an evidence-based, precision medicine approach.

**Key points:**

* Sleep problems should be systematically assessed in children and adolescents with ASD
* Evidence on behavioral intervention is based on a limited number of RCTs
* Melatonin is the pharmacological intervention with the largest body of supporting evidence

1. **Introduction**

Autism spectrum disorder (ASD) is characterized by qualitative impairment in social interaction/communication and repetitive, restrictive or unusual sensori-motor behaviors/interest [1]. According to the latest estimate from the World Health Organisation (WHO) [2], ASD affects on average one in 160 children worldwide. ASD can be associated with other disorders, such as genetic diseases (e.g., fragile X syndrome), with other neuropsychiatric disorders, including Intellectual Disability, Attention-Deficit/Hyperactivity Disorder (ADHD), anxiety disorders, mood disorders, and with impairing symptoms, such as high levels of irritability [3].

Sleep problems are one of the most common complaints in individuals with ASD [4]. Correctly identifying and properly managing sleep problems associated with ASD is highly relevant from a clinical standpoint as they can add to the burden of the disorder and exacerbate specific associated symptoms, such as inattention or irritability.

Here, we provide an overview of the diagnosis, epidemiology and treatment of sleep problems associated with ASD

This review is based on meta-analytic evidence (when available), rather than individual studies, integrated with published recommendations from expert consensus. Indeed, although it is not intended as a formal systematic review, with a structured qualitative and quantitative appraisal of each pertinent study, the present narrative review was informed by available systematic reviews, retrieved via a search in Pubmed and PsycInfo (last search: 10 October 2019), with no language restrictions. Additionally, with regards to the evidence from randomized controlled trials (RCTs) of the treatment of sleep problems in ASD, to retrieve any additional study not included in available systematic reviews, we conducted a search in Pubmed and PsycInfo using the following search terms/syntax: (sleep OR insomnia) AND (autis\* OR pervasive developmental disorder\*) AND (random\*) AND (child OR children OR youth\* OR young people OR young person OR paediatr\* OR pediatric\* OR school-age OR teen).

1. **Diagnosis**

As for the diagnosis of sleep disorders in any child, the diagnostic definition of sleep disorders in children with ASD is based on standardised criteria from the International Classification of Sleep Disorders (ICSD)– third edition [5] or the DSM-5 [1]. Table 1 reports the main sleep disorders according to the DSM-5. Whilst the diagnosis of many sleep disorders requires so-called subjective methods, for some disorders (e.g., sleep*-*disordered*-*breathing) subjective methods are also needed. Subjective methods, typically relying on interviews, questionnaires, and/or sleep diaries, allow the clinicians to estimate subjective sleep items (Table 2), whilst objective methods, including actigraphy, polysomnography and multiple sleep latency test, focus on objectively defined parameters (Table 3). It goes without saying that the communication difficulties that individuals with ASD struggle with, may make the diagnostic process more challenging.

1. **Epidemiology**

A recently published systematic review with meta-analysis [6] on the prevalence of mental health conditions in individuals with ASD included 13 studies (for a total of 26 datapoints) reporting data on sleep disorders, defined as “any sleep disorder”, “all sleep disorders”, or “at least one sleep disorder” according to DSM-IV, DSM-5 or International Classification of Diseases, ICD-9/10 criteria. The authors found that the pooled prevalence of sleep disorders was 13% (95% Confidence Interval, CI = 9 to 17) in the ASD population, compared with 3.7 % in the general population. Of note, previous studies using less stringent criteria report higher prevalence of sleep “problems” [7]. The prevalence of sleep disorders in population/registry-based studies and in clinical sample-based studies was 11% (95% CI = 7 to 17) and 16% (95% CI = 8 to 25), respectively. Even though no sensitivity analysis limited to the studies (n = 9)[4, 8-15] in children was presented, a meta-regression did not find any significant effect of age on the pooled estimated prevalence of sleep disorders.

Another systematic review with meta-analysis [16] aimed to elucidate the specific sleep alterations, subjectively or objectively measured, significantly associated with ASD. Analysing data from 47 datasets, Díaz-Román et al. extracted subjective and objective sleep outcomes from 37 and 15 studies, respectively, with a number of participants ranging from 75 to 5430 for studies focusing on subjective sleep parameters and from 144 to 312 for sleep objective studies. Concerning subjective measures, children with ASD did not significantly differ from controls in terms of sleep quality (as defined in the individual publications), sleep efficiency or sleep duration (in minutes). However, compared with controls, children/adolescents with ASD presented with significantly higher bedtime resistance (Standardised Mean Difference = 1.00, 95% CI 0.67 to 1.33), sleep-onset delay (0.98, 0.66 to 1.29), sleep anxiety (0.96, 0.61 to 1.32), night awakenings (0.72, 0.44 to 1.01), parasomnias (0.88, 0.60 to 1.15), sleep-disordered*-*breathing (0.48, 0.28 to 0.67), daytime sleepiness (0.34, 0.16 to 0.52), sleep-onset latency (in min) (0.81, 0.59 to 1.02), restorative value of sleep (0.13, -0.96 to 1.02) and general sleep problems (0.93, 0.67 to 1.20), as well as significantly lower sleep duration (−0.88, –1.18 to −0.57). In relation to objective measures, considering Polysomnography, PSG-related outcomes, children with ASD were found to have significantly lower total sleep time (−0.90, –1.51 to −0.30), longer sleep-onset latency (0.53, 0.21 to 0.86), higher time spent in stage 1 sleep (0.48, 0.06 to 0.90), lower time of Rapid Eye Movements, REM sleep (−0.88, –1.56 to −0.21), lower sleep efficiency (−1.20, –1.98 to −0.41) and higher time awake-after-sleep-onset (0.49, 0.11 to 0.87), whilst no significant difference were detected for stage 2 and slow wave sleep duration, as well as REM latency. As for actigraphic measures, children with ASD showed significantly longer sleep-onset latency than controls (0.80, 0.55 to 1.05).

**4.Treatment**

4.1 Evidence-base

*4.1.1 Non-pharmacological treatment*

A recent meta-analysis by Keogh et al. [17] included RCTs of sleep-based behavioural interventions for children with ASD (≤ 18 years). According to the inclusion criteria, “behavioural interventions” were defined as any intervention using behavioural techniques, including reinforcement to support the desired behaviour. Based on a comprehensive search strategy to retrieve published reports, only three studies [18-20] met the inclusion criteria. In total, 146 participants were randomized across the three studies, with sample sizes in each arm ranging between 18 and 33 patients and a mean age ranging from 6.3 years to 10.3 years. Two studies [18, 19] relied on parental report of sleep difficulties, including sleep-onset latency, wake-after-sleep-onset or night-time awakenings. The third study [20] diagnosed participants with sleep-onset disorder, limit-setting disorder, delayed sleep phase or insomnia according to the American Academy of Sleep Medicine. The specific type of behavioural intervention varied across the three studies. In the study by Adkins et al. [18], an education pamphlet was provided to parents to read, without additional instruction from the study staff. In the study by Cortesi et al. [19], clinical psychologists delivered four-weekly 50-minute face- to-face Cognitive Behavior Therapy (CBT) sessions. Finally, Papadopoulos and colleagues [20] used two face-to-face sleep consultations and a follow-up phone call with a trained clinician. As for the study arms, whilst the study by Adkins et al. [18] and Papadopoulos et al. [20] included the active treatment vs placebo control, Cortesi et al. [19] compared melatonin, cognitive behavioral therapy (CBT), melatonin + CBT and placebo control. Given the need to pool outcomes measured with the same methods, Keogh et al. [17] were able to pool only two studies per outcome. The authors found a statistically significant increase in total sleep time in patients assigned to the behavioural sleep intervention arm (24.41 min, 95% CI 5.71, 43.11, P = 0.01), with no indication of statistical true heterogeneity (I2 = 0%), alongside a significant between-groups mean difference (-18.31 min, 95% CI -30.84, -5.77, P = 0.004) in sleep-onset latency in the intervention group as well as a statistically significant effect on sleep efficiency (5.59, 95% CI 0.87, 10.31, P = 0.02), albeit this last analysis was characterised by substantial heterogeneity (Chi2 = 3.92, df = 1, P = value = 0.05; I2 = 75%); an additional analysis found a significant improvement of the Children’s Sleep Habits Questionnaire (CSHQ) in the sleep behavioral group (-4.71, 95% CI -6.70, -2.73, P<0.00001), with no evidence of statistical true heterogeneity (I2 = 0%). Of note, in terms of the appraisal of the risk of bias, as it was not possible to blind participants to the arm of the intervention, all studies were considered by Keogh et al. [17] to be of high risk of bias in relation to the ‘blinding of participants and personnel’ of the Cochrane Risk of Bias assessment tool. This resonates with a previous meta-analysis by Meltzer and Mindell [21] focused on behavioural interventions for pediatric insomnia, concluding that there is low-level evidence for the use of behavioural interventions for children with special needs.

We note that additional non-pharmacological options, such as those based on physical activity, have been shown to produce medium albeit short-term effects on sleep in in pilot studies [22, 23]. Rigorous RCTs need to be conducted to provide evidence on these additional non-pharmacological options.

*4.1.2 Pharmacological treatment*

The bulk of the evidence is around melatonin, an endogenously produced indoleamine secreted by the pineal gland which, among others, has hypnotic and chronobiotic properties [24]. Melatonin should be administered 2-3 hours before the dim light melatonin onset when used as chronobiotic, and about 30 minutes before sleep as sleep inductor [24]. Doses range in general from 1 to 3 mg/night (5 mg in adolescents) [24], with small additional benefit when doses beyond 9 mg/night are used [24, 25]. No major side effects have been reported with melatonin. Reported side effects include morning drowsiness increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia. Concerns around impact on pubertal devolvement, hypothesised based on research in animal, remain unclear in humans [24]. No clear guidelines on the duration of treatment are available. A limited number of follow-up studies, showing maintenance of efficacy and generally good tolerability up to 4 years of use, are available [24, 26].

In terms of available evidence on the pharmacological treatment, Rossignol and Frye [27] conducted a systematic review and meta-analysis of five double-blind, placebo-controlled randomized cross-over trials of melatonin for children with non-syndromic ASD (n= 4 studies) or syndromic ASD (Rett syndrome, n =1 study). In four of out the five studies, a wash-out period between pre and post cross- over phases was implanted. The meta-analysis showed significant improvements, with large effect size, favouring melatonin, in sleep duration (73 min compared with baseline, Hedge's g 1.97 [95% confidence interval CI 1.10-2.84]; 44 min compared with placebo, Hedge's g 1.07 [95% CI 0.49-1.65]) and sleep-onset latency (66 min compared with baseline, Hedge's g-2.42 [95% CI -1.67 to -3.17]; 39 min compared with placebo, Hedge's g-2.46 [95% CI -1.96 to -2.98]). However, no significant effects were found in night-time awakenings. No evidence of publication bias was found. The mean study quality, rated with the Downs and Black checklist, was 19.9 (Standard Deviation, SD: 1.66) out of 31 (range 17-22). Small sample sizes and variability in study protocols related to the measurement of changes in sleep parameters were the main factors decreasing the overall study quality. Of note, no or minimal adverse events during treatment with melatonin were reported.

*4.1.3 Meta-synthesis*

In addition to the above-mentioned individual systematic reviews/meta-analysis, a recent meta-review (i.e., systematic review of systematic reviews) by Cuomo et al. [28] collected all available systematic reviews with or without meta-analyses and rated their quality. Cuomo and colleagues [28] included eight systematic reviews, among which only one, the above mentioned study by Rossignol and Frye [27], included also a meta-analysis. Interventions included in the retained studies were as follows: melatonin, pharmacologic treatments other than melatonin (clonidine, benzodiazepines, risperidone), behavioral interventions, parent education, and alternative therapies. A meta-synthesis was performed using 38 studies, retrieved from the eight systematic reviews, that shared a common set of inclusion criteria established by the authors. Seventeen sleep parameters were considered as outcomes: sleep latency, sleep duration, longest sleep episode, night wakings, morning waking, disturbed sleep, sleep efficiency, nocturnal activity, bedtime resistance, co-sleeping, self-settling, parasomnias, restless sleep, periodic leg movement, sleep-disordered*-* breathing, sleep anxiety, and sleep problems Not Otherwise Specified, NOS.

The meta-synthesis showed that, overall, melatonin had a level of efficacy ranging from weak to strong across all sleep outcomes. The efficacy was deemed strong for the following parameters: sleep latency, sleep duration, bedtime resistance, and co-sleeping. For longest sleep episode, night wakings, nocturnal activity, parasomnias, sleep- disordered*-*breathing, sleep anxiety and sleep problems NOS the efficacy was deemed moderate. Weak effects were found for sleep efficiency. Regarding other pharmacological interventions, porcine secretin and the a2-adrenergic agonist clonidine had overall moderate effects in relation to sleep duration. Additionally, clonidine was moderately efficacious for night wakings and sleep latency. The efficacy of porcine secretin on sleep bedtime resistance was deemed very weak. Furthermore, clonidine efficacy on morning wakings was rated weak. Benzodiazepines effects on parasomnias were deemed as very weak in a single study, while risperidone showed a strong effect in terms of improving sleep duration.

As for behavioral interventions, they were deemed to have very strong effects for morning waking, co- sleeping, and self-settling, even though heterogeneity across study outcomes was substantial. Additionally, behavioral interventions had moderate effects on night wakings and only a weak effect on the other sleep problems. Parent education/education programs had the strongest effect, across all the included interventions, on the sleep problem “self-settling”, but low moderate or only weak effects on the other sleep problems. Finally, regarding alternative therapies (massage therapy, aromatherapy, and multivitamin and iron supplementation), with the exception of massage therapy which had strong effects on sleep problems not otherwise specified (NOS), no significant effects were found.

*4.1.4 Additional trials*

In our own search that we conducted for the present review, we found only 2 RCTs [29, 30] not included in the systematic reviews/meta-analyses discussed in this review (Table 4). A trial by Gringras et al. [29] showed the efficacy and good tolerability of a new formulation of prolonged-release melatonin (pediatric-appropriate, prolonged-release melatonin mini-tablets PedPRM), which can be easily swallowed given the small size of the tablet, that has been approved by the FDA and in some European countries specifically for the treatment of sleep problems in children with ASD. The study by Gringras et al. [29] included a 2-week, single-blind placebo run-in, a randomized double-blind efficacy and safety assessment of 13 weeks of PedPRM /placebo treatment, and an open-label treatment comprising 13 weeks of PedPRM. A total of 95 participants completed the double-blind phase. The dose titration was from 2-5 mg/day up to 10 mg/day. At the end of the double-blind phase, children slept on average 57.50 minutes longer in the PedPRM group compared to 9.14 minutes longer in the placebo- group (p = .034), as reported by caregivers via a Sleep and Nap Diary (SND). Furthermore, sleep latency reported via SND decreased by 39.6 minutes on average in the PedPRM and 12.5 minutes in the placebo arm, respectively (p =0.011). The significant differences between PedPRM and placebo effects were already evident at week 3. Treatment-emergent adverse events were reported by 85.0% of the participants in the PedPRM group and 76.9% in the placebo group, with most of these events similar between groups. Somnolence and headache were more common in the PedPRM group. In the open-label efficacy and safety follow-up study on the same sample [31], 95 participants received PedPRM (2/5 mg) according to the double-blind phase dose, for an additional 39 weeks, with optional dose adjustment up to 10 mg/day after the first 13 weeks. After 52 weeks of treatment, those in the PedPRM group slept 62.08 (SE: 21.5) minutes longer (p = 0.007), fell asleep 48.6 (SE: 10.2) minutes faster (p < 0.001); had 89.1 (25.5) minutes longer uninterrupted sleep episodes (p = 0.001); 0.41 (0.12) less nightly awakenings (>50% decrease; p = 0.001); and better sleep quality (p < 0.001) compared with baseline. PedPRM continued to be a generally safe treatment. The most commonly observed treatment-related adverse events were fatigue (in 5.3% of participants) and mood swings (in 3.2% of participants).

The second RCT [30] that we found was a 2-month, double-blind, randomized and placebo-controlled trial testing the effects of carnosine, an antioxidant, antitoxic and neuroprotective agent. Out of the 50 initially randomized, 43 patients completed the study. Results showed significant reduction in the daytime sleepiness and total sleep disorders score of the Iranian version of Children’s Sleep Habits Questionnaire (CSHQ) in the carnosine- group when compared with the pre-test values (p=0.022 and p<0.001, respectively). At the end of intervention, significant reduction was observed in sleep duration, parasomnias and total sleep disorders score in the carnosine group (<0.05), even though no effect sizes were provided in the article.

4.2 Guidance on the management of sleep problems in children with ASD

Guidance is available to support the management of sleep disorders/problems in children with ASD. The National Institute for Health and Clinical Excellence (NICE) guidelines [32] highlight the importance of assessing the type of sleep environment, as well as the role of possible comorbidities (e.g., ADHD), sleep breathing alterations and/or ongoing pharmacological treatments in contributing to the subjective sleep complaints. They also recommend that pharmacological treatments should be used only when behavioral strategies are not effective and should be implemented in conjunction with behavioral strategies.

Likewise, the Sleep Committee of the Autism Treatment Network (ATN) [33] recommended to: 1) systematically screen children with ASD for sleep problems; 2) identify possible medical contributors to insomnia, such as gastrointestinal disorders, epilepsy, pain, nutritional issues, sleep-disordered*-*breathing, restless legs, psychiatric conditions (including anxiety, depression, and bipolar disorder), and medications, a careful review of medications should be performed; 3) use educational/behavioral interventions as first-line of treatment. The committee noted that the core problems of ASD, including difficulty with emotional regulation, and deficits in communication skills, may hamper the establishment of sound bedtime behaviors and routines. Behavioral strategies recommended by the ATN include extinction (e.g., withdrawal of reinforcement for inappropriate bedtime behaviors) and positive reinforcement of adaptive sleep behavior, accompanied by sleep hygiene. However, the ATN highlights that the evidence base for behavioral intervention for sleep problems in ASD is limited; 4) consider pharmacological options as second-line approach, as the bulk of the evidence is for melatonin.

We also mention here a guidance paper by Bruni et al. [34] based on available RCTs (mostly, for melatonin), or, when lacking, authors’ experience, on the management of sleep problems in children with neurodevelopmental disabilities, including ASD. Bruni et al. [34] point out that, even though behavioral interventions, supported by low-to-moderate level of evidence, should be considered the first-line treatment, they are often difficult to implement due to the paucity of skilled therapists in child and adolescent (neuro)psychiatric services. Even though antihistamine agents are commonly used, the evidence base underpinning their use is very limited. The use of benzodiazepines is discouraged in children and should only be used for transient insomnia, especially in the presence of daytime anxiety. An increasing body of evidence supports melatonin as the safest choice for children with NDDs. Very limited evidence is available for zolpidem, zaleplon, and eszopiclone. Alpha-agonists such as clonidine to improve sleep-onset latency could be an option, especially with comorbid ADHD and Tourette’s syndrome. Bruni et al. [34] discouraged in general the use of tricyclic antidepressants, due to their safety profile, and acknowledged trazodone and mirtazapine as promising options albeit further studies are required. In line with other recommendations, Bruni et al. [34] point out how evidence favours melatonin as efficacious and well tolerated agent. Bruni et al. [34] also provided specific recommendations for the choice of the pharmacological agent according to the specific sleep problem/disorder, as follows: 1) irregularity and difficulty in sleep-onset: possible options: melatonin, antihistamines, clonidine, clonazepam, Z drugs; 2) middle of the night awakenings: 5-hydroxy-tryptophan, sedating antidepressants (trazodone, mirtazapine), atypical antipsychotics (risperidone), especially with associated irritability and/or aggression; 3) frequent nocturnal awakenings: antihistaminics, benzodiazepines, Z drugs, atypical antipsychotics; 4) motor hyperactivity with nocturnal awakenings: if Restless legs syndrome/periodic limbs movement disorder: iron, vitamin D, gabapentin, dopamine agonists; 5) abnormal pattern of sleep-wake timing (circadian rhythm disorder): melatonin; 6) Non-Rapid Eye Movement, NREM parasomnias: clonazepam, 5-hydroxy-tryptophan.

1. **Conclusions and future perspectives**

Sleep problems are an important, frequent, and impairing comorbidity in children and adolescents with ASD. To date, evidence from RCTs on the short-term treatment of sleep problems in youth with ASD is limited, with melatonin being the option with the largest amount of evidence pointing to its efficacy and good tolerability. Evidence is also limited on the treatment in the longer term. An increased body of RCTs is desperately needed on available options, which will then make it possible to pool in comparative meta-analyses (i.e., network meta-analyses, NMA) allowing the establishment of a hierarchy of treatments in terms of efficacy and tolerability. Additionally, sequential studies are needed to establish how best to sequence pharmacological and non-pharmacological approaches in specific profiles of patients. Finally, a large body of RCTs will allow the conduct of individual patient data NMA, providing indications of the best approach according to the specific profile of individual patients. This will move the management of sleep problems in children and adolescents with ASD from a trial-and-error strategy to an evidence-based, precision medicine approach.

**Table 1. Main sleep-wake disorders according to the DSM-5 (excluding “other” or “unspecified” types).**

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Insomnia disorder (Inadequate quantity or quality of sleep)

Hypersomnolence disorder (Excessive daytime sleepiness)

* *Narcolepsy* (with periods of extreme daytime sleepiness, often accompanied by muscle weakness)

Breathing-related sleep disorders

* *Obstructive Sleep Apnea Hypopnea* (blood oxygen desaturation due to respiratory obstruction during sleep)
* *Circadian Rhythm Sleep-Wake Disorders* (disruption of alignment between endogenous and exogenous rhythm of sleep/wake)

Parasomnias (non epileptic paroxysmal events during sleep)

* *Non-rapid Eye Movement Sleep Arousal Disorders*
* *Nightmare Disorders*
* *Rapid Eye Movement Sleep Behavior Disorder*

Restless Legs Syndrome (defined by urge to move the legs (or other body parts) accompanied by uncomfortable sensations)

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**Table 2. Subjective sleep parameters.**

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| *1. Bedtime Resistance* (BR) | Includes a series of behaviors such as refusal to get ready for bed/ to remain in the bed, or requiring a parent to be present at bedtime. Additional reasons for the sleep resistance include: inappropriate sleep schedule, delayed sleep phase, nighttime fears, Restless Legs Syndrome |
| 2. *Sleep*-*Onset Difficulties* (SOD) | Difficulty with falling asleep (within 20 min after going to bed). Psychopathological conditions (e.g. mood or anxiety disorders), inappropriate sleep hygiene, or specific sleep disorders (e.g. Restless Legs Syndrome) may contribute to SOD |
| 3. *Night Awakenings* (NA) | They are often related to inappropriate sleep-onset associations (conditions that the child learns to need in order to fall back to sleep):. Risk factors include: co-sleeping, breast-feeding, sleep-disrupting events (e.g. illness), difficult temperament, insecure maternal-child attachment, maternal depression, medical concerns such as reflux and pain, underlying sleep-disrupting conditions such as Periodic Limb Movement Disorder, obstructive sleep apnea, or inadequate sleep hygiene. |
| 4. *Sleep Duration* (SD) | Duration of total sleep, as perceived by the parent or the child. Defined as time asleep at night, or as time asleep plus in bed awake at night, or as total time asleep across 24 h. |
| 5. *Difficulties with Morning Awakenings* (DMA) | The child refuses to wake up by himself or having difficulty getting out of bed in the morning. It may be the consequence of inadequate sleep or the result of parental difficulties in setting limits and managing behavior. |
| 6. *Daytime Sleepiness* (DS) | It can be caused by chronic sleep deprivation, underlying sleep disrupters (e.g. obstructive sleep apnea, Restless Legs Syndrome and Periodic Limb Movements in Sleep), psychiatric disorders (e.g. anxiety or mood disorders), and neurologic causes (e.g. posttraumatic hypersomnia). An excessive daytime sleepiness with an urge to fall asleep is the hallmark of narcolepsy. Rarely, it can be the expression of Kleine-Levin syndrome. |
| 7. *Sleep-Disordered-Breathing* (SDB) | A continuum , ranging from primary snoring, upper airway resistance syndrome (characterized by snoring and increased respiratory effort), partial obstructive hypoventilation hypopneas (characterized by snoring, increased respiratory effort, and arousals), to obstructive sleep apnea (characterized by snoring, apneic pauses, and arousals). Of note, the diagnosis of SDB requires a polysomnographic recording. |
| 8. *Restless Sleep* (RS) | Children present with excessive movements of some parts of the body or the whole body. |
| 9. *Parasomnias* (PA) | Undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep. They include: sleepwalking, sleep terrors, nightmare disorder, enuresis, sleep-related groaning, etc. |

**Table 3. Objective sleep parameters**

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| 1. *Sleep*-*Onset Latency evaluated with Polysomnography* (SOL-PSG) | The time in minutes from lights-off to the first epoch of stage 2 sleep. |
| 2. *Sleep*-*Onset Latency evaluated with Actigraphy* (SOL-a) | Time in minutes from getting into bed/“lights out” to  actigraphically defined sleep-onset (the first 10-minute interval in which there is activity in no more than 1 epoch that is above the threshold set for determining “wake”). |
| 3. *Number of Stage Shifts in total sleep time* (SHIFTS) | Number of shifts from one sleep stage to another during the total sleep time. |
| 4. *Number of Stage Shifts/hour sleep* (SHIFTS/h) | Number of shifts from one sleep stage to another in a hour of sleep. |
| 5. *Percentage of Stage 1* (ST1%) | Percentage of stage 1 sleep (defined by disappearance of the EEG alpha pattern and the establishment of theta waveforms (2-7 cps) and slow, rolling eye movement) in total sleep time (i.e., total sleep episode less awake time). |
| 6. *Percentage of Stage 2* (ST2%) | Percentage of stage 2 sleep (defined by the appearance of low-frequency, high amplitude discharges (K complexes) and brief high-frequency (12-14 CPS), variable amplitude discharges (sleep spindles) on a background of theta waveforms) in total sleep time. |
| 7. *Percentage of Slow-Wave Sleep* (SWS%) | Percentage of stage 3 (characterized by slow waves, high amplitude, low frequency (0.5-2 cps) delta waveforms in at least 20% of total sleep time) + stage 4 (characterized by slow waves in more than 50% of total sleep time) in total sleep time. |
| 8. *Rapid Eyes Movements* (REM) *sleep latency* (REML) | The time from sleep-onset to the first appearance longer than 2 minutes of REM sleep (defined by rapid bursts of back-and-forth eye motion, muscle atonia, and EEG waveform (theta and beta activity) typical of lighter sleep stages). |
| 9. *Percentage of REM* (REM%) | Percentage of REM sleep in total sleep time. |
| 10. *Sleep Efficiency* *assessed with Polysomnography* (SE-PSG) | Ratio of total sleep time, assessed with PSG, to nocturnal time in bed. |
| 11. *SE assessed with Actigraphy* (SE-a) | Ratio of total sleep time, assessed with actigraphy, to nocturnal time in bed. |
| 12. *True Sleep on Actigraphy* (TS) | Sleep time (assessed by actigraphy) excluding all periods of wakefulness. |
| 13. *Night Wakings on Actigraphy* (NW) | Number of wakings during night, as assessed by actigraphy, which last at least 5 minutes. |
| 14. *Average times to fall asleep at MSLT* (MSLT) | Means of average times on all Multiple Sleep Latency Test naps opportunities to fall asleep. The lower it is, the higher the sleepiness during daytime. |
| 15. *Apnea-Hypopnea Index* (AHI) | The number of apnea and hypopnea episodes per hour (Apnea = cessation of airflow for at least 10 seconds; =50% reduction in airflow (measured with a validated technique) or a reduction in airflow associated with a 3% fall in arterial oxygen saturation and/or an arousal). |

**Table 4. Additional RCTs of Pharmacological and No-pharmacological Treatments in Sleep Disorder in Children with ASD not included in currently published systematic reviews/meta-analyses (up to 10 October 2019)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Country | Participants  (Male) | Age, y | Sleep Disorder | Comorbid Disorder | Intervention | Sleep measures | Main results found |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Gringras  (2017) [29] | USA& Europe | 125 (92) | 2-17.5 | Insomnia | ASD and NGD (100%) | Melatonin  (Melatonin group VS. Placebo group) | SND  CSDI | After 3 weeks, participants with PedPRM had significant improvements in total sleep time, sleep latency and longest sleep episode compared to those with placebo.  After 13 weeks, participants with PedPRM had significant improvements in total sleep time and sleep latency compared to those with placebo. |
|  |  |  |  |  |  |  |  |  |
| Mehrazad-Saber (2018) [30] | Iran | 50 (NS) | 4–16 | Sleep disorder  (not mention the criteria of sleep disorder) | ASD  (100%) | L-Carnosine  (L-Carnosine group VS. Placebo group) | CSHQ | Carnosine supplementation significantly improved sleep duration, parasomnias and total sleep disorders score compared with the control group. |

ASD = autism spectrum disorder, NGD = Neurogenetic disorders

CSHQ = Child Sleep Habits Questionnaire, SND = parent-reported Sleep and Nap Diary, CSDI = Composite Sleep Disturbance Index

**Compliance with Ethical Standards**

***Conflicts of interest***

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