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REVIEW

# Melatonin Treatment for Pediatric Patients with Insomnia: Is There a Place for It?

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**Abstract:** Sleep is a vital physiological function that is impaired in ranges from 10% in the typically developing pediatric population to over 80% in populations of children with neurodevelopmental disorders and/or psychiatric comorbidities. Pediatric insomnia disorder is an increasing public health concern given its negative impact on synaptic plasticity involved in learning and memory consolidation but also on mood regulation, hormonal development and growth, and its significant impact on quality of life of the child, the adolescent and the family. While first-line treatment of pediatric insomnia should include parental education on sleep as well as sleep hygiene measures and behavioural treatment approaches, pharmacological interventions may be necessary if these strategies fail. Melatonin treatment has been increasingly used off-label in pediatric insomnia, given its benign safety profile. This article aims to identify the possible role of melatonin treatment for pediatric insomnia, considering its physiological role in sleep regulation and the differential effects of immediate release (IR) versus prolonged release (PR) melatonin. For the physician dealing with pediatric insomnia, it is particularly important to be able to distinguish treatment rationales implying different dosages and times of treatment intake. Finally, we discuss the benefit–risk ratio for melatonin treatment in different pediatric populations, ranging from the general pediatric population to children with different types of neurodevelopmental disorders, such as autism spectrum disorder or ADHD.

**Keywords:** melatonin, prolonged release, immediate release, pediatric insomnia, sleep, circadian, autism spectrum disorder, ADHD, delayed sleep phase syndrome

## Introduction

Sleep is fundamental for the optimal development and overall health of children and adolescents, with both sufficient sleep duration and sleep quality being essential.[1] Recent consensus statements have highlighted recommended sleep durations during childhood,[2] as sleep needs vary by age. Additionally, uninterrupted night sleep is important for brain plasticity underlying learning and memory consolidation, and healthy sleep has shown many daytime benefits across development.[1]

However, sleep problems are common in children, and pediatric insomnia in children and adolescents ranges from 10% in typically developing children to over 80% in children with neurodevelopmental disorders (NDD) or psychiatric comorbidities,[3] depending on age and definitions of insomnia used across studies. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5[4]) defines insomnia as a persistent disorder and the *International Classification of Sleep Disorders, third Edition* (ICSD-3[5]) as chronic, with criteria of symptom frequency, duration since the start of the symptoms and associated daytime repercussions in the child, the parents or the family; if symptoms are mild or transient, ie if they appear only occasionally (thus they do not meet frequency criteria) or if they have no significant daytime repercussions, they should not be considered an insomnia disorder.

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Pediatric sleep disturbances overall and insomnia in particular are increasingly considered a public health concern, as inadequate or disrupted sleep has been shown to have detrimental effects on daytime behavior, cognition (memory, attention and even language acquisition in the developing child)[6–9] as well as on overall physical (eg obesity)[10] and mental health, with higher risks of depression and suicide or self-harm behaviours in children and adolescents.[11,12] Furthermore, pediatric insomnia and sleep disturbances have a high impact on quality of life of the entire family,[13] and once insomnia is diagnosed, it tends to persist throughout childhood and adolescence if not treated.[14,15]

It is thus essential for the overall development of the child as well as for the well-being of the entire family to identify pediatric insomnia early on, and to design efficient treatment interventions. First-line treatment of pediatric insomnia should include parental education on sleep, taking into account the child's individual development, as well as sleep hygiene measures and/or behavioural treatment approaches, which have been extensively described elsewhere in the literature.[15] These non-pharmacological approaches have shown high efficiency (over 80%) in typically developing children but are often insufficient in children with NDD or psychiatric comorbidities.

When first-line treatment is insufficient, pharmacological alternatives exist but until recently, there was no approved drug for the treatment of insomnia in children. Because of its benign safety profile, melatonin has been increasingly used off-label in pediatric insomnia all over the globe,[16–23] despite being approved only in specific indications and populations and not in all countries. This article aims to identify the possible role of melatonin treatment for pediatric insomnia, considering its physiological role in sleep regulation and the differential effects of immediate release (IR) versus prolonged release (PR) melatonin. For the physician dealing with pediatric insomnia, it is important to be able to distinguish treatment rationales, especially to differentiate melatonin treatment as an etiological treatment approach in some conditions where underlying melatonin or circadian rhythm abnormalities have been described, versus as a symptomatic treatment of pediatric insomnia, which implies different dosages and times of treatment intake.

For studies cited in this paper, a literature search was conducted using Medline (PubMed) in February 2022, using the terms "melatonin", "sleep", "circadian" and "children" or "adolescents". In addition to the electronic search, we also used "pearling", ie the examination of reference lists of identified articles for additional articles that may have been missed in our searches. Search criteria were inclusive of primary research studies, systematic reviews and meta-analyses related to melatonin use for sleep complaints in pediatric populations. For evaluating melatonin efficacy, the review included studies in children without underlying chronic conditions and children with NDD. To assess safety of melatonin treatment, we reviewed all available studies, including those patients with neurodevelopmental comorbidities and sleep disorders.

The first part of our paper will thus focus on the physiology of endogenous melatonin and on the differential effects of immediate release versus prolonged release melatonin in healthy subjects and different patient populations, as well as on safety of melatonin treatment. The second part reviews the conditions under which melatonin can be considered an etiological treatment, ie directly addressing a well described pathophysiology for insomnia in subgroups of pediatric patients; for these disorders, this paper will review the evidence for differential treatment with immediate versus prolonged release melatonin, as well as optimal dosages and times of treatment intake. Finally, the third part of the paper discusses the possible role of melatonin as a symptomatic treatment in pediatric insomnia, beyond indications described in the second part.

# Part I. Melatonin

## Melatonin Physiology

Melatonin (or 5-methoxy-*N*-acetyl-tryptamine) is a neuro-hormone mainly synthesized by the pineal gland from tryptophan. Both melatonin synthesis and secretion are controlled by the master biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus which generates the internal circadian rhythm for each individual and regulates major physiological functions (sleep/wake, temperature, secretion of hormones, etc) with a rhythmicity of approximately 24 hours. Physiologically, the main external synchronizer (*Zeitgeber*) of the biological clock is the alternation of light and darkness. At the onset of darkness, the reduction of the retinal light supply leads in several steps to the disinhibition of enzymes responsible for melatonin synthesis within the pineal gland, whereas during light

exposure melatonin synthesis and secretion is naturally blocked. Melatonin is therefore not the "sleep hormone" but the hormone that gives the signal to "switch to night mode" and reinforces the day/night contrast via the circadian clock. Melatonin thus plays a role as an endogenous synchronizer capable of reinforcing the circadian rhythms, stabilizing them and maintaining their phase relationship (internal synchronization), thus contributing to physiological coherence and to the adaptation of the whole organism to the photoperiod (see Figure 1). In addition, the concordance between the core body temperature nadir (around 4 a.m.) and the melatonin peak (around 3 to 4 a.m.) contributes to sleep maintenance.

This physiological role of melatonin explains its effect in the treatment of sleep problems, its effect on hypertension and diabetes (reduction of insulin levels), its oncostatic effect and the reduction of cancer side effects, as well as its effect on certain gastrointestinal pathologies (see Figure 1).[24–26] Melatonin acts through two main pathways: a receptor-mediated pathway (specifically MT1 and MT2 receptors) and a receptor-independent pathway.[27,28] The receptor-mediated pathway acts on sleep promotion and circadian modulation, with three main effects of melatonin on sleep and circadian rhythms being identified: 1) a chronobiotic; 2) a chronohypnotic; and 3) a soporific effect.

The chronobiotic effect is the main effect described for melatonin. It consists of the ability of a substance to modify the position of the sleep/wake rhythm by advancing or delaying it within the day–night cycle. The administration of exogenous melatonin in its IR formula allows to modify the position of the physiological secretion of melatonin according to time of administration.[29–31] When melatonin is administered in the afternoon (beginning or end), an advance in melatonin secretion is observed subsequently, with a maximum phase shifting effect obtained with melatonin intake 4 to 5 hours before the beginning of endogenous secretion (see Figure 2). This "phase advance" effect can be reinforced by the morning administration of light (natural or light therapy). On the contrary, with morning administration of exogenous melatonin, the physiological secretion is delayed ("phase delay"). The chronobiotic effect therefore consists of the induction of a phase shift (advance or delay) of the internal biological clock. This chronobiotic action is the

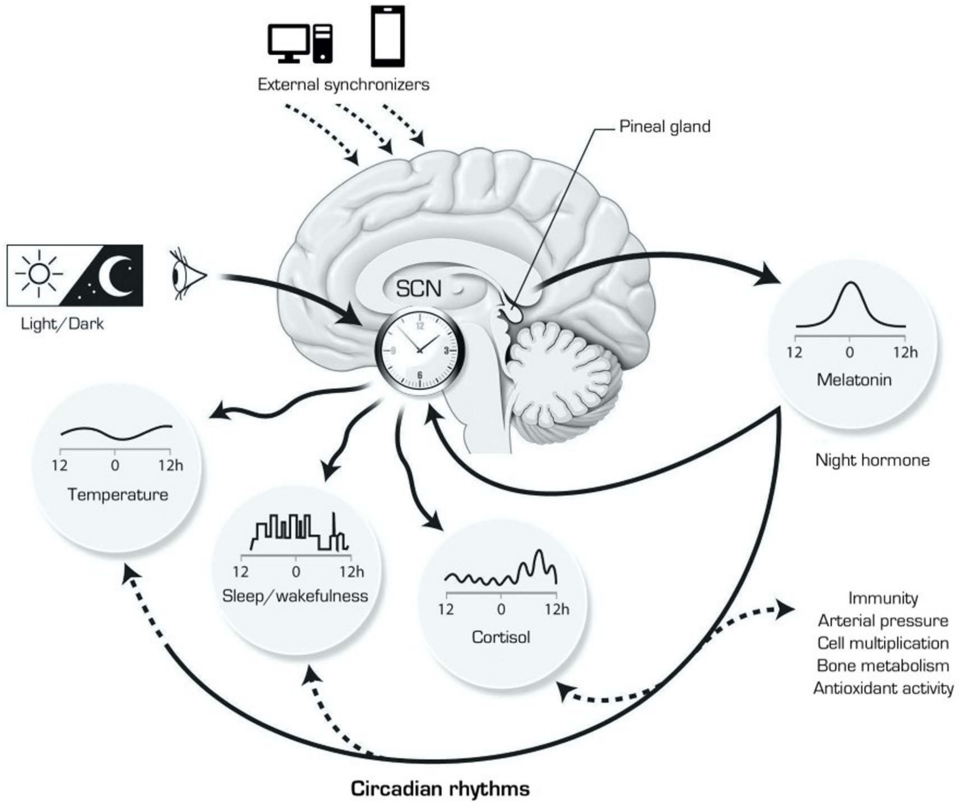


**Figure 1** Melatonin, an endogenous synchronizer of the circadian system. Adapted from Claustrat B. Mélatonine et troubles du rythme veille-sommeil. *Médecine Sommeil*. 2009;6(1):12–24. Copyright©2009. Elsevier Masson SAS. All rights reserved.[31] and Schröder CM, Broquère MA, Claustrat B, et al. Approches thérapeutiques des troubles du sommeil et des rythmes chez l'enfant avec TSA. *L'Encéphale*. 2022:S0013700621002177.Open Access.[138]
**Abbreviation**: SCN, suprachiasmatic nuclei.

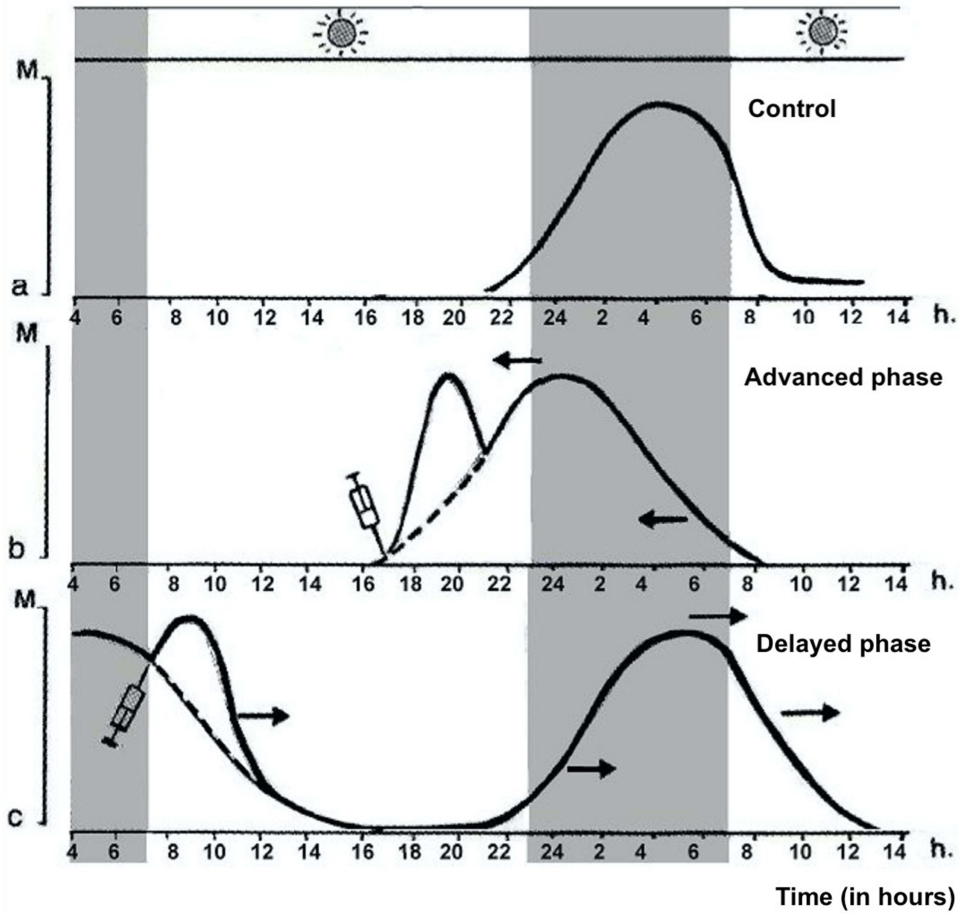


**Figure 2** The chronobiotic action of melatonin: modification of endogenous melatonin secretion after administration of immediate release melatonin according to the phase response curve. Depending on the time of administration of immediate release melatonin, the central clock responds with a phase advance or delay. The melatonin rhythm constitutes a faithful marker of the activity of the clock allowing to objectify the phenomenon. (**A**) Control. (**B**) The plasma profile shows a phase advance after administration in the afternoon or evening, and (**C**), a phase delay after administration in the morning. The critical time (or turning point) which corresponds to the change in the direction of the phase change is around 15:00. Adapted from Claustrat B. Mélatonine: aspects biochimiques, physiologiques et pharmacologiques en relation avec les phénomènes rythmiques et le sommeil. *Médecine Sommeil.* 2020;17(3):177–194 and Claustrat B. Mélatonine et troubles du rythme veille-sommeil. *Médecine Sommeil*. 2009;6 (1):12–24. Elsevier Masson SAS. All rights reserved.[28,31]

physiological basis for the treatment of circadian rhythm disturbances (jet lag syndrome, delayed sleep phase syndrome (DSPS), free-run in the visually impaired, etc). Some authors distinguish a chronohypnotic effect which is characterized by the inhibition of the arousal signal emanating from the circadian clock after melatonin administration, mostly through MT1 receptors on the SCN, facilitating the switch into "night mode".[28]

The soporific effect of melatonin is characterized by the induction of sleep when the homeostatic sleep pressure is insufficient, ie usually during the day and outside of the natural endogenous melatonin secretion phase.[32] This effect has been explored through thermoregulation research: melatonin administration during the day mimics the endogenous thermophysiological processes that occur in the evening and which induce sleepiness (see Figure 3).[32] Through an increase of distal heat loss, melatonin thus enhances the decrease in core body temperature in the late evening which promotes sleep propensity at the beginning of the night.[33]

There is a great individual variability in physiological melatonin levels and the rate of endogenous melatonin secretion.[26] The effects of exogenous melatonin as a treatment for insomnia do thus also vary on an individual level, and depend on the time of administration, dosage, the type of formulation (IR or PR) and on the association with other substances such as tobacco or contraceptive pills.[26] Currently there are two treatment formulas of melatonin available, IR and PR melatonin, with differential effects on sleep and circadian rhythms.

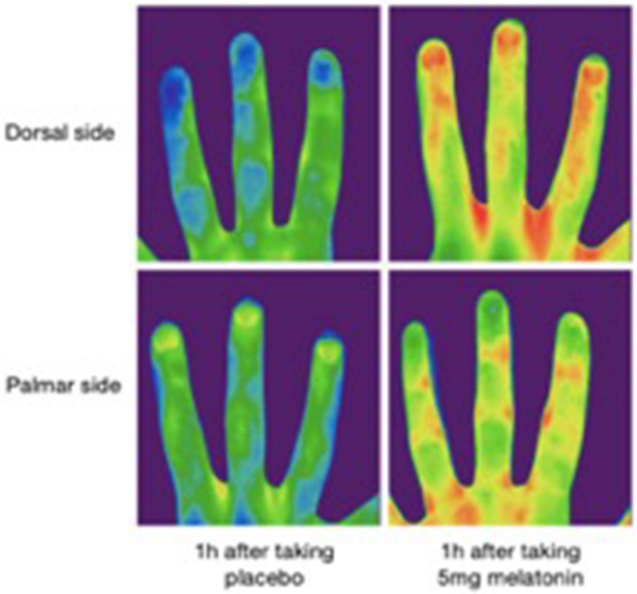


**Figure 3** Effect of immediate release melatonin on distal vasodilatation. Illustration of the analysis of the topographic temperature with infrared thermometry in an individual (dorsal and palmar side of the hand) 1 h after taking a placebo and 1 h after taking 5 mg of immediate release melatonin (oral intake), the latter indicating a greater increase in skin blood flow by melatonin in the fingertip than in the proximal finger, most likely by opening arteriovenous anastomoses. Immediate release melatonin administration during the day (absence of endogenous melatonin secretion) mimics the endogenous thermophysiological processes that occur in the evening and induces sleepiness. Adapted from Kräuchi K, Cajochen C, Pache M, Flammer J, Wirz-Justice A. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiol Int*. 2006;23(1–2):475–484, Taylor & Francis Ltd, http://www.tandfonline.com by permission of the publisher.[32]

## Effects of Immediate Release Melatonin

There are many studies evaluating the effects of IR melatonin coming from the field of basic and applied research in chronobiology. Conversely, there are fewer clinical studies conducted,[34–40] notably by the pharmaceutical industry, due to the wide availability of melatonin which is sold as a dietary supplement over the counter in many countries. Clinical studies are even rarer in the pediatric population than in the adult population. In addition, meta-analyses evaluating the efficacy of melatonin often include both IR and PR formulas, even though their mode of action and dosages differ. Thus, studies evaluating the efficacy of IR melatonin in primary or secondary insomnia have sometimes been realized, especially in the beginning, with high doses of several milligrams of melatonin to counteract the elimination related to the hepatic first-pass effect (plasma half-life is of the order of 20 to 30 minutes after oral intake).[41] Peak plasma concentrations are reached between 20 and 240 minutes after oral administration for 2 mg IR melatonin, with a shorter peak duration than that of an endogenous profile (1–2 hours versus 8–10 hours) and with a shorter peak duration than those of PR formulation (see Figure 4).

The effects of IR melatonin are explained through the combination of chronobiotic, chronohypnotic and soporific actions (see above and Figures 2 and 3). The soporific effect induces sleepiness, especially when given before the onset of the endogenous melatonin secretion, and the chronobiotic and chronohypnotic effects inhibit the wake signal emanating from the biological clock and induce a sleep phase advance. The combined effect is a decrease in sleep latency, consistently observed throughout studies,[34–40] but which can also induce an earlier morning awakening, an effect few physicians are aware of. As such, Gringras et al demonstrated in a large RCT in 146 children aged 3 years to 15 years 8 months with NDD significantly earlier waking times compared to placebo (on average 29.9 minutes earlier, range: 13.6 to 46.3 minutes).[106] The efficacy of IR melatonin in pediatric insomnia may thus partly be related to the treatment of an undiagnosed underlying circadian rhythm disorder through its chronobiotic effect, in particular delayed sleep phase syndrome (see below).

## Effects of Prolonged Release Melatonin

The pharmacokinetic characteristics of IR melatonin which differ significantly from endogenous melatonin profiles have led to the development of PR formulations which mimic more closely the endogenous profile of the molecule (see

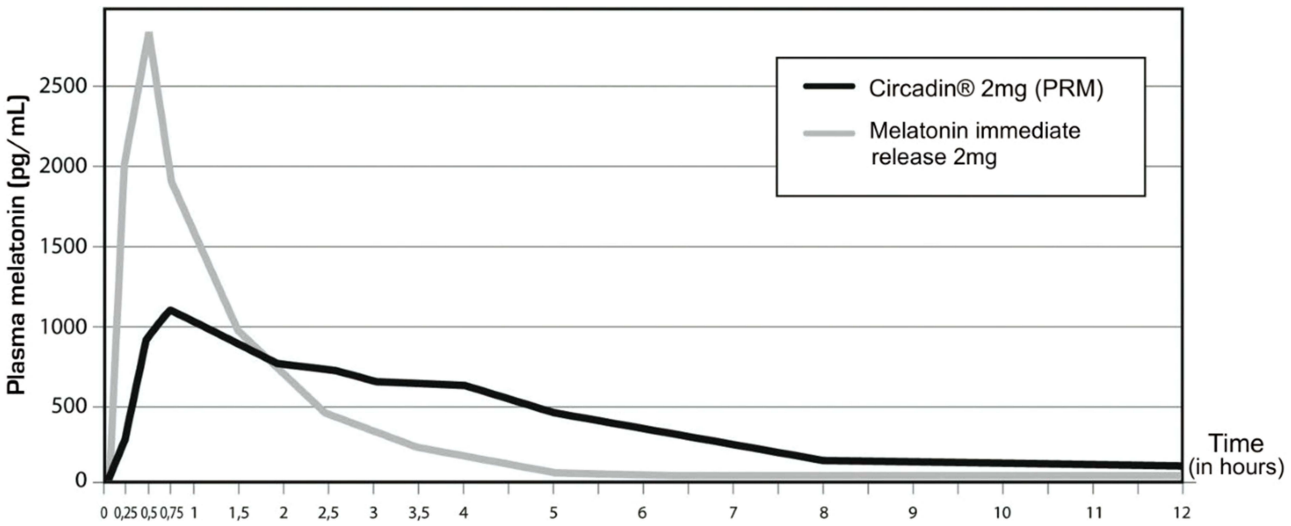


**Figure 4** Comparison of plasma pharmacokinetics after administration of immediate release and prolonged release melatonin preparations. Plasma kinetics after administration of administration of immediate release melatonin (2 mg dose, light grey curve) versus prolonged release melatonin (2 mg dose, dark curve). Adapted from Zisapel N. Melatonin and sleep. *Open Neuroendocrinol J.* 2010;3:85–95.[139]

Figure 4).[42] PR melatonin can thus be prescribed to substitute melatonin over the entire night in case of insufficient endogenous melatonin secretion (for indications: see Part II). The PR form has been less studied in basic and applied chronobiology research compared to the IR form, and only few studies have been conducted in typically developing children; in contrast, scientific evidence is high in in children and adolescents with autism spectrum disorder (ASD) or neurogenetic disorders. PR melatonin produces a gradual increase in blood concentration, with a peak reached about 3 hours after administration, a plateau phase lasting about 3–4 hours at a maximum concentration of about 1000 pg/mL for a 2 mg dose, and a return to baseline within 10 hours after dosing (see Figure 4). No undesired effect on sleep phase advance has been reported. The aim of PR melatonin treatment is to improve sleep latency (like IR melatonin), but also to ensure that sleep continuity and total nighttime sleep duration are maintained. Historically, the marketing authorization for PR melatonin (Circadin®) was limited to older adults (age 55 years or older) with insomnia. Then, its efficacy and good tolerance in adults as well as empiric success in treatment of severe sleep disorders in children with ASD led to consider its use for this population. In 2015, Circadin® was first granted a temporary recommendation for use in some countries for the treatment of sleep disorders in children with ASD or neurogenetic disorders (Rett disease, Smith–Magenis syndrome, tuberous sclerosis of Bourneville and Angelman syndrome). In September 2018, pediatric PR melatonin received European marketing authorization in children with ASD.[43] The recommended initial dose is 2 mg of pediatric PR melatonin that can be increased to 10 mg (increase to a 5 mg dosage over 2–4 weeks, then to 10 mg on the same schedule). The effectiveness of the treatment is evaluated clinically. In case of chronic prescription, an at least annual re-evaluation is recommended.[44]

## Safety of Melatonin Treatment

Across studies, melatonin (IR as well as PR) has overall displayed a very benign safety profile (for studies and reviews in children and adolescents, see references.[45–61] In terms of toxicology, melatonin has a good safety profile event at extremely high doses (up to 1600 mg) in adults, as shown by a recent meta-analysis,[62] even though some authors suggest possible effects on the hypothalamic pituitary gonadal axis and the cardiovascular system in healthy adults.[63] No suicide has ever been reported with melatonin even with very high doses (Texas Poison Centers, 779 cases between 1998 and 2003).[26,64] The most common short-term side effects are, as expected, daytime somnolence, especially in the morning for PR melatonin, as well as headaches, probably linked to its vasodilatory effects (see Figure 3).[65] As some children and adolescents with NDD are prescribed melatonin for more than two years,[16,66,67] long-term side effects have also been studied in this population.[48] In a RCT with PR melatonin for pediatric insomnia in children with ASD over a two-year

study period, fatigue, agitation, cough and dyspnea were slightly more frequently reported in the PR melatonin-treated group, with no evidence, however, of impact on height, BMI or pubertal development.[49] There were no withdrawal effects following long-term use and no safety concerns on concomitant therapy with stimulants.[49] Another prospective 3.8-year follow-up study of 44 children with NDD who had participated in a RCT with PR melatonin for circadian rhythm sleep/wake disorders (CRSD) reported a similar mild adverse effects profile with no evidence of impact on development and puberty, no cardiovascular effect and no interactions with other medications.[57]

However, reports on isolated cases have raised awareness of rare side effects in adults,[68,69] some of which may be linked to interactions with other medications metabolized by the same liver enzyme, cytochrome CYP1A2, among which several antidepressants and antiepileptics. On the other hand, some authors have suggested melatonin may have an inhibitory effect on CYP1A2, thus the serum concentration of substrates such as caffeine may be increased when taken together with melatonin.[142] Data are unfortunately scarce regarding the prevalence of slow metabolizers of melatonin within the pediatric population, which may cause increased side effects especially with PR melatonin; future research should address this important topic.

Finally, it must be considered that not all countries have the same safety regulation rules, creating discrepancies between countries in terms of safety profiles of melatonin products. Especially in the United States where melatonin treatment production is less regulated compared to Europe, US over-the-counter melatonin formulations should be considered with caution concerning their efficacy and safety.[70]

# Part II. Melatonin as an Etiological Treatment in Pediatric Insomnia

In several pediatric populations at high risk for insomnia, melatonin treatment can be considered an etiological treatment approach: 1) either to supplement a deficient endogenous melatonin synthesis, eg in children with ASD; 2) to correct abnormal melatonin profiles, eg in children with neurogenetic disorders (eg Smith–Magenis syndrome, Rett's disorder, tuberous sclerosis, Angelman syndrome); or 3) to correct a circadian phase disorder, eg in children or adolescents with delayed sleep phase disorder (DSPD), in particular if associated with attention-deficit hyperactivity disorder (ADHD) or other psychiatric conditions (eg anxiety, depression). Melatonin treatment has thus already been codified with several consensus guidelines as a treatment for pediatric and/or non-neurotypical patients for these indications, by the American Academy of Neurology, the British Association for Psychopharmacology, and the French Medical and Research Sleep Society, among others.[108,132,143]

## Insomnia in Children with ASD

### Prevalence and Symptomatology

ASD is a neurodevelopmental condition that affects 1% of children.[71] ASD is defined by alterations in social interactions and communication, repetitive and stereotypic behaviors, and sensory integration and processing deficits. In 70% of cases ASD is associated with comorbidities, such as ADHD and other neurodevelopmental, psychiatric, and physical conditions.[72,73] Sleep problems concern 50 to 80% of children with ASD,[72,74] whereas in comparison, short-term insomnia appears during development in 27% of typically developing children and becomes a chronic disorder in only 4% of them.[75] While any sleep disturbances are present in 50–80% of children with ASD, a recent meta-analysis reports a prevalence of diagnosed sleep–wake disorders of 13% in the ASD population compared to 3.7% in the general population.[73] The relative risk of ASD children to have a sleep disorder diagnosis compared to their TD peers is thus at least two-fold.[74]

Insomnia is the most common sleep complaint in ASD children, with parents reporting mainly difficulties initiating sleep (51%) and long night awakenings (10%) that affect both the child's and family's daily functioning (20% and 23% respectively).[76] The objective sleep data from actimetry and polysomnography shows that children with ASD have a longer sleep onset latency, a shorter total sleep time, a longer wake after sleep onset (WASO), a lighter sleep (more sleep time spent in N1) and less REM sleep.[77] The subjective data gathered through parent-report questionnaires and sleep diaries in that same meta-analysis reported that parental complaints of children with ASD concerned mainly the difficulties to fall asleep: bedtime anxiety, bedtime resistance, prolonged sleep latency; more parasomnias are also reported in ASD children than in TD children.[77]

Insomnia being frequently related to circadian rhythm disorders, these have also been assessed in the ASD population.[78,79] Studies report that circadian rhythm disorders such as phase delay of sleep periods and irregular sleep–wake patterns are more frequent in children with ASD and tend to persist during adulthood.[74,80]

## Impact of Sleep Deprivation on ASD Symptomatology

Chronic sleep deprivation in children with ASD is associated with impaired memory consolidation,[81] cognitive performance alterations,[82] daytime behavioral problems,[82–84] lower adaptive functioning,[85,86] increased severity of ASD core symptoms,[82,87,88] more internalizing problems and emotion dysregulation.[84,87,89,90] Sleep problems can mimic or worsen associated ADHD symptoms such as attention difficulties, and motor hyperactivity may appear as a way of fighting perceived sleepiness.[83,84,87] Poor sleep continuity is also reported in the ASD population with negative effects on mood and behavior.[91] Sleep disturbances in children with ASD have been associated with a lower quality of life for the families and significantly higher parental distress.[92–95]

## Etiology of Sleep Disorders in ASD

The etiology of sleep problems in ASD is thought to be multifactorial with genetic, hormonal, neurological and environmental compounds. To date, alterations in the core melatonin production pathway seem to be the most fitting hypothesis to explain sleep and circadian rhythm disorders in ASD. Indeed, elevated serotonin plasmatic levels associated with low melatonin plasmatic levels and elevated platelet *N*-acetyl-serotonin (NAS) have been found in children and adults with ASD compared to controls.[96] 63% of children and adolescents with ASD have nocturnal urinary 6-sulfatoxymelatonin (melatonin metabolite) excretion values which were less than half of the mean excretion rate observed in the control group.[97] Diurnal and nocturnal melatonin excretion levels of adolescents and adults with ASD are lower than those of TD controls, and the circadian rhythmicity is flattened in this population instead of presenting a nocturnal peak (dim light onset of melatonin, DLMO).[98]

Genetic and neurobiological findings showed that sleep is a necessary component of synaptic homeostasis and that synaptic and clock genes could interact and be associated in the susceptibility to ASD.[99,100] Polymorphisms in clock genes may be involved in the abnormalities of the melatonin pathway in the ASD population.[101,102] A study from Pagan et al in 2017 reported reduced activities of two enzymes involved in melatonin synthesis, aralkylamine *N*-acetyltransferase (AANAT) and acetylserotonin-*O*-methyltransferase (ASMT) in the pineal gland, gut and platelets of ASD subjects compared to controls.[103] In this study, a correlation has been found between the reduction of ASMT activity, an elevated NAS level in the platelets and a lower plasma melatonin level. A previous study from Melke et al in 2008 similarly showed a significant decrease in ASMT activity and melatonin level in individuals with ASD compared to controls, indicating that a low melatonin level caused by a primary deficit in ASMT activity could be a risk factor for ASD.[104]

## Prolonged Release Melatonin: An Etiological Treatment for Insomnia in Children with ASD

Clinical guidelines recommend sleep hygiene and behavioral interventions as first-line treatment for insomnia in children with ASD,[105] but only 25% respond to combined sleep hygiene and behavioural treatment approaches alone.[106] As around two thirds of ASD children and adolescents present an altered core melatonin production,[97] a substitutive treatment with synthesized melatonin administered orally has been recommended in the most recent practical guidelines[105,107,108] for sleep and circadian rhythm disorders in this population and has been increasingly prescribed in this indication.[109] Previous systematic reviews and meta-analysis evaluated the efficacy and safety of melatonin, but often without discriminating IR and PR formulations and limited by the variability in dosage across studies, and sometimes pooling ASD and other NDD (ADHD, neurogenetic disorders motor disorders, intellectual disabilities, etc).[44,110–113] Whereas previous studies had shown a significant effect of IR melatonin mostly on sleep onset,[106] results of a randomized controlled trial (RCT) with PR melatonin with doses ranging from 2 to 10 mg per day showed not only improved sleep onset latency, but also longer sleep duration and better sleep continuity,[65] as well as improvement of externalizing problem behaviours and familial quality of life.[114–116] 76% of children with ASD with symptoms of insomnia responded to PR melatonin treatment.[117] The recommended initiation dose is 2 mg per day 30 minutes to 1 hour before bedtime, with efficacity assessment after 2–4 weeks of treatment. In case of a partial effect obtained at 2 mg, the dose can be increased to 5–10 mg per day. A very good safety profile of melatonin has been

shown in this specific pediatric population, as detailed previously (see Part I. above). Melatonin is to date the first and only pharmacological treatment to be approved by the European regulatory agencies (European Medicines Agency, EMA) for insomnia in children and adolescents from 2 to 18 years old with ASD or Smith–Magenis syndrome.[43]

## Insomnia Associated with Delayed Sleep–Wake Phase Disorder (DSPD) in Children and Adolescents

### Insomnia Associated with DSPD in Adolescents

#### Prevalence and Developmental Characteristics

The ICSD-3[5] defines DSPD as a CRSD which corresponds to CRSD common criteria: persistent or recurrent sleep–wake pattern disturbances due to alterations of the endogenous circadian system or to misalignment between the endogenous circadian rhythm and exogenous factors; leading to insomnia, excessive daytime sleepiness or both; and associated with impairment of social, occupational and/or other areas of functioning. Specific DSPD criteria include a significant and chronic delay in the phase of the major sleep period (minimum 2 hours of sleep-onset delay for at least three months, confirmed by actigraphy or sleep diaries), with inability to fall asleep and awaken at a desired and socially acceptable clock time. In DSPD the endogenous melatonin rhythm is delayed (measured through dim-light melatonin onset (DLMO) in the evening) and endogenous circadian rhythms are not synchronized with social constraints and desired times for sleep: this phenomenon is known as "social jet lag".[118] DSPD is often misinterpreted as sleep-onset insomnia. Around 10% of outpatients assessed in specialized sleep centers for insomnia complaints actually suffer from DSPD.[119]

Circadian sleep–wake rhythms can be objectively measured through DLMO assessment or indirectly derived through chronotype. A study by Paine et al in New Zealand identified a prevalence of 8.90% of moderate to extreme evening chronotypes in a sample of 9100 adults (assessed using the Munich Chronotype Questionnaire).[120] The chronotype has intraindividual variations through life with a physiological developmental delay in sleep–wake rhythms during adolescence and a progressive advance with age during adulthood (see Figure 5).[118] DSPD is by far the most frequent CRSD and compared to a prevalence of only about 0.17–1.51% in the adult population,[121] its prevalence is highest during adolescence with 3.3–17% of teenagers suffering from it;[122,123] furthermore, in teenagers, DSPD has been linked to higher rates of depression, anxiety, and ADHD symptoms.[124]

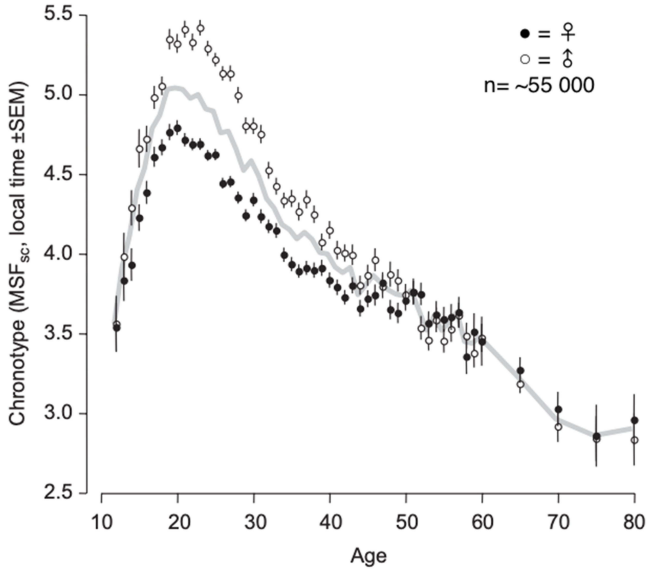


**Figure 5** Chronotype variation across lifetime, depending on gender. Chronotype was assessed through the Munich Chronotype Questionnaire, with lower values indication morning chronotypes and higher values evening chronotypes (Adapted from *Sleep Med Rev.* 11(6). Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. 429–438, Copyright 2007, with permission from Elsevier).[118] During adolescence, studies have shown a significant phase shift towards evening types. This phase delay is more important and lasts longer in boys compared to girls.

## Insomnia Associated with DSPD in Children with ADHD

### Prevalence and Symptomatology

ADHD is a neurodevelopmental disorder characterized by inattentive symptoms, impulsivity and hyperactivity, that affects 5–7% of children.[125,126] 25–55% of parents of children with ADHD report that their children have sleep problems.[127] The results of a meta-analysis from Cortese et al in 2009 on subjective sleep-related measures showed a higher bedtime resistance, more sleep onset difficulties, more night awakenings, more difficulties with morning awakenings and significantly more daytime sleepiness in children with ADHD compared to the general pediatric population.[127] The same meta-analysis results on objective sleep data reported a longer sleep latency, a higher number of stage shift per hour of sleep and a lower sleep efficiency in children with ADHD compared to controls. Additionally, a significantly higher apnea–hypopnea index (AHI) was shown in children with ADHD compared to controls.[127]

### Bi-Directional Effects of Insomnia and ADHD Symptomatology

Excessive sleepiness during the day may not only cause attention difficulties, but also induce hyperkinetic behavior to fight against perceived somnolence, therefore mimicking or aggravating ADHD symptoms.[128] Symptoms of ADHD in the evening, such as hyperactivity, restlessness and poor planification skills, may contribute to difficult behavior around bedtime, increase bedtime resistance and thus delay sleep. A rebound effect at the end of the medication effectiveness in the late afternoon or evening may also contribute to sleep initiation difficulties. On the contrary, persistent effects of prolonged release psychostimulant in the evening may have a direct negative effect on sleep initiation. Restless leg syndrome (RLS) is also more frequent in ADHD and can mimic evening hyperactivity and explain an increased nocturnal motor activity and agitation during sleep in children with ADHD, possible related to higher rates of periodic limb movement disorder which is commonly associated with RLS.[128] As iron is a cofactor in dopamine synthesis whose pathway is involved in ADHD, iron deficiency has been pointed as a possible common underlying etiopathophysiological factor to RLS and ADHD.[128] Iron supplementation is proven to be effective on both RLS and ADHD symptoms in children with iron deficiency.[129] Finally, given the prevalence of sleep-onset insomnia, studies have assessed the presence of DSPD in children and adolescents with ADHD through measure of DLMO,[128] and have been able to show a delayed sleep phase and delayed DLMO in this population.[130]

### Immediate Release Melatonin: An Etiological Treatment for Insomnia Symptoms Related to DSPD in Children with ADHD and Adolescents

IR melatonin treatment is the gold standard pharmacological approach for DSPD in children, adolescents and adults.[131,132] Chronobiological research had shown for a long time that the chronobiotic phase advance effect of IR melatonin exists already at dosages as low as 0.3 mg and does not benefit from dose increases.[133] However, IR melatonin is available as a dietary food supplement in many countries and as such has not been evaluated or approved by any regulatory agency to treat sleep or circadian rhythm disorders. A review of 19 randomized controlled trials of IR melatonin daily treatment on a total of 841 children and adolescents with DSPD showed a consistent improvement of sleep latency by 22 to 60 min without serious adverse effects.[47] A meta-analysis of seven RCTs assessing efficacy and safety of melatonin in 387 children and adolescents with sleep-onset insomnia associated with DSPD from 6 to 19 years old concluded that melatonin advanced mean sleep-onset time by 37 min and DLMO by 49 min,[46] including two RCTS on children and adolescents with ADHD (see Table 1).[134,135] Another study from Mohammadi et al in 2012 evaluated the effect of combined treatment of melatonin (3–6 mg) and methylphenidate (1 mg/kg) in a group of 26 children with ADHD whose sleep symptoms were assessed using the Sleep Disturbance Scale for Children (SDSC) parent-questionnaire, with a placebo group of 24 children treated with placebo +methylphenidate (1 mg/kg).[136] The results showed a partial improvement of total sleep score at SDSC in the melatonin group versus placebo group but failed to reach significance, possibly due to the fact that they did not restrict the inclusion criteria to children with insomnia symptoms or diagnosed DSPD. This sum of scientific evidence points out that IR melatonin is an efficacious and safe chronobiotic treatment for DSPD in children and adolescents with or without ADHD when administered at 0.5 mg, 3 to 5 h before DLMO (corresponding to 4–6 h before usual sleep initiation time) for an optimal chronobiotic phase advance effect. Alternatively, for a combination of the chronobiotic, chronohypnotic and soporific effect of IR melatonin (see Part I, above), a prescription of 1 to 3 mg at bedtime is equally interesting (though the degree of the induced phase shift will be

**Table 1** IR or PR Melatonin as an Etiological Treatment: Summary of Indications, Evidence and Approvals

| | | **Prolonged Release Melatonin** | | **Immediate Release Melatonin** | |
|---|---|---|---|---|---|
| **Indications** | Type of insomnia | Sleep initiation and maintenance disorders | Sleep initiation and maintenance disorders | Sleep initiation disorder associated with DSPD | Sleep initiation disorder associated with DSPD |
| | Population | ASD Smith–Magenis syndrome | Other NDD | ADHD | Children and adolescents without comorbidities |
| | Age | 2–18 years old | 2–18 years old | 6–18 years old | 6–18 years old |
| **Suspected mechanism of effect** | | Substitution of a decreased endogenous production | Substitution of a possibly reduced endogenous production | Chronobiotic and soporific effects | Chronobiotic and soporific effects |
| **Prescription overview** | Objectives | Sleep parameters:<br>• Sleep latency <30 minutes<br>• Longest continuous sleep episode >6 hours<br>• Total sleep time in a physiological range for the age<br>Other parameters:<br>• Improvement of daytime functioning, cognitive performance, patient and parental satisfaction | Sleep parameters:<br>• Sleep latency <30 minutes<br>• Longest continuous sleep episode >6 hours<br>• Total sleep time in a physiological range for the age<br>Other parameters:<br>• Improvement of daytime functioning, cognitive performance, mood, patient and parental satisfaction | Sleep parameters:<br>• Sleep latency <30 minutes<br>• Total sleep time in a physiological range for the age<br>Other parameters:<br>• Improvement of daytime functioning, cognitive performance, mood, patient and parental wellbeing | Sleep parameters:<br>• Sleep latency <30 minutes<br>• Total sleep time in a physiological range for the age<br>Other parameters:<br>• Improvement of daytime functioning, cognitive performance, mood, patient wellbeing |
| | Dosage | Start at 2 mg per day 30 min−1 h before bedtime:<br>• If the objectives are obtained continue at 2 mg per day and reassess every 6 months<br>• if partial effectiveness is obtained at 2 mg per day in 2–4 weeks, increase dosage to 5 mg per day<br>• if partial effectiveness is obtained at 5 mg per day in 2–4 weeks, increase dosage to 10 mg per day<br>If the objectives are not met at 10 mg, lower the dosage or stop the medication and reassess the indication | Start at 2 mg per day 30 min–1 h before bedtime:<br>• If the objectives are obtained continue at 2 mg per day and reassess every 6 months<br>• if partial effectiveness is obtained at 2 mg per day in 2–4 weeks, increase dosage to 5 mg per day<br>• if partial effectiveness is obtained at 5 mg per day in 2–4 weeks, increase dosage to 10 mg per day<br>If the objectives are not met at 10 mg, lower the dosage or stop the medication and reassess the indication | • 0.5 mg per day 4 to 6 hours before bedtime for a maximum chronobiotic effect (phase advance)<br>Or<br>• 1 to maximum 3 mg on bedtime to combine soporific and chronobiotic effects | • 0.5 mg per day 4 to 6 hours before bedtime for a maximum chronobiotic effect (phase advance)<br>Or<br>• 1 to maximum 3 mg on bedtime to combine soporific and chronobiotic effects |

(*Continued*)


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**Table 1** (Continued).

| | | Prolonged Release Melatonin | | Immediate Release Melatonin | |
|---|---|---|---|---|---|
| | Proportion of responders | 76%[117]: 29% of responders improved with 2 mg, 47% improved with 5 mg, 24% improved with 10 mg per day | – | 93%[56] | – |
| | Frequent side effects | Tiredness<br>Sleepiness<br>Headache<br>Irritability[117] | Somnolence<br>Increased excitability<br>Mood swings[140,141] | Sleep maintenance Insomnia<br>Morning sedation<br>Decreased mood<br>Headache[56] | Tiredness<br>Cold feelings |
| **RCTs** | | One large RCT:<br>Maras et al, 2018 (PR-melatonin dose from 2 to 10 mg per day in 125 children from 2–18 years) (3 months RCT[65] followed by 3 years of open-label)[117] | Two RCTs including one with controlled-release and one with IR-melatonin:<br>Wasdell et al, 2008 (combined melatonin dose used 1 mg IR +4 mg PR per day in a crossover trial with 51 children from 2–18 years old)[140]<br>Appleton et al, 2012 (IR-melatonin dose used from 0.1 to 12 mg per day)[141]<br>These two RCTs are included in a meta-analysis of thirteen RCTs including various NDD with IR and/or PR-melatonin[113] | Two RCTs:<br>Van Der Heijden et al, 2007 (IR melatonin dose of 3 mg per day if body weight <40 kg or 6 mg if body weight >40 kg, in 54 children with ADHD from 6–12 years old versus a placebo group of 53 matched children)[134]<br>Weiss et al, 2006 (IR melatonin dose of 5 mg per day, in 23 children with ADHD from 6–14 years old in a crossover design)[135]<br>These two RCTs are included in a meta-analysis of seven RCTs (including six RCTs with children with or without ADHD from 6 to 14 years old; one with adolescents from 14 to 19 years old; PR-melatonin dose from 1 to 5 mg per day)[46] | Two RCTs:<br>Eckerberg et al, 2012 (IR-melatonin dose of 1 mg per day at 4:30 to 6 p.m. in 21 adolescents from 14–19 years old with a placebo group of 21 matched adolescents)[38]<br>van Geijlswijk et al, 2010 (IR melatonin dose of 0.1 mg/kg/day in 55 children of 6–12 years old versus a placebo group of 17 matched children)[37]<br>These two RCTs are included in a meta-analysis of seven RCTs (including six RCTs with children with or without ADHD from 6 to 14 years old; one with adolescents from 14 to 19 years old; PR-melatonin dose from 1 to 5 mg per day)[46] |
| **Authorizations by regulatory agencies** | | Authorized by EMA (September 2018)[43] | Not authorized | Not authorized | Not authorized |

**Abbreviations**: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; DSPD, delayed sleep–wake phase disorder; EMA, European Medicines Agency; NDD, neurodevelopmental disorder; RCT, randomized controlled trial.

less than if given several hours earlier, see Figure 2).[47,132] Even though the benign safety profile of melatonin is established (see above), as chronotype varies across lifespan and endogenous circadian rhythm may change during long-term treatment, it is recommended to stop and reassess the indication of melatonin treatment regularly (at least once a year, for example during the summer holidays).

## Part III. Is There a Role for Melatonin in Pediatric Insomnia?

We have hereabove reviewed in detail scientific evidence from clinical as well as from basic chronobiology research, in order to clarify the differential roles of IR versus PR melatonin treatment as an etiological treatment in several pediatric populations, with recommendations on differential dosing and timing of melatonin administration. Based on these data, the question arises of whether melatonin (IR or PR) could also be used as a symptomatic treatment in pediatric insomnia disorder outside of the indications described in Part II (above), if sleep hygiene measures and behavioural treatment approaches have not been successful. Some have argued, for occasional sleeplessness in the pediatric population which is different from pediatric insomnia described here, that the benefit–risk ratio may be in favor of occasional melatonin treatment, in particular when taking into account its benign safety profile (see above) compared to other pharmacological agents available for children.[44,137]

Overall scientific evidence for the efficacity of melatonin treatment in pediatric insomnia remains limited,[34–40] and only few randomized controlled trials have been conducted to date.[34,38–40] Furthermore, many studies have not clearly distinguished insomnia complaints from pediatric insomnia disorder and from DSPD, adding a significant bias to some of the study results.

Taking into account these different evidences, and in line with the expert consensus of the French Medical and Research Sleep Society (SFRMS),[132] we suggest that IR melatonin in particular may have a relevant role in treating pediatric insomnia if a first line of sleep hygiene measures and behavioral treatment approaches have not been successful, and after ruling out other underlying sleep disorders such as sleep apnea syndrome, restless leg syndrome or central hypersomnolence disorders. Additional arguments in favor of IR melatonin treatment in an individual child with pediatric insomnia disorder are: 1) if the problem is mainly sleep-onset insomnia; 2) if the pediatric insomnia disorder is associated with a sleep phase delay (even if DSPD criteria are not completely met); 3) if there is a positive family history of DSPD or late chronotype; and finally 4) when daytime repercussions are major and/or repercussions on the life of the family, eg very high stress levels and/or appearance of depressive or anxious symptomatology in parents related to the lack of sleep due to their child's insomnia disorder. Under these conditions, IR melatonin treatment has a highly positive benefit–risk ratio, given the severe repercussions of pediatric insomnia disorder in the long run and its persistence into adulthood if not treated (see above), on one hand, and the benign safety profile of melatonin on the other. The dosages and times of administrations are similar to the ones described above for IR melatonin.

## Conclusion

Solid scientific evidence from clinical as well as from basic chronobiology research underlines the differential roles of IR versus PR melatonin treatment as an etiological treatment in several pediatric populations, in particular in children with NDD, or if the insomnia complaint is associated with delayed sleep phase disorder. For these indications, treatment recommendations regarding differential dosing and timing of IR versus PR melatonin administration are provided. Additionally, IR melatonin may have a role in pediatric insomnia disorder, when first-line therapy with sleep hygiene measures and behavioural treatment approaches have failed, and when other underlying sleep disorders have been ruled out. Taking into account the many negative repercussions of pediatric insomnia disorder on the child's daytime functioning and long-term development on the one hand, the benign safety profile of IR melatonin and its beneficial effect on sleep (in particular sleep onset) and quality of life of the child and the family on the other, the benefit–risk ratio weighs largely in favor of a role for melatonin treatment in pediatric insomnia, under conditions detailed above. Future research should address efficacy of PR melatonin in pediatric insomnia beyond the autism spectrum and neurogenetic disorders, eg in children with ADHD and other neurodevelopmental or child psychiatric disorders, as well as conduct head-to-head studies on IR versus PR melatonin for different types of pediatric insomnia, in order to further refine treatment melatonin treatment indications and modalities in children and adolescents.

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