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Sleep Disorders in children & Adolescents with ASD

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دانشگاه علوم پزشکی مشهد

Sleep Disorders in children & Adolescents with ASD

- Sleep problems are one of the most common complaints in individuals with 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.**

- **Diagnosis**

- **Like** for the diagnosis of sleep disorders in any child, the diagnostic definition of sleep disorders in children with ASD is based on **standardized criteria** :

- From the third edition of the ***International Classification of Sleep Disorders*** (ICSD).
- Or the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* **(DSM-5)**

Main sleep–wake disorders according to the DSM-5 (excluding “other” or “unspecified” types)

- 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)

- **Subjective sleep parameters**

1. 1. Bedtime resistance (BR)
2. 2. Sleep-onset difficulties (SOD)
3. 3. Night awakenings (NA)
4. 4. Sleep duration (SD)
5. 5. Difficulties with morning awakenings (DMA)
6. 6. Daytime sleepiness (DS)
7. 7. Sleep-disordered breathing (SDB)
8. 8. Restless sleep (RS)
9. 9. Parasomnias (PA)

Objective sleep parameters

- 1. Sleep-onset latency
- 2. Sleep-onset latency evaluated with actigraphy (SOL-a)
- 3. Number of stage shifts in total sleep time (SHIFTS)
- 4. Number of stage shifts/hour sleep (SHIFTS/h)
- 5. Percentage of stage 1 (ST1%)
- 6. Percentage of stage 2 (ST2%) me
- 7. Percentage of slow-wave sleep (SWS%)
- 8. Rapid eye movement sleep latency (REML)
- 9. Percentage of REM (REM%)
- 10. Sleep efficiency assessed with polysomnography (SE-PSG)
- 11. Sleep efficiency assessed with actigraphy (SE-a)
- 12. True sleep on actigraphy (TS)
- 13. Night wakings on actigraphy (NW)
- 14. Average times to fall asleep at MSLT (MSLT)
- 15. Apnea–Hypopnea Index (AHI) The number

- **Subjective** methods,typically relying on **interviews, questionnaires, and/or sleep diaries**, allow clinicians to estimate subjective sleep items.

- Whilst **objective** methods, including **actigraphy, polysomnography** (PSG), and the Multiple

Sleep Latency Test, focus on objectively defined parameters

- **It goes without saying that the communication difficulties that individuals with ASD struggle with, may make the diagnostic process more challenging.**

Epidemiology

- **A recently published systematic review with meta-analysis** on the prevalence of mental health conditions in individuals with ASD included :

- 13 studies (for a total of 26 data points) reporting data on sleep disorders, defined as “anysleep 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] 9–17) in the ASD population,compared with **3.7%** in the general population.

- **In pre school** children sleep disorders stand out as one of the most commonly reported; their prevalence in ASD children range from **45% up to 86% .**

Epidemiology

- However, compared with controls, children/adolescents with ASD presented with :

- **significantly higher bedtime resistance ,sleep-onset delay, sleep anxiety night awakenings ,**
- **parasomnias ,**sleep-disordered breathing, daytime sleepiness ,sleep-onset latency (in minutes)
- ,restorative value of sleep, **and general sleep problems ,as well as significantly lower sleep duration .**

- In relation to **objective measures**, considering **PSG**-related outcomes, children with ASD were found to have
- **significantly lower total sleep time** ,longer sleep-onset latency, **higher time spent in stage 1 sleep**
- , **lower time** of rapid eye movement (REM) sleep,lower sleep efficiency, and higher time awake after sleep onset
- , whilst no significant difference was 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** .

Treatment

- **Non-pharmacological Treatment**

- A recent meta-analysis by Keogh et al included RCTs of sleep-based behavioral interventions for children with ASD (≤ 18 years).
- According to the inclusion criteria,“behavioral interventions” were defined as any intervention
- using behavioral techniques, including **reinforcement** to support **the desired behavior.**

- Relied on parental report of sleep difficulties,including sleep-onset latency, wake after sleep onset
- or night-time awakenings.
- In the study by Cortesi et al., clinical psychologists delivered four-weekly 50-min face-to-face cognitive
- behavior therapy (CBT) sessions.to be of **high risk of bias** in relation to the “blinding of participants and personnel” of the Cochrane risk-of-bias assessment tool

- Meltzer and Mindell focused on behavioral interventions for pediatric insomnia, concluding
- that there is **low-level evidence** for the use of behavioral interventions for children with special needs.

- Rigorous RCTs need to be conducted to provide evidence on these additional non-pharmacological
- options.

Treatment

- **Pharmacological Treatment**

- The bulk of the evidence is around **melatonin**, an endogenously produced indoleamine secreted by the pineal gland which has, among others**, hypnotic and chronobiotic properties.**
- Melatonin should be administered **2–3 h before** the dim light melatonin onset when used as a **chronobiotic,**
- and about **30 min before sleep as a sleep inductor .**
- Dosages range in general from **1 to 3 mg/night (5 mg in adolescents**), with small additional benefit when dosages beyond **9 mg/night** are used.

- **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**, hypothesized based on **research in animals**, remain unclear in humans

Treatment

- **Pharmacological Treatment**

- **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.

- 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**.

Treatment

Pharmacological Treatment

- Regarding other pharmacological interventions, **porcine secretin** and the α2-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.

- **Benzodiazepine's** effects on parasomnias were deemed as very weak in a single study, while **risperidone** showed a **strong effect** in terms of **improving sleep duration**.

Treatment

- **Additional Trials**

- A trial showed the efficacy and good tolerability of a **new formulation of prolonged release**
- **melatonin** [pediatric-appropriate, prolonged-release melatonin mini-tablets **(PedPRM)]** (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.

- Efficacy and safety assessment of 13 weeks of PedPRM/placebo treatment. A total of 95 participants completed the double-blind phase. The dose titration was **from 2–5 mg/day up to 10 mg/day**.

- **Treatment-emergent adverse events :**
- **Somnolence and headache were more common** , The most commonly observed treatment-related
- adverse events were **fatigue** (in 5.3% of participants) and **mood swings**

Treatment

Additional Trials

- The second RCT that we found was a 2-month, double-blind, randomized, placebo-controlled trial testing the effects of **carnosine (betea alanine and histidine), 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 CSHQ in the carnosine group when compared with the pre-test values.
- .

- **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 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) recommends 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 treatment; and
- (4) consider pharmacological options as a second-line approach, the bulk of the evidence being for melatonin.

- 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.

- A guidance paper by Bruni et al.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. point out that , even though behavioral interventions, supported by a **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 neurodevelopmental disorders.**

- **Alpha-agonists such as clonidine to improve sleep-onset latency** could be an option, especially

with comorbid ADHD and Tourette’s syndrome.

- **Trazodone and mirtazapine as promising options albeit further studies are required**.

- Bruni et al. 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, and Z drugs;
- **(2)** *middle of the night awakenings*: 5-hydroxy-tryptophan, sedating antidepressants
- (trazodone, mirtazapine), and atypical antipsychotics(risperidone), especially with associated irritability and/or aggression;
- **(3)** *frequent nocturnal awakenings*: antihistaminics, benzodiazepines, Z drugs, and atypical antipsychotics;

- **(4)** *motor hyperactivity with nocturnal awakenings*: if restless leg syndrome/periodic limbs movement disorder:**iron, vitamin D, gabapentin, and dopamine agonists**;
- **(5)***abnormal pattern of sleep–wake timing* (*circadian rhythm disorder*): melatonin; and
- **(6)** *non-rapid eye movement parasomnias* : clonazepam and 5-hydroxy-tryptophan.

- **Key points :**
- Sleep problems should be **systematically assessed** in children and adolescents with autism spectrum disorder.
- Evidence on **behavioral intervention** is based on **a limited** number of randomized controlled trials.
- **Melatonin** is the pharmacological intervention with the **largest** body of supporting evidence.