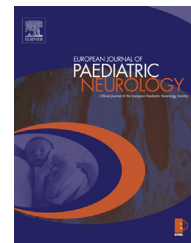




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## Review article

# Current role of melatonin in pediatric neurology: Clinical recommendations



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## ABSTRACT

**Background/purpose:** Melatonin, an indoleamine secreted by the pineal gland, plays a key role in regulating circadian rhythm. It has chronobiotic, antioxidant, anti-inflammatory and free radical scavenging properties.

**Methods:** A conference in Rome in 2014 aimed to establish consensus on the roles of melatonin in children and on treatment guidelines.

**Results and Conclusion:** The best evidence for efficacy is in sleep onset insomnia and delayed sleep phase syndrome. It is most effective when administered 3–5 h before physiological dim light melatonin onset. There is no evidence that extended-release melatonin confers

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Epilepsy  
ADHD  
Autism

advantage over immediate release. Many children with developmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability have sleep disturbance and can benefit from melatonin treatment. Melatonin decreases sleep onset latency and increases total sleep time but does not decrease night awakenings. Decreased CYP 1A2 activity, genetically determined or from concomitant medication, can slow metabolism, with loss of variation in melatonin level and loss of effect. Decreasing the dose can remedy this. Animal work and limited human data suggest that melatonin does not exacerbate seizures and might decrease them. Melatonin has been used successfully in treating headache. Animal work has confirmed a neuroprotective effect of melatonin, suggesting a role in minimising neuronal damage from birth asphyxia; results from human studies are awaited. Melatonin can also be of value in the performance of sleep EEGs and as sedation for brainstem auditory evoked potential assessments. No serious adverse effects of melatonin in humans have been identified.

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## 1. Introduction

Melatonin is an endogenously produced indoleamine secreted by the pineal gland. It is usually secreted during darkness and its secretion is suppressed by light. It plays a key role in regulating the circadian rhythm.<sup>1,2</sup> Melatonin has many other biological functions including chronobiotic and antioxidant properties, anti-inflammatory effects, and free radical scavenging.<sup>3</sup> It is critically involved in early development through its direct effects on placenta, developing neurons and glia, and its role in the ontogenetic establishment of diurnal rhythms.<sup>4,5</sup> Furthermore melatonin regulates the vigilance states depending on the activated melatonin receptors (MT1, MT2 or both); MT2 and MT1 receptors are mainly involved in NREM and REM sleep, respectively.<sup>6</sup>

Several studies have demonstrated the key chronobiotic role of melatonin as a modulator of the sleep–wake rhythm; it

has both chronobiotic and hypnotic properties<sup>7</sup> that influence circadian rhythmicity and affect circadian rhythm sleep disorders.<sup>8–10</sup> Because of these strong chronobiotic and hypnotic properties, melatonin can improve sleep–wake rhythm disturbances and decrease sleep latency in children with sleep disorders, when it is administered at the right time and in the right dose.<sup>7,9–12</sup> As a result, it is one of the most commonly used drugs by pediatricians for infants, children and adolescents with sleep problems.<sup>13–16</sup> A recent study carried out in Norway showed that hypnotic drug use in young people 0–17 years old increased during the period 2004–2011, from 8.9 to 12.3 per 1000, mainly owing to doubling of melatonin use. The hypnotic drug use peaked at 15 per 1000 among those aged 1–2 years and melatonin use increased steadily from 6 to 12 years of age. Summarising the results of this study, the authors reported that melatonin was dispensed more frequently than any of the other hypnotic drugs.<sup>16</sup>

Melatonin is prescribed by pediatricians mainly for sleep onset insomnia (89%), delayed sleep phase syndrome (66%) and night-time awakenings (30%). It is prescribed both for typically-developing children and for children with developmental disorders, including autism, developmental delay, ADHD, and behavioral disorders.<sup>17</sup> Although melatonin is widely used in children and is currently recommended by many practitioners as a “natural sleeping aid” due to its endogenous origin,<sup>17</sup> there are no clinical guidelines on how to prescribe melatonin in children with different neurological disorders.

A European consensus conference was held in Rome on October 4th 2014 with the aims of assessing the current role of melatonin in childhood sleep disturbances and answering some key questions, including those relating to the correct dosage in infants, children and adolescents, timing of administration, duration of the treatment, benefits and pitfalls of immediate compared to controlled release, and predictors of response to melatonin treatment. This paper reports the main points discussed at this conference, starting with the physiology and pharmacokinetics of melatonin, followed by a review of the use of melatonin in the most relevant neuropsychiatric disorders based on meta-analyses/systematic reviews or individual studies. Finally, we provide consensus recommendations for the use of melatonin in both typically developing children and those with neuropsychiatric disorders in daily clinical practice.

## 2. Physiology

Night-time melatonin production during pregnancy increases after 24 weeks gestation until term. The fetus receives melatonin by rapid trans-placental transfer depending on maternal circadian secretion.<sup>18</sup> In 1997 Sadeh studied 20 normal, healthy infants for 1 week with actigraphy and determined the levels of 6-sulphatoxymelatonin (aMT6s), a melatonin metabolite.<sup>19</sup> He identified two groups of infants: 1) infants with “mature” secretion patterns (rise of aMT6s during the evening hours and suppression during the morning); and 2) infants with “immature” type, with flat distribution or rise of melatonin during the early morning hours. **Those infants with the immature pattern showed a delayed peak of melatonin that was associated with more fragmented sleep during the night, suggesting that melatonin plays an important role in the development of the sleep–wake rhythm. Another recent research study attempted to relate dim light melatonin onset (DLMO) with sleep disturbances in toddlers. Toddlers with later DLMO had later bedtimes, sleep onset times, mid-sleep times, and wake times. This study highlighted the large inter-individual differences in DLMO.**<sup>20</sup> Furthermore, morning melatonin concentrations in infants showed a negative correlation with nocturnal sleep duration and were associated with early waking time.<sup>21</sup>

As well as being associated with sleep disturbance, Tautman et al. suggested that 6-sulfatoxymelatonin levels at 16 weeks of age were significantly lower in infants with abnormal vs normal development at 3 and 6 months of age.<sup>22</sup> No other significant relation was evident between 6-sulfatoxymelatonin excretion and growth, perinatal complications or medical problems.

Several studies have shown that melatonin concentrations remain extremely low in the first 3 months and increase abruptly after 3 months of age.<sup>23,24</sup> This effect could be related to the fact that melatonin in human milk showed a clear circadian curve but was immeasurable in all artificial milks, and could contribute to the consolidation of sleep–wake rhythm of infants until the maturation of their own circadian system. Furthermore, endogenous nocturnal levels of melatonin show a strong age effect: they are much higher in children than in adults, they decline with age from 210 pg/ml in preschoolers (1–5 years of age) to 130 pg/ml in school-aged children (6–11 years) and to 50 pg/ml in young adults.<sup>25</sup> This decrease is mainly related to an increase in body size rather than to decreasing pineal secretion.<sup>26</sup>

## 3. Pharmacokinetics

As an exogenous compound, melatonin advances sleep onset in patients with circadian rhythm sleep disorders i.e. delayed sleep phase disorder, improving health status and decreasing parental stress.<sup>7,9,27,28</sup> Long term treatment is usually needed.<sup>29,30</sup>

Melatonin is a peculiar drug because timing of its administration plays a critical role in the results of treatment. **According to the melatonin phase-response curve of 0.5 mg melatonin in adults, phase advances occur with from  $\pm 8$  h before DLMO to  $\pm 2$  h after, with maximum effect at 3–5 h before DLMO. When administered two or three hours after DLMO, no effects or reverse effect can occur. The optimal administration time is earlier for higher doses of melatonin.**<sup>31</sup> **This information was not available when the European Food and Safety Authority (EFSA) concluded incorrectly that melatonin should be administered before desired bedtime.**<sup>32,33</sup> Furthermore, knowing DLMO helps to predict melatonin treatment success: the earlier the melatonin is administered before the DLMO the larger the phase-advance of sleep onset. Within a window of 1–6 h before DLMO, each advance of intake time of one hour resulted in an increase in effect on sleep onset of 19 min.<sup>34</sup> DLMO cannot be predicted by sleep diary, actigraphy or polysomnography.<sup>31,35</sup> It can, however, be assessed easily in home situations by measuring melatonin in saliva.<sup>35,36</sup> **When measuring melatonin levels, children aged 6–12 yrs are invited to chew on a cotton plug for 1–2 min hourly between 7 and 11 pm, whilst it is suggested that adolescents do so between 8 and 12 pm.** In cases with severe delayed or advanced sleep phase disorder, saliva should be collected at later or earlier times or hourly for 24 h<sup>35</sup>

Some pitfalls can be encountered when interpreting DLMO. It is advisable to measure DLMO before starting melatonin, to prevent inappropriate timing or doses of melatonin treatment.<sup>29,36</sup> When DLMO is measured in patients who stopped melatonin use 1–6 weeks before measuring DLMO, often strange, zig-zag, melatonin curves are seen<sup>35</sup> and DLMO cannot be determined reliably. It is therefore recommended that DLMO be measured before starting melatonin treatment. The main action of exogenous melatonin in patients with sleep onset insomnia and late DLMO is to “pull” at the advance of the endogenous melatonin rhythm and with it the sleep–wake rhythm. There is no evidence that prolonging the

presence of melatonin in the bloodstream is of value, implying that there is no evidence to indicate that extended-release melatonin has advantages over immediate-release acting melatonin. If maintenance of sleep is the main problem, melatonin treatment usually is ineffective.

#### 4. Delayed sleep phase syndrome and chronic sleep onset insomnia

Delayed sleep phase syndrome (DSPS) is a circadian rhythm sleep disorder characterized by a rigid delay in the timing of the major sleep period in relation to desired sleep–wake times. It is associated with a delayed 24-h melatonin rhythm, possibly linked to a PER3 polymorphism.<sup>37–39</sup> The etiology is likely to be heterogeneous, including delayed circadian timing, longer than normal circadian rhythm period, slower accumulation in homeostatic sleep drive, increased sensitivity to phase-delaying evening light, or an insensitivity to resetting properties of morning light.<sup>40,41</sup>

Recent meta-analyses have indicated that melatonin is an effective and apparently safe for treatment of primary sleep disorders or DSPS in children.<sup>9,42,43</sup> However, the effects probably vary from patient to patient because of inter-individual differences in etiology. Another aspect to influence variation in effect is the timing of intake in reference to endogenous circadian rhythm, as explained earlier. There are currently six published randomized controlled trials (RCTs) on melatonin treatment for primary DSPS or chronic sleep-onset insomnia in children and adolescents.<sup>10,27,44–47</sup> Sleep phase advanced in all but one study.<sup>47</sup> Sleep length increased in two studies but did not change significantly in two other studies.<sup>27,47</sup> Daytime sleepiness improved in one study,<sup>45</sup> but not in another study,<sup>46</sup> and health status and functional status was improved in one study.<sup>27</sup> Two studies showed no significant effects on various tests of cognitive performance.<sup>27,46</sup> The dose of melatonin varied from 1 to 5 mg/night. A dose-finding study with melatonin 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg and a placebo group<sup>10</sup> showed advanced sleep onset time (SOT) and DLMO by approximately 1 h and decreased sleep onset latency (SOL) by 35 min; these effects were significantly different from placebo. No significant differences were found between the three melatonin doses. Several studies have shown that effects on SO, SOL, and DLMO increase with earlier circadian administration time. Adverse events were mild. In two studies, adverse events occurred only with melatonin treatment,<sup>44,45</sup> but in two other studies adverse events occurred in both the melatonin and in the placebo groups.<sup>10,27</sup>

When melatonin was administered at a time related to DLMO, meta-analyses showed that melatonin decreased sleep onset latency.<sup>9,48</sup> However, in the meta-analysis of melatonin administration without knowing DLMO, melatonin did not improve sleep.<sup>49</sup> This difference in results might be ascribed to the difference in melatonin administration strategy; however, other factors might also be involved, such as differences in primary diagnosis. For example, the study by Buscemi et al. showed much more pronounced effects with DSPS than with insomnia.

Melatonin treatment for primary DSPS or chronic sleep onset insomnia in children and adolescents advances

sleep–wake rhythm and DLMO, possibly lengthens sleep, and appears to be safe both in the short term and in the long term. More studies are needed to evaluate the effects on daytime sleepiness and health/behavior/cognition, particularly in adolescents, given the high prevalence of DSPS in this population.

No specific studies on the use of melatonin in infants with insomnia have been reported. However, a recent survey reported that the melatonin dose administered in infants ranged from 0.5 to 3.5 mg (mean 2.1 mg), in children from 1 to 10 mg (mean 3.5 mg) and in adolescents from 2 to 12 mg (mean 5.3 mg). Maximum prescribed doses were 5 mg (infants), 10 mg (children) and 18 mg (adolescents) with a wide range. The most commonly reported starting dose was 3 mg. Duration of treatment ranged from 0 to 200 weeks, with an average of 16.5 weeks (SD 26.3 weeks).<sup>17</sup>

#### 5. Melatonin in neuropsychiatric disorders

##### 5.1. Attention-deficit/hyperactivity disorder (ADHD)

As many as 70% of children with ADHD have been reported as having mild to severe sleep problems. The most recent meta-analysis of sleep disturbances in ADHD, focused on children and adolescents, found significantly more sleep problems in children with ADHD than a normal comparison group, based upon subjectively-rated sleep items, including bedtime resistance, sleep onset difficulties, night awakenings, difficulties with morning awakenings, sleep disordered breathing, and daytime sleepiness.<sup>50</sup> The meta-analysis also indicated that children with ADHD were significantly more compromised than the comparison group with regard to several parameters assessed with objective methods (PSG or actigraphy), such as sleep onset latency (on actigraphy), the number of stage shifts/hour of sleep, the apnea–hypopnea index, sleep efficiency on polysomnography, true sleep time on actigraphy, and average times to fall asleep on the Multiple Sleep Latency Test. These results indicated that children with ADHD had higher levels of daytime sleepiness. Sleep onset insomnia is arguably the most commonly reported problem.<sup>51</sup> The causes of sleep onset insomnia in children with ADHD are likely to be heterogeneous and multifactorial.<sup>52</sup> Currently, there is no established consensus on how to treat sleep disorders in ADHD and the grade of available empirical evidence is generally low. Melatonin may be an option, at least when sleep onset insomnia is related to a delayed sleep phase disorder.<sup>53</sup> There is initial evidence that the use of melatonin in children with ADHD and sleep disturbance is grounded on a pathophysiological rationale, since a delay in dim-light melatonin onset (DLMO) has been reported in children with ADHD and sleep onset insomnia.<sup>54</sup> In addition, melatonin genetic pathways have been found to be abnormal in children with ADHD.<sup>55</sup>

In a systematic review of the literature, searching Pubmed, Ovid and Web of Knowledge databases (to September 29th, 2014), performed in preparation for the European Consensus meeting, we found a total of five trials of melatonin in children with ADHD, including 3 RCTs (two rated at “low risk” of bias and 1 at “uncertain risk” by means of the Cochrane tool of

bias).<sup>56</sup> All these trials concurred in showing that melatonin given in doses ranging from 3 to 6 mg/night) significantly reduced sleep onset delay and increased total sleep duration, but did not impact on daytime ADHD core symptoms as might have been expected, considering that better sleep quantity/quality has been related to improvement in cognitive and behavioral functioning.<sup>57</sup> This last finding might be accounted for by the short duration of most of the available trials that is below 3 months,<sup>58–61</sup> with only one long-term study (mean follow-up: 3.7 years).<sup>29</sup> **In these studies, melatonin was generally well tolerated both in the short term and in the long term. Most of the participants who discontinued treatment did so because sleep problems were no longer a major issue rather than because of intolerable treatment effects. Adverse events included sleep maintenance insomnia, excessive morning sedation, low mood and headache, profuse perspiration and “daytime laziness”.**

## 5.2. Autism spectrum disorders (ASD)

Sleep disturbances such as reduced total sleep and longer sleep latency, as well as nocturnal and early morning awakenings, are commonly observed in population studies of individuals with ASD, with prevalence estimates ranging from 30 to 53%, depending on study design and definition of sleep problems.<sup>62,63</sup> Sleep problems can worsen the symptoms of autism and can result in challenging behaviors. Abnormalities in daytime or night-time values of melatonin compared to typically-developing controls have been often reported<sup>64,65</sup> suggesting that melatonin supplementation might be effective in improving sleep parameters in children with ASD. Furthermore, gene abnormalities that could contribute to decreased melatonin production have been reported in a subgroup of children with ASD and comorbid sleep onset delay.<sup>66</sup>

A meta-analysis of randomized double-blind placebo-controlled crossover studies showed significant improvements with large effect size in sleep duration and sleep onset latency, but not in night-time awakenings in individuals with ASD who took melatonin.<sup>67</sup> Children with ASD and insomnia who are responsive to low dose of melatonin, have been shown to present with relatively normal profiles of endogenous and supplemental melatonin.<sup>65</sup> Patients in whom the effect of melatonin disappeared have been shown to be CYP1A2 poor metabolizers due to a single nucleotide polymorphism (SNP) in the CYP1A2 gene.<sup>68</sup> The majority of children with ASD responded to a dose of 1–3 mg given 30 min before bedtime, with improvement in sleep latency and total sleep duration.<sup>67,69</sup> The overall improvement rate with melatonin was 80%. Melatonin was well tolerated with minimal adverse effects.<sup>67</sup>

Melatonin is of special interest in ASD, in view of the reported abnormalities in central and peripheral serotonin neurobiology<sup>70,71</sup>; however, the relationship between melatonin and serotonin needs to be clarified in children with ASD and comorbid sleep disorders. Further research into the sleep problems of people ASD is required both to elucidate the mechanism of action of supplemental melatonin and to identify which individuals are most likely to benefit from melatonin treatment.

## 5.3. Neurodevelopmental disabilities (NDD)

Sleep problems are reported to occur in 13–86% of individuals with NDD, depending on study design, participant characteristics, and definition of sleep problems. Such problems are often complex and usually more difficult to treat than in individuals without NDD. Melatonin is used widely in children with insomnia and NDD, because of its apparently safe profile, but there are no specific clinical guidelines on how to prescribe melatonin in this group of children.<sup>72</sup>

A meta-analysis of nine of randomized, placebo-controlled trials, including a total of 183 individuals with NDD, showed that melatonin decreased sleep latency by a mean of 34 min, increased total sleep time by a mean of 50 min and less significantly decreased the number of awakenings per night.<sup>11</sup> A recent placebo-controlled study in 146 children (age 3–15 years) with intellectual disability showed similar results.<sup>73</sup> In some patients with NDD and sleep problems, the initial good response to melatonin disappeared within a few weeks of starting treatment and the good response returned only after considerable dose reduction.<sup>11</sup> The loss of efficacy of melatonin treatment after an initial good response is a major problem possibly caused by slow metabolism because of decreased activity of the CYP1A2 enzyme.<sup>74</sup> This may result in increasing daily melatonin levels. Consequently melatonin levels accumulate and after some time the circadian melatonin rhythm is lost. This loss of circadian rhythm might explain why exogenous melatonin loses its effectiveness.

If the melatonin dose is high and/or the individual is a poor metabolizer, high daytime melatonin levels may result. Braam (personal communication) analyzed daytime melatonin levels in 150 patients who visited a sleep clinic between 2009 and 2014. Of the 150 patients, 74 were already taking melatonin at the first visit and 76 were not taking melatonin. In 58 (78.4%) of those who had already been taking melatonin, the daytime melatonin levels in saliva were extremely high (>50 pg/ml), whereas daytime melatonin levels in 72 of 76 those who had not already been taking melatonin users (95%) were <10 pg/ml (W. Braam, personal communication). In 40 out of 76 non-melatonin users at first visit (52.8%) a loss of effect and high daytime melatonin levels after 4–12 weeks of melatonin treatment (0.5 – 3 mg) were observed. This loss of effect may be linked to the decreased activity of the CYP1A2 enzyme that resulted in slow melatonin metabolism; slow melatonin metabolizers have been reported as being 12%–14% of the general population, but might be much higher in persons with NDD.<sup>68</sup>

Melatonin has been also used in clinical practice to treat severe sleep problems associated with various genetic syndromes (Table 1). In two genetic syndromes severe sleep problems are included in the diagnostic criteria and are related to melatonin disturbance. Smith Magenis syndrome is characterized by daytime somnolence, night waking and early waking caused by an inversed circadian melatonin rhythm.<sup>75,76</sup> **Recommended treatment includes a combination of melatonin inhibition by acebutolol (10 mg/kg in one early morning dose) and evening melatonin supplementation (no dose guidelines). Children with Angelman syndrome may present with sleep onset insomnia as well as sleep maintenance problems.**<sup>77</sup> Melatonin levels are low and melatonin

**Table 1 – Summary of studies of melatonin treatment for sleep problems associated with different genetic syndromes.**

Genetic syndrome	Sleep disturbances	Melatonin dosage	Results	Reference
Smith-Magenis	Multiple awakenings Inverted circadian rhythm of melatonin	NA	Sleep amelioration (with exogenous melatonin used in combination with endogenous melatonin blockers)	De Leersnyder 2006, Chick et al., 2010, Boone et al., 2011
Angelman	Sleep onset and sleep maintenance problems	0.3–5 mg in different case series	Decreased SOL Increased total sleep time	Zhdanova et al., 1999, Braam et al., 2008, Takaesu et al., 2012
Rett	Multiple awakenings	2.5–7.5 mg	Reduction of night awakenings Decreased SOL	McArthur & Budden, 1998, De Leersnyder et al., 2011
Tuberous Sclerosis	Multiple awakenings	5–10 mg	Decreased SOL Improved total sleep time	Bruni et al., 1995, O'Callaghan et al., 1999, Hancock et al., 2005

treatment has shown to be effective in open and in blinded studies. The melatonin dose should be low (0.3 mg) because the prevalence of slow melatonin metabolisers in Angelman syndrome is very high. Tuberous Sclerosis Complex (TSC) can be associated with different types of sleep disorders, including multiple night awakenings and reduced total sleep time.<sup>78</sup> Melatonin has been shown to reduce SOL and improve total sleep time<sup>79,80</sup> in patients with TSC. Melatonin was also reported to reduce sleep problems in children with Rett syndrome<sup>81,82</sup> and Sanfilippo syndrome (mucopolysaccharidosis type III).<sup>83,84</sup>

## 6. Melatonin in other neurological disorders

### 6.1. Epilepsy

Because a high proportion of children with neurodevelopmental disorders have sleep problems and either have or develop epilepsy, there is great interest in determining whether melatonin is liable to exacerbate or precipitate seizures. The increased prevalence of sleep disorders in children with NDD has been discussed earlier. The prevalence of epilepsy in NDD depends on the type of the disorder and the severity of any intellectual disability. For example, in ASD, the prevalence of epilepsy is much higher than in the general population. Woolfenden et al.<sup>85</sup> carried out a systematic review on outcomes of children with autism. They estimated from two studies of children with autism for whom the age at follow up was under 12, and in whom the majority did not have intellectual disability (mental retardation), that the rate of epilepsy was 6.1% (95% confidence interval 3.8%–9.0%); in nine studies in which the majority of subjects did have intellectual disability and the age at follow-up was 12 years or more, the pooled percentage estimates of those having epilepsy at follow-up was 23.7% (95% confidence interval 17.5–30.5%) In a double-blind placebo controlled crossover trial of the effect of melatonin on seizures of 12 patients with uncontrolled epilepsy, Goldberg-Stern observed a statistically significant reduction in diurnal seizures.<sup>86</sup> However, in subsequent reviews it was concluded that it was not possible to draw any definitive conclusion about the role of melatonin in reducing seizures frequency or improving quality of life in people with epilepsy.<sup>87,88</sup> There is no clear evidence that melatonin exacerbates seizures. The very limited number of randomized controlled trials and more extensive animal data not only suggest that melatonin is unlikely to exacerbate seizures but indicate that it might even protect against them, although the data are too sparse to allow firm conclusions to be drawn.

### 6.2. Headache

Melatonin can have a role in both biological regulation of sleep and headache. A strict relationship between sleep and headache has been recognized for a long time. Melatonin may play a role in headache pathophysiology via several mechanisms. The antinociceptive effects of melatonin have been demonstrated in animal models, both in inflammatory and neuropathic pain.<sup>89,90</sup> Melatonin interacts with a number receptor

sites, including opioid, benzodiazepine, muscarinic, nicotinic, serotonergic,  $\alpha$ 1-adrenergic,  $\alpha$ 2-adrenergic and most importantly MT1/MT2 melatonin receptors present in the dorsal horn of the spinal cord, as well at multiple central nervous system levels (hypothalamus, hippocampus, medulla oblongata, pons and retina).<sup>90</sup> Because of its ability to scavenge toxic free radicals, melatonin can reduce macromolecular damage in all organs. Melatonin also reduces the up-regulation of a variety of pro-inflammatory cytokines, interleukins and TNF- $\alpha$ .<sup>90</sup> Melatonin has been shown to reduce transendothelial cell migration and oedema; it is involved in membrane stabilization, as well as inhibiting the activity of nitric oxide synthase. It can decrease dopamine and glutamate release; it can also potentiate the receptor-mediated response of GABA and the opioid immune response.<sup>91,90</sup>

Melatonin might regularize the sleep–wake pattern through its “chronobiological” and “sleep-hygiene effects”.<sup>92,93</sup> Adequately timed and dosed melatonin treatment decreased headache in 78.6% of 328 patients with circadian rhythm sleep disorders and headache, while adequately timed and dosed melatonin induced (slight) headache in 13.8% of 676 patients with circadian rhythm sleep disorders without headache.<sup>94</sup> Individuals with migraine report a high prevalence of sleep disturbances in parents, and sleep disturbances in infancy, as well as an elevated level of familiarity of migraine, suggesting a genetic link between headache and sleep disorders.<sup>95</sup> An alteration of serotonergic and dopaminergic neurotransmitter pathways could predispose to both these disorders at different ages: earlier for sleep disorders and later for headache, as consequence of such a neurotransmitter imbalance.<sup>95</sup> In an open-label trial in children with primary headache, melatonin 3 mg twice daily reduced the number (by more than 50%), intensity and duration of headache attacks in 14 of 21 children.<sup>96</sup> A decrease in nocturnal melatonin secretion has also been identified in patients with cluster headaches. A study of melatonin in a single dose of 0.3 mg/kg for three months indicated that melatonin might be considered as an effective and safe drug in the prophylaxis of migraine in children.<sup>97</sup> However, these studies have several limitations. In particular, small samples were investigated. There is still no definitive consensus about the therapeutic use of melatonin for headache in children.

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## 7. Neuroprotective effects of melatonin

Birth asphyxia in term newborn infants remains a significant problem throughout the world, contributing to 510,000–717,000 neonatal deaths, 1.15 million new cases of neonatal encephalopathy and 413,000 impaired survivors,<sup>98</sup> which may suffer from long-term neurological consequences such as cerebral palsy, mental retardation and epilepsy. To date, therapeutic hypothermia is the only clinical intervention that has shown to be effective in reducing brain damage in asphyxiated babies; however infants treated with hypothermia may have adverse outcomes, implying that there is a need for new and more effective treatments to provide safe and successful neuroprotection against neonatal encephalopathy.

Optimizing therapy for neonatal brain injury requires capitalizing on multiple pathways. Experimental evidence has demonstrated the multiple neuroprotective benefits of melatonin, such as reducing infarct volume and neuronal loss, minimizing lipid and protein peroxidation, inhibiting free radical production, blocking apoptosis and decreasing inflammation.<sup>99</sup> Indeed, its benign safety profile and relative ease of administration to both fetus and neonate make melatonin an attractive emerging neuroprotective agent with strong potential for clinical translation. As hypoxic-ischemic brain injury is often unpredictable, one of the key challenges for a new intervention strategy is to be able to ameliorate ongoing or secondary injury, by being administered as a post-insult therapy.

In animal studies, melatonin has been shown to be protective when given to neonatal rats 5 min after the injury and repeated 24 and 48 h later, reducing the percentage of ipsilateral damage and decreasing behavioral asymmetry and learning deficits, with long-lasting benefit.<sup>100</sup> Melatonin has also been shown to maintain the number of well-preserved neurons after the injury, an effect related to reduction in delayed cell death and reactive astrogliosis and also to the maintenance of myelination.<sup>101</sup> In addition, Robertson et al.<sup>102</sup> showed that melatonin augmented hypothermic neuroprotection by improving cerebral energy metabolism, as indicated by magnetic resonance spectroscopy biomarkers, and reducing cell death across the brain.

The prevention of neurological disabilities following preterm birth remains a major public health challenge. Various experimental studies have tested the neuroprotective effects of antenatal and postnatal melatonin administration in different animal models (e.g. rat, mouse, sheep, and pig) of brain lesions mimicking the lesions observed in human neonates.<sup>103</sup> These data strongly emphasize the neuroprotective properties of melatonin, whatever animal species has been used and in several types of brain damage across various developmental stages.<sup>104</sup>

The fact that melatonin easily crosses the placental barrier and can therefore be administered antenatally is a powerful argument for researching its use in minimizing, if not preventing, brain lesions in human subjects. Even though the dose and timing for optimal neuroprotection remain to be elucidated, all these data, along with the apparently benign safety profile and relative ease of melatonin administration, have favored the consideration of some small phase I and II clinical studies, the results of which should provide further relevant information about the real potential of melatonin for clinical translation.

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## 8. Melatonin as pre-medication for neurologic diagnostic procedures

Melatonin has been used as a sleep inducing agent in neurophysiological and neuroimaging procedures in child neurology. Obtaining sleep to record EEG in childhood is of major importance because sleep can activate epileptiform abnormalities, thus helping clinicians to achieve a more accurate electroclinical assessment.<sup>105</sup> However, sleep deprivation, which is usually necessary to make the child fall asleep in the EEG laboratory, can be difficult and burdensome for the family,

especially in the case of challenging children. If spontaneous sleep is difficult to achieve, sedative drugs can be used. However, in the last two decades, melatonin has been used widely to induce sleep for EEG recording, initially in adults, and subsequently in children. When melatonin is administered, the yield of epileptiform abnormalities is similar to that reported for sleep-deprived EEGs, underlining that melatonin administration does not interfere with EEG interpretation nor does it hide epileptiform abnormalities.<sup>106</sup> Melatonin, administered at different doses ranging from 2 to 20 mg, was able to induce sleep in a high percentage of children (79–88%), reducing sleep onset latency; sleep duration was usually brief, but sufficient for an adequate EEG recording, and was rarely associated with mild somnolence after the exam.<sup>105–108</sup>

Melatonin has also been used to induce sleep as an alternative to sedation for performing brainstem auditory evoked

potentials,<sup>109,110</sup> and for successfully performing brain magnetic resonance imaging (MRI) in about half of the patients.<sup>111,112</sup>

## 9. Adverse effects of melatonin

**No serious safety concerns have been attributed to melatonin use in children.** Systematic reviews showed that for sleep disorders such as jet lag and shift work, melatonin appears to be safe for short-term and long-term use.<sup>42,49</sup> Rossignol and Frye (2011) stated that no adverse effects were reported with the use of melatonin in children with ASD in 7 of the 12 studies included in their meta-analysis.<sup>67</sup>

The most frequently reported side effects associated with melatonin use in children include morning drowsiness,

**Table 2 – Recommendations for prescribing melatonin in children with sleep–wake rhythm disorders or sleep onset insomnia.**

Consider melatonin treatment in children with sleep onset problems and/or difficulty waking up in the morning at conventional times. Usually melatonin is not effective for sleep maintenance problems. Measure DLMO (if possible). Minimum age for administration	No studies reported the minimum age for administering melatonin. Since it has been used in high dosage in infants to prevent neuronal injuries without side effects we can expect that melatonin administration after 6 months of age could be quite safe If used as chronobiotic, 2–3 h before DLMO When DLMO cannot be measured: administer melatonin 3–4 h before actual sleep onset time If used as sleep inductor 30 min before bedtime If used as chronobiotic, start with a low dose of 0.2–0.5 mg fast release melatonin 3–4 h before bedtime; increase by 0.2–0.5 mg every week as needed (maximum 3 mg; adolescents: 5 mg) until effect If no response after 1 week: increase dose by 1 mg every week until effect appears When 1 mg is effective: try lower dose Maximum dose: <40 Kg: 3 mg; >40 Kg: 5 mg If used as a sleep inductor start with 1–3 mg 30 min before sleep or before the examination (EEG, Evoked potentials or MRI)
Time of administration in children	Treatment duration should be tailored to the specific patient in relation to the peculiar neurodevelopmental disabilities but in general should be not less than 1 month Treatment can be withdrawn just before puberty (age around 12 yrs) or shortly after puberty (18–24 yrs) Stopping successful treatment too early (i.e. 4 weeks after its start) may results in reappearance of insomnia Stop melatonin treatment once a year during one week (preferably in summer) after a normal sleep cycle is established
Dosage	Check timing of administration: melatonin intake time may be shifted to too late Be aware that loss of efficacy of melatonin treatment most likely is caused by slow melatonin metabolism Reconsider diagnosis: look for neuropsychiatric comorbidity and treat that together with the insomnia For very severe delayed sleep wake rhythm: consider chronotherapy Comedication can influence melatonin metabolism:
Treatment duration	<ul style="list-style-type: none"> <li>• Metabolism slower: oral contraceptives, cimetidine, fluvoxamine</li> <li>• Metabolism faster: carbamazepine, esomeprazole, omeprazole</li> </ul>
When melatonin treatment is not effective (any more):	In some cases dose reduction is warranted instead of dose escalation Melatonin dose is probably too high
If sleep maintenance problems after start melatonin treatment:	



increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.<sup>73,113,114</sup> Slight transient headache and gastrointestinal symptoms are mainly reported during the first days of the treatment.<sup>115</sup> In elderly the administration of 3 mg of melatonin induced hypothermia and plasma melatonin elevated into the daylight hours.<sup>116</sup>

Effects of the melatonin on human reproduction<sup>117</sup> and in auto-immune disorders<sup>118</sup> remain unclear. No melatonin-associated alterations of laboratory values were noted.<sup>119</sup>

Since melatonin is primarily metabolized by CYP1A2 and CYP2C19, inhibitors of CYP1A2 (e.g., tricyclic antidepressants, fluvoxamine, cimetidine) may increase melatonin concentrations.<sup>120</sup> Because melatonin may decrease blood pressure or serum glucose, particular attention should be given in patients who receive concomitant therapy with agents that affect blood pressure or serum glucose.<sup>121</sup>

In supporting the safety of melatonin it should be noted that melatonin has been administered in very high doses to animals (from 5 to 20 mg/kg and even >100 mg) without adverse effects but has shown neuroprotective properties. The lethal dose in animals has yet to be determined, with the implication the high doses administered so far have not been lethal. However, these data cannot be taken as assurance that melatonin can be administered in infants and children at high doses without adverse effects.

## 10. Clinical recommendations

As evident from the previous sections, the dose, timing and modalities of administration of melatonin vary considerably across studies. Table 2 presents the consensus of the authors regarding the use of melatonin in infants and children with sleep–wake rhythm disorders or sleep onset insomnia. It must be emphasized that these represent general recommendations that need to be tailored to each individual.

So far, the best evidence for the indication of melatonin treatment in children is for insomnia caused by circadian rhythm sleep disorders. Because insomnia due to other situations and disorders, including bad sleep hygiene, ADHD/ADD, personality disorders and depression, can mimic insomnia caused by circadian rhythm sleep disorders, the diagnosis should be only be made after careful clinical assessment and possibly measuring DLMO. There is a strong argument for determining DLMO, not only for an optimal diagnosis, but also for optimal melatonin treatment, as melatonin is most effective when it is administered 3–5 h before DLMO in children with sleep onset insomnia and late DLMO. DLMO can be measured relatively easily by collecting saliva at home. DLMO measurements contribute substantially both to optimal diagnosis and treatment of patients with chronic insomnia.

## 11. Conclusions and future directions

Melatonin can be effective not only for primary sleep disorders but also for sleep disorders associated with several neurological conditions. Controlled studies on melatonin for sleep disturbance in children are needed since melatonin is very commonly prescribed in infants, children and

adolescents, and there is a lack of certainty about dosing regimens. The dose of melatonin should be individualized according to multiple factors, including not only the severity and type of sleep problem, but also the associated neurological pathology. Future controlled clinical studies should clarify the possible neuroprotective role of melatonin administration in infants with hypoxic-ischemic encephalopathy. Because of the lack of research and controlled trials, there is a pressing need for studies on melatonin in infants and children with sleep disorders, to identify those who will benefit from melatonin treatment and to determine the doses appropriate for the severity and type of disorder.

## Conflict of interest

None.

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