

Melatonin as an aid to a child's sleep? A cautionary note

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Key points

- ▶ Difficulty falling asleep and/or maintaining sleep may be due to a variety of sleep issues or disorders.
- ▶ Always approach a sleep problem in a child with a thorough sleep and medical history, combined with a careful physical examination.
- ▶ Attention to good sleep habits and behavioural sleep measures remains first-line treatment for children with difficulty sleeping.
- ▶ Melatonin may be used second line and "off label" for children with protracted difficulty sleeping, particularly if they have underlying neurodevelopmental problems.
- ▶ Follow-up and review of prescriptions of melatonin are suggested due to the lack of studies on the potential side effects of prolonged usage in children.

Melatonin is increasingly being used to facilitate sleep in the paediatric population

CHILD HEALTH

Poor sleep in a child is a prospect no parent relishes, and no child benefits from. And when it becomes a long-term problem, a whole-of-patient approach is needed before trialling medication

◆ Sarah Currie, Elizabeth Edwards and Dawn Elder

Difficulty with sleep is a common problem in both neurotypical children and those with neurodevelopmental disorders (eg, attention deficit hyperactivity disorder, ADHD; autism; and blindness). And melatonin is increasingly being used to facilitate sleep in the paediatric population.

Melatonin is frequently perceived as a safe "natural hormone" rather than a drug. Parents surfing the internet are likely to get conflicting information on its safety and side effects. Health professionals also vary in their thresholds for the use of melatonin, and for the dosage, timing and duration of prescribing. This article reviews the indications for melatonin in children, and the evidence of benefits and of safety for melatonin use by children presenting with difficulty falling asleep or maintaining sleep.

First, take a history...

Accurate diagnosis is critical before pharmacological therapy is trialled. Sleep disorders are common in children, but they often go unrecognised. Difficulty with falling asleep and/or maintaining sleep may be due to a number of conditions, including pain, gastro-oesophageal reflux, sleep disordered breathing and anxiety. These should be considered and treated, and concomitant medication use reviewed, before any trial of melatonin.

What questions to ask? A thorough history should include daytime activities and meal times, bedtime routine and behaviours, the sleeping environment and bedtime schedule, including time to sleep onset. The child's sleep/wake pattern, recorded over a couple of weeks, should be reviewed. School-day versus weekend routines may be particularly important for teenagers. Specific areas of the history to cover, include:

- duration of the problem – transient (days) versus sustained (weeks/months)
- triggers (eg, illness, jet lag, hot weather, new school or exams)
- daytime symptoms – tiredness, napping (naps in children older than five years are unusual, and suggest inadequate sleep) or poor school performance
- drugs – use and effect of over-the-counter hypnotics, caffeine intake (drinks and foods, eg, chocolate), other medications (eg, methylphenidate) and other treatments/therapies trialled
- mood – anxiety, low mood, family history of similar sleep symptoms or mood disorder
- medical history – acute and chronic medical conditions can precipitate or exacerbate sleep difficulties (eg, pain, gastro-oesophageal reflux disease, asthma, cough, nasal obstruction, allergies, headache)
- other causes of sleep disturbance/disorders (eg, restless leg syndrome, obstructive sleep apnoea – refer to the New Zealand sleep disordered breathing guidelines; <http://bit.ly/2v1aveq>)
- poor sleep hygiene – see later, "Healthy sleep habits".

What is melatonin?

Melatonin is a hormone produced primarily by the pineal gland within the brain. It helps regulate other hormones and its secretion has a circadian pattern, with peak production during the hours of darkness and suppression of secretion caused by light. There is typically a 10 to 15-fold increase in production one to two hours before bedtime.

The melatonin available as a pharmaceutical product is a synthetic form of the hormone. In New Zealand, from 1 July, only a 2mg modified-release tablet of melatonin (Circadin) is available on Special Authority for children and adolescents up to the age of 18 with neurodevelopmental disorders. Apart from this, no form of melatonin is currently approved for use in children, and any use is "off label". Specialist approval is required for both the initial application and renewal of Special Authority subsidy, following an adequate trial of environmental and behavioural strategies in the young person.



Sleep disorders are common in children, but they often go unrecognised

Can melatonin help children sleep?

There is good scientific evidence that melatonin can shorten the time to sleep in children, including children with ADHD, autism and other neurodevelopmental disorders. There is much less evidence that melatonin helps children stay asleep, even when used in its long-acting form.

Evidence for the effectiveness of melatonin in children is based on generally small-to-moderate-sized studies, and data extrapolated from adult studies. Study designs vary, and include retrospective studies and case reports, as well as randomised controlled trials; the trials encompass broad age ranges, different dosages and variable methods used to measure sleep outcomes (eg, subjective questionnaires, sleep diaries, actigraphy).

Reduction in sleep-onset latency (time to onset of sleep) and increase in overall sleep duration are reported in the majority of studies but, when placebo effects and the effect of behavioural interventions are taken into account, the effects are more modest: latency typically reduced by 15–40 minutes (but only seven minutes in one meta-analysis), and an increase in sleep duration of 20–40 minutes. While melatonin reduces sleep-onset latency, it also results in earlier waking, reducing the effect on overall sleep time.

Is melatonin safe for children?

In general, melatonin appears to be well tolerated in children. Side effects tend to be mild and self-limiting and include headache, nausea, dizziness, increased nocturnal enuresis and sedation. The safety of very long-term use is unknown, but habituation is not described.

While melatonin is typically prescribed for its effects on sleep, it is known to have a much broader range of effects including antioxidant and immunomodulatory effects. Chronic melatonin administration causes activation of the immune system, and this should be avoided in children with autoimmune or lymphoproliferative disorders, and those on immunosuppressive medication.

Based on animal studies, there are ongoing concerns melatonin has effects on pubertal development and seasonal reproduction. There is very little evidence to suggest adverse effects on puberty and reproduction in humans, and there are no long-term clinical trials investigating this. Weak conflicting evidence suggests melatonin may either increase or decrease the seizure threshold in epilepsy, and caution is recommended.

Important caveats when prescribing melatonin

Melatonin is available in both short-acting and controlled-release forms. Short-acting forms are regarded as more effective for shortening sleep-onset times, and long-acting forms for sleep maintenance; however, there are no studies available to support this. Breaking or crushing the modified-release tablet removes the modified-release properties.

Melatonin can be prescribed for use as both a hypnotic (to induce sleep) – typically as a higher dose given 30–60 minutes before the desired bedtime – and as a chronobiotic (to alter the timing of sleep) with a smaller dose given two to four hours prior to sleep onset. It is important to acknowledge that all of the suggested exogenous melatonin treatment regimens are vastly in excess of physiological levels. Therefore, only use the lowest dose to achieve the desired effect. Doses as small as melatonin 0.5mg are effective in children, and little additional benefit is seen with doses over 6mg.

For most children, medium to long-term use of melatonin is required to sustain the effect. However,

Recommended sleep duration for children and young people

Age	Sleep needed (hours)
0–3 months	12–18
3–12 months	14–15
1–3 years	12–14
3–5 years	11–13
6–12 years	10–11
12–18 years	8.5–9.5

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melatonin use should be discontinued for one week each year after a normal sleep cycle is established to assess the need for ongoing therapy.

In some patients, those who are slow metabolisers of melatonin, the initial response diminishes within a few weeks of treatment, as melatonin accumulates and the circadian melatonin rhythm is lost. This is thought to affect 12 to 14 per cent of the population, but it may be more common in children with neurodevelopmental disabilities. Clinical response is usually restored following a washout period and dose reduction.

When should melatonin not be prescribed?

Melatonin is predominantly metabolised in the liver, and is a cytochrome P450 inducer. Caution is required in children with liver disease, or when used alongside other medications such as antidepressants (eg, fluoxetine), calcium channel blockers or beta-blockers. It is also advised melatonin not be used with corticosteroids or other immunosuppressants.

Focus on healthy sleep habits and avoid melatonin when the child is less than three years old, and if the sleep difficulty is short term or precipitated by an event (eg, school exams, jet lag) or an illness.

Do not increase the prescription above suggested limits or persist with melatonin if the sleep disturbance fails to resolve.

If the history suggests an underlying sleep disorder (eg, obstructive sleep apnoea, restless legs), or the difficulty with sleep persists, refer the child to a local paediatrician or the Paediatric Sleep Medicine Clinical Network (<http://bit.ly/2v1aveq>).

Healthy sleep habits for children and young people

- Sleep schedule – go to bed at the same time every night. Bedtimes and wake times should not differ by more than one hour whether a weekend, holiday or school night.
 - Naps – have an age-appropriate nap schedule. If naps are taken by a school-age child, they should not be multiple, longer than 45 minutes or late in the day.
 - Sunshine and exercise – encourage children outside in the sunshine, especially in the early morning, and exercise regularly but not in the hour or so before bed.
 - Bedtime routine – have a consistent relaxing and calm bedtime routine (eg, reading, quiet music) for 30–60 minutes before lights out. Do not watch TV, study or exercise.
 - Bedroom environment – this should be cool, dark and quiet. Use the bed only for sleep. Children should be encouraged to fall asleep independently.
 - Avoid bright light at bedtime and during the night, and increase light exposure in the morning. Keep all screen activities (eg, TV, computers, phones) out of the bedroom.
 - Caffeine and meals – avoid foods or drinks containing caffeine and heavy meals within one to two hours of bedtime, and keep meals regular during the day. Likewise, do not go to bed hungry – in the younger child, a light snack (eg, milk and biscuit) before bed may be helpful. ■
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References are available under 'GP Resources' on nzdoctor.co.nz