

# Focused clinical question regarding National Clinical recommendation on the use of Melatonin for children and adolescents with sleep disorders

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**PICO question: Should melatonin be used in children and adolescents with sleep disorders where sleep hygiene measures have not had sufficient effect?**

## **Background:**

Sleep is of great importance for children and young people's health, development and well-being, as both the body and the brain recover during sleep. Therefore, sleep problems may have major negative effects on the child's and young person's daily life. Insufficient sleep can cause daytime fatigue, irritability, mood swings, behavioral problems, difficulty concentrating, impaired learning ability and poorer performance in school and educational context<sup>1,2,3</sup>. Sleep problems not only affect the child or young person, but can have a negative impact on the whole family.

Sleep disorders among children and adolescents are very common. Sleep disorders are particularly common among children and adolescents with mental health problems, but also among children and adolescents without known mental health problems, sleep disorders are common<sup>1,4</sup>. In a Danish study among young people between the ages of 15 and 25, 28% of girls and 21% of boys stated that they had sleep problems weekly<sup>5</sup>.

Sleep hygiene measures are first-line treatment for children and adolescents with sleep disorders<sup>2</sup>. Other non-pharmacological treatment initiatives are, for example, the use of weight blankets<sup>4</sup>, cognitive behavioral therapy<sup>6</sup>, light therapy<sup>7</sup> etc.

<sup>1</sup> Danish Medicines Agency. Bivirkninger hos børn og unge – et litteratur studie. Lægemiddelstyrelsen 2016

<sup>2</sup> Danish Health Authority. Vejledning om forebyggende sundhedsydelse til børn og unge. Sundhedsstyrelsen 2019.

<sup>3</sup> Combs et al. Insomnia, health related quality of life and health outcomes in children. A seven year longitudinal cohort. Sci Rep 2016 Jun 13;6:27921. doi: 10.1038/srep27921.

<sup>4</sup> Agersted og Pagsberg. Søvnforstyrrelser hos børn og unge. Ugeskrift for læger 2021. Apr 26;183(17):V11200826.

<sup>5</sup> National Institute of Public Health. Unges søvnvaner. Resultater fra UNG 2019-Sundhed og trivsel på gymnasiale uddannelser 2019. Statens Institut for Folkesundhed juni 2020.

<sup>6</sup> Dewald-Kaufman et al. Cognitive Behavioral Therapy for Insomnia (CBT-i) in School-Aged Children and Adolescents. Sleep Med Clin. 2019 Jun;14(2):155-165.

<sup>7</sup> Wei et al. Efficacy and safety of melatonin for sleep onset insomnia in children and adolescents: a meta-analysis of randomized controlled trials. Sleep medicine 68 (2020) 1-8.

Pharmacological treatment of sleep disorders in children and adolescents in Denmark primarily includes melatonin<sup>8</sup>. Melatonin is a sleep-regulating hormone that helps establish and maintain sleep and plays an important role in regulating our circadian rhythm. Unlike other sleeping pills (e.g. Benzodiazepine and Promethazine), intolerance of or dependence on melatonin has not been reported, nor are there any known serious side effects<sup>1</sup>. However, the long-term effects are sparsely elucidated, and there is currently insufficient knowledge to be able to rule out harmful effects of long-term use<sup>1,9</sup>.

In Denmark, melatonin-containing drugs are approved for the treatment of children and adolescents aged 2-18 years with autism and/or Smith-Magenis syndrome<sup>10</sup>, as well as children and adolescents aged 6-17 years with Attention Deficit Hyperactivity Disorder (ADHD)<sup>11</sup>.

From 2011 to 2020, the number of users of prescription melatonin among 0 to 17 year olds has more than doubled, as the number of users has increased from 4,630 per year in 2011 to 13,295 per year in 2020<sup>12</sup>. Among 18 to 24 year olds, the number of users has more than quintupled, and the number of users has increased from 1,760 in 2011 to 9,695 in 2020<sup>12</sup>. The increase is seen for both children and young people who have a registered diagnosis that may constitute a relevant indication for use of melatonin (e.g. behavioral and emotional disorders or mental development disorders)<sup>8</sup> and for children and adolescents who do not have a registered relevant diagnosis for melatonin use<sup>8</sup>.

The Danish National Board of Health recommends the use of melatonin in sleep disorders where sleep hygiene measures do not have a sufficient effect, for both children and adolescents diagnosed with ADHD<sup>11</sup> and diagnosed with autism<sup>10</sup>. Given the general increase in melatonin consumption in children and adolescents, the working group wants to clarify the beneficial and harmful effects of using melatonin. Therefore, national clinical recommendations for treatment with melatonin for children and adolescents with sleep disorders that are not covered by the previous recommendations are being developed.

## **Population**

### **Children and adolescents aged 5-20 years with sleep disorders where sleep hygiene measures have not had a sufficient effect.**

The population includes children and adolescents both with and without comorbidity. Any psychiatric and somatic comorbidity, as well as social problems / strains, must be investigated and tried to be treated.

Children and adolescents with autism and ADHD are not covered by this recommendation, as the National Board of Health has recommendations for the use of melatonin for sleep disorders in children and adolescents with ADHD and autism spectrum disorders<sup>9,10</sup>.

<sup>8</sup> Danish Medicines Agency. Sovemedicin til børn og unge (esundhed.dk) accessed august 5th 2021.

<sup>9</sup> Berring-Uldum et al. Melatonin til børn med søvnproblemer. Ugeskrift for læger 2018. maj 1;180 (19):V08170628

<sup>10</sup> Danish Health Authority. NKR for behandling af autismespektrumforstyrrelser hos børn og unge. Sundhedsstyrelsen 2021

<sup>11</sup> Danish Health Authority. NKR for udredning og behandling af ADHD hos børn og unge. Sundhedsstyrelsen 2021

<sup>12</sup> Medstat.dk accessed august 5th, 2021.

## **Intervention**

### **Treatment with melatonin as an add-on to sleep hygiene measures.**

We will look broadly at the whole group of melatonin preparations including depot form. No delimitation has yet been defined in relation to dose, time of dosing and duration of treatment. Duration of treatment may depend on whether the population is children and adolescents with or without comorbidity.

Recommended dose, preparations, administration (pills, prolonged-release tablets) and time of dosing may be elucidated in subgroup analyzes.

## **Comparison**

- 1) Regular treatment with advice and guidance on sleep hygiene
- 2) Regular treatment with advice and guidance on sleep hygiene and in addition other non-pharmacological treatment eg cognitive behavioral therapy, use of weight blanket, physical activity / training, relaxation exercises, mindfulness, light therapy, acupuncture (eg National Acupuncture Detoxification Association (NADA))

## **Outcomes**

<b>Outcomes</b>	<b>Priority scale and indication of MCID</b>	<b>Time scale</b>	<b>Critical/Important</b>
<i>Serious adverse effects (SAE), (total number of persons with serious adverse events)</i>		<i>2-4 weeks</i>	<i>critical</i>
<i>Sleep quality in general *</i>		<i>2-4 weeks</i>	<i>critical</i>
<i>Function level in the child / adolescent (Clinician-rated *)</i>	<i>Vineland, ABAS, SDQ (2-17 yr), COPM and ADL-I</i>	<i>2-4 weeks</i>	<i>critical</i>
<i>Adverse effects (AE), (total number of persons with not serious adverse events)</i>		<i>2-4 weeks</i>	<i>important</i>
<i>Dropouts, all causes</i>		<i>2-4 weeks</i>	<i>important</i>
<i>Sleep onset time</i>		<i>2-4 weeks</i>	<i>important</i>
<i>Total sleep time</i>		<i>2-4 weeks</i>	<i>important</i>
<i>Drowsiness and drowsiness during the day</i>		<i>2-4 weeks</i>	<i>important</i>

<i>Sleep quality in general</i>		<i>3-6 months</i>	<i>important</i>
<i>Number of awakenings</i>		<i>2-4 weeks</i>	<i>important</i>
<i>Quality of life in the child / young person</i>	<i>QOLWHO, Kidscreen (8-18 yr)</i>	<i>2-4 weeks</i>	<i>important</i>
<i>Function level in the child / young person (Clinician-assessed)</i>		<i>3-6 months</i>	<i>important</i>
<i>Influence of puberty development</i>	<i>For example, premature or delayed puberty development</i>	<i>Longest follow up</i>	<i>important</i>
<i>Bone mineral density</i>		<i>Longest follow up</i>	<i>important</i>

\* According to report from McMaster University, calculating estimates for the smallest clinically relevant differences (MID).