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REVIEW ARTICLE

Potential safety issues in the use of the hormone melatonin in paediatrics

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Abstract: Melatonin is a hormone produced by the pineal gland during the night in response to light/dark information received by the retina and its integration by the suprachiasmatic nucleus. When administered to selected populations of adults, in particular those displaying delayed sleep phase disorder, melatonin may advance the time of sleep onset. It is, however, being increasingly prescribed for children with sleep disorders despite the fact that (i) it is not registered for use in children anywhere in the world; (ii) it has not undergone the formal safety testing expected for a new drug, especially long-term safety in children; (iii) it is known to have profound effects on the reproductive systems of rodents, sheep and primates, as well as effects on the cardiovascular, immune and metabolic systems; and (iv) there is the potential for important interactions with drugs sometimes prescribed for children. In this review, I discuss properties of melatonin outside its ability to alter sleep timing that have been widely ignored but which raise questions about the safety of its use in infants and adolescents.

Key words: behavioural; developmental; endocrinology; pharmacology; sleep.

The use of melatonin as a drug for the treatment of sleep disorders is increasing, particularly in the paediatric setting.[1,2] In the USA, melatonin is considered a dietary supplement and therefore not regulated by the FDA, and as a consequence, it is freely available in pharmacies and supermarkets in that country. However, in Australia and many other jurisdictions, melatonin can only be obtained through compounding pharmacies on prescription. A new formulation of melatonin, Circadin (Neurim Pharmaceuticals LTD, Tel-Aviv, Israel), has however recently been registered in Australia for use as a 'monotherapy for the short term treatment of primary insomnia, characterised by poor quality of sleep in patients who are aged 55 years and over'. Any use of melatonin in children or adolescents is clearly 'off label', and there is poor information provided to consumers and health-care providers about the appropriate use and safety of melatonin generally and for paediatric use in particular. The aim of the current review is to provide information on the documented actions and properties of melatonin outside its ability to alter sleep timing that have been widely ignored but which raise questions about the safety of its use in infants and adolescents.

Key Points

1. Melatonin is increasingly being prescribed off label for children and adolescents for difficulty in initiating and maintaining sleep.
2. There is extensive evidence from animal and human studies that melatonin acts on multiple physiological systems, including the reproductive, cardiovascular, immune and metabolic systems.
3. Long-term safety studies on children and adults are lacking.

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What Is Melatonin?

Melatonin is an indole hormone synthesised enzymatically in the pineal gland from the amino acid, tryptophan. It was originally isolated from cattle pineal glands in a program investigating agents that promote skin lightening.[3] Secretion of melatonin from the pineal gland is controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus, the site of the biological clock. It appears in blood during the early evening, with peak concentrations occurring around 0200–0300 h and then decreases to be undetectable by the time people are breakfasting. As a consequence, melatonin is often termed the 'hormone of darkness'. The timing of melatonin production is influenced by light perception by the retinae and the endogenous rhythmicity of neurons within the SCN. The SCN controls the pineal gland via neural signals in a multi-synaptic pathway that involves the superior cervical ganglia and adrenergic neurons innervating the pineal gland. This control system allows the duration and timing of melatonin secretion to change with the seasons such that the duration of melatonin secretion is longer during the short days of winter than the long days of summer in a wide range of animal species. Although humans are not normally considered to exhibit seasonality, this is thought to be a masking effect of our life-style in recent times with the widespread use of supplemental lighting.[4] Another important feature of melatonin secretion is that even domestic lighting can inhibit the onset of production and secretion of the hormone.[5]

What Does Melatonin Do?

Melatonin research has a colourful history. Although originally linked to skin pigmentation changes, it proved to be ineffective clinically for treating human skin disorders. By 1963, however, it had been shown that injection of microgram amounts of melatonin into rats decreased the incidence of estrus and reduced the weights of the ovary. For example, when immature female rats were injected with 1–20 μg of melatonin daily for 28 days, there was a highly significant decrease in ovarian weight and a delay in spontaneous vaginal opening and onset of estrus.[6] As little as 1 μg melatonin (20 μg/kg) caused a significant decrease in the weight of the ovary. This led to the early focus of melatonin research on its reproductive effects in non-seasonal laboratory animals (rats, mice). Subsequent experiments in seasonal reproducing hamsters showed that doses in the range of 75–185 μg/kg injected into adult males in late afternoon decreased their testicular weights, while doses as low as 20 μg/kg reduced the number of adult female hamsters that were ovulating.[7] In these early studies on melatonin and reproductive processes, it was often termed an 'anti-gonadal hormone'.

More contemporary evidence, while not in any way challenging the earlier findings, suggests that the effects on reproduction across species are quite complex. Indeed, when melatonin is administered to female sheep (ewes) during the time of year when they are not ovulating, it can actually promote the re-initiation of ovulation and subsequent fertility. My group used these findings to develop a veterinary drug preparation of melatonin (Regulin; Ceva Animal Health Pty Ltd., Glenorie, NSW, Australia) that produces continuous levels of melatonin for more than 10 weeks in the night-time physiological range and which is used to advance the start of the fertile period and increase their ovulation rate and offspring numbers.[8,9] It is still available as a registered veterinary drug in Australia and elsewhere. These melatonin implants have also been used as a means of controlling the seasonality of cats by inhibiting the occurrence of estrus,[10] while in primates, administration of 0.7 μg/kg per day *advanced* the onset of puberty by 5 months.[11] Several groups have shown that melatonin appears in human ovarian follicular fluid,[12] and its concentration is increased following oral administration.[13] A recent review on the physiological and pathophysiological roles of melatonin on the ovary concluded that 'numerous data suggest the involvement of melatonin in ovarian physiology including follicular development, ovulation, oocyte maturation, and luteal function'.[13] It is worth noting also that in the early 1990s, high doses of melatonin were being investigated as a potential human contraceptive in conjunction with progestins,[14] although the research has not been followed up.

While it can be misleading to compare doses of drugs that have physiological outcomes in animals with those administered to humans, it is important to recognise that the doses used in the rodent and primate experiments which had physiological effects are well *below* the doses currently administered to children with sleep disorders (i.e. a 3-mg melatonin dose equates with 200 μg/kg for a 15-kg child and 60 μg/kg for a 50-kg child). The role of melatonin in reproductive processes was reviewed in 1980[15] and again in 1991[16] by the same author. In the 1991 review, Russell Reiter wrote, 'In particular, melatonin as a mediator of photoperiodically induced changes in pubertal development and seasonal reproduction in nonhuman mammals has been repeatedly confirmed. *Considering the pronounced effects of the pineal gland and melatonin on reproductive physiology in these nonhuman mammals, to assume they would not have some sexual effects in humans would almost seem naive.* Whereas only 30 years ago the pineal was generally considered to be vestigial, it now appears it may be functionally involved with every organ system in the body.'[16] Subsequent research supports the widespread influence of melatonin on a wide range of physiological systems.[17]

Melatonin as a Drug

Adults produce approximately 20- to 60-μg melatonin endogenously over a period of 8–10 h each day,[18] while most melatonin tablet preparations contain from 2 to 5 mg. Following oral administration of 'fast release' preparations, melatonin is rapidly absorbed and metabolised on first pass through the liver, with a half-life of 30–40 min and bioavailability of 1–37%.[19] In the liver, it is metabolised to 6-hydroxymelatonin by CYP1A2[20] and then sulphated to 6-sulphatoxy melatonin or conjugated to glucuronide and excreted. Comprehensive pharmacokinetic studies on Circadin have not been published; however, Zisapel[21] reported 'peak concentration of melatonin in the blood occurred 2.6 h and persisting over 3.5 h after ingestion. . . . and yields about 6–8 fold higher blood levels than the endogenous levels at night'. Little is known about the pharmacokinetics of melatonin in infants, but a recent study in premature infants reported a half-life of 17–21 h[22] making replacement of a typical maternal circadian rhythm problematic for preterm infants. In 3- to 8-year-olds, the half-life of orally administered melatonin is approximately 30–45 min,[23] similar to the adult half-life. Because liver CYP1A2 levels are at 20–25% of adult levels in children aged 3–12 months and 50–55% of adult levels in children from 1 to 9 years of age,[24] children who are administered melatonin are clearly being exposed to extremely high levels of the hormone compared with adults receiving the same dose.

It is to be expected that many adult and paediatric patients being treated with melatonin for a sleep disorder will also be receiving other prescription drugs (and perhaps complementary and alternate medicines too). As just indicated, the primary pathway of melatonin metabolism involves CYP1A2 (and to a lesser extent CYP2C19), and as these enzymes are involved in the metabolism of many drugs, there is the opportunity for important drug interactions. Fluvoxamine, an inhibitor of CYP1A2 and CYP2C19, raises endogenous plasma melatonin levels[25] and its bioavailability,[26] as does caffeine[27] and presumably the related theophylline. Inhibitors of CYP2C19, like citalopram, also altered the metabolism of orally administered melatonin.[28] Although prescription of these drugs and co-administration of melatonin in paediatrics may be limited, a Canadian study reported that approximately 25% of SSRI prescriptions for children and adolescents were for citalopram and 5% for fluvoxamine.[29]

Melatonin and Sleep

The primary reason for the prescription of melatonin for adults and children is to treat sleep disorders. Use of melatonin to treat

sleep disorders in paediatric patients was first reported in 1991, and initially, its use was restricted to children with severe neurodevelopmental disorders (visual impairment, epilepsy, cerebral palsy, Angelman syndrome, etc.) Many studies were small, uncontrolled and relied on subjective parent assessments. As stated by Jan and Freeman,[30] 'because of a misconception that melatonin promotes sleep in the same way as a sleeping pill, its research has been conducted in a similar way to studies of hypnotics'. Accordingly, doses of melatonin were increased when there was no response, administration times were not standardised, adherence to strict sleep hygiene and bedroom lighting conditions was not included in the protocols, and there was often a lack of documented circadian rhythm disturbance to justify the treatment. The other over-simplification was the misconception that 'circadian rhythm sleep disorders were simply due to a deficiency in melatonin secretion, so that the aim of therapy therefore was only hormone replacement.'[30]

In the most recent meta-analysis of 19 adult and child studies, it was found that melatonin significantly reduced objectively recorded sleep onset latency by 5.5 min.[31] Melatonin significantly increased total sleep time by 11.9 min when determined by subjective measures but not by objective measures (0.33 min). Since the publication of the meta-analysis, Gringras *et al.*[32] have reported the results of children aged between 3 and 15 years treated with an escalating dose of melatonin 45 min before the child's age-appropriate bed time. Using objective actigraphy measures, melatonin treatment advanced sleep onset by 45 min and waking time by 30 min but did not affect total sleep time. Cortesi *et al.*[33] treated children (mean age 6 years) with autism spectrum disorders with a 3-mg controlled-release melatonin preparation at 2100 h, with cognitive behavioural therapy (CBT), a combination of melatonin and cognitive therapy or placebo. Melatonin alone resulted in an earlier bed time, an advance of sleep onset by 36 min and an increase in total sleep of 71 min. Interestingly, CBT also decreased sleep onset latency by 17 min and increased total sleep by 37 min, with the combination therapy more effective than CBT alone.

Melatonin and Epilepsy

Since the initial report that melatonin administration may lower the electrical amplitude of EEG recordings,[34] there have been a number of studies conducted to determine if the hormone can provide control over epileptic seizures. Two recent reviews have summarised the outcomes of studies on the topic. The first, a Cochrane Review on melatonin as an add-on treatment for epilepsy, concluded that it is not possible to draw any conclusions about the role of add-on melatonin in reducing seizure frequency or improving the quality of life or about the safety profile of this drug in people with epilepsy.[35] The second review also examined published data to assess the evidence for melatonin affecting seizure control and found that all the studies involved relatively small numbers of patients, and most were neither blinded nor placebo controlled. No firm conclusions could be drawn with respect to efficacy.[36] These findings are not entirely surprising as there is little evidence that the timing of melatonin secretion is dramatically altered in epilepsy;[37] indeed, if anything, melatonin production may be increased in these patients.[37,38]

Potential Benefits of Melatonin Administration

The actions of melatonin when administered orally are not those of a hypnotic (i.e. capable of rapidly initiating and increasing the duration of sleep) but as a chronobiotic (i.e. altering the *timing* of sleep). In adults with sleep timing problems, especially those with delayed sleep phase disorder, it has been recommended that the onset of melatonin secretion (dim light melatonin onset (DLMO)) be determined prior to commencement of any therapy to determine if there is a circadian timing system abnormality.[39] If the delayed sleep onset occurs in a patient with a normal melatonin onset, there is less prospect of the treatment being successful in advancing the sleep onset, and other treatment options should be explored. Determination of the DLMO is not currently widely used, but it can be easily performed through home saliva collection and subsequent laboratory assessment of the timing of the melatonin rise from baseline. In the paediatric setting, there is little impediment to establishing the DLMO (unless there are severe behavioural issues), and there are several publications demonstrating its utility.[40–44] In addition, objective measures of sleep should be obtained either through actigraphy or polysomnography.

Safety

Because melatonin is considered a dietary supplement and not a drug in the USA, it has not been appropriately evaluated for safety by the FDA in any population group, including children. Despite this, melatonin use has generally been regarded as safe by study authors and reviewers, despite the lack of rigorous clinical trials assessing its safety.[1] Those studies that have attempted to address the issue in children have had major shortcomings. van Geijlswijk *et al.* asked 69 children who had taken melatonin for an average of 3.1 years three Tanner score questions (the age at first ejaculation for boys, the ages of menarche of their mothers and the first ejaculation of their fathers) and compared the results against the Dutch population.[45] There were no endocrine assessments performed. Only 33% of the children had reached the age of 13 in the study, and only 62% of boys and 91% of girls answered the questions, but the authors concluded that puberty onset seems to be undisturbed after 3.1 years of melatonin usage. A previous study by Hoebert *et al.*[46] did not conduct any laboratory endocrine tests or address any reproductive issues but concluded that long-term use of melatonin did not show safety concerns in children regarding serious adverse events. A study by Carr *et al.*[47] of 44 children with multiple neurodevelopmental disabilities treated with melatonin for an average of 4.3 years between the ages of 6 and 9.9 years of age stated that there were no adverse physical or neurological changes, but it did not provide details of their evaluations. These studies highlight the inadequacies of the studies aimed at determining safety beyond acute effects. If melatonin is to be used for treatment of sleep disorders in children, it is important that appropriate rigorous follow-up studies are conducted into early adulthood.

In Australia, a Therapeutic Goods Administration (TGA) report[48] stated in relation to paediatric melatonin use, 'There are *no adequately conducted nonclinical studies in young animals to*

support the use of melatonin in children, and treatment of paediatric patients is not proposed'. And specifically for Circadin, it stated that it 'is *not recommended for use in children and adolescents* below 18 years of age due to insufficient data on safety and efficacy'. The National Institutes of Health (NIH) states that '*Melatonin should not be used in most children. It is possibly unsafe*. Because of its effects on other hormones, melatonin might interfere with development during adolescence.'[49] These statements actually underplay the knowledge in the area because, as just discussed, there have been hundreds of experiments on young and adult animals reporting major influences on the reproductive system and indeed other systems not discussed here.

The Australian Sleep Health Foundation is a body that aims to foster the common ground between community, professional and business interests in relation to identifying and dealing with sleep problems. One of its partners is the Australasian Sleep Association. In contrast to the statements by the TGA and NIH, it states on its website that melatonin 'may benefit children who are developing normally as well as children with Attention Deficit Hyperactivity Disorder, autism, other developmental disabilities or visual impairment. Short term use is effective and safe. Studies so far suggest that *long term use in children is also safe*.'[50] Clearly, there are mixed signals being sent to the health profession, the patients and their carers. Of course in some situations, the sleep disorders of children with neurological or other disorders may be so severe, and the impact upon their carers so great that the potential risks of prescribing melatonin are outweighed by the benefits of achieving control over sleep behaviours. In these situations, the short-term use of melatonin may be acceptable; however, a thorough evaluation of the sleep disorder should still be conducted before prescribing melatonin.

Summary and Conclusions

Melatonin is a hormone with widespread physiological actions that include a major role in the timing of sleep. When administered as a drug at an appropriate time of the day, it can produce small advances in the timing of sleep onset and its own endogenous production by the pineal in adults as well as children who have an unacceptable late onset of sleep and melatonin secretion. There have been no appropriate studies to show that melatonin is safe in the long term for children or adults. Indeed as Circadin, melatonin has been registered for use only in patients over 55 years of age with primary sleep disorder, and all other uses of the hormone are off label. There is a long history of research indicating that melatonin has important effects on the reproductive organs of rodents, cats, ruminants and primates, and it is in fact registered as a veterinary drug for this purpose. We do not know the long-term endocrine effects of melatonin administration to children and adolescents. The effects of melatonin, however, go beyond the potential reproductive consequences highlighted in this review, including effects on cardiovascular, immune and metabolic systems.[17]

Prescription of melatonin to any child whether severely physically or neurologically disabled or developing normally should be considered only after the biochemical diagnosis of an underlying sleep timing abnormality and after full disclosure to the carers of information about the known actions of melatonin on reproductive and other systems in animal models and the disclosure that there is a lack of appropriate studies conducted in children. Should endocrine or other abnormalities appear in the future in children previously treated with melatonin, it will not be tenable to argue that we were surprised.

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Multiple Choice Questions

1. Melatonin is:
   a. a protein hormone derived from an X-linked gene.
   b. a small molecular weight compound derived from tryptophan.
   c. produced by the pituitary gland.
   d. produced throughout the day.

Answer: 'b' Melatonin is a small molecular weight indole compound derived *enzymatically* from the amino acid tryptophan during the *night* in the *pineal* gland.

2. Treatment with melatonin is a viable approach to improve sleep in children who have
   a. low endogenous melatonin levels.
   b. difficulty falling asleep.
   c. many awakenings after sleep onset.
   d. early morning awakening.

Answer: 'b' Treatment with melatonin is a potentially viable option for treating children who have difficulty falling asleep and possibly to increase the duration of sleep, who also have been shown to have a delay in the onset of production of their endogenous melatonin. 'a' is incorrect because there is no evidence that children with sleep disorders are deficient in melatonin; instead they may have delayed production of the hormone. 'c' is incorrect because there is little evidence that melatonin decreases the incidence of awakening in children or

adults. 'd' is incorrect because melatonin treatment is more likely to increase the incidence of early morning awakening because it can advance sleep onset.

3. Melatonin is being used in children to treat sleep disorders, but care is warranted because:
   a. some formulations contain melatonin derived from animals.
   b. it can cause dependence.
   c. it has not been adequately tested for long term safety.
   d. it suppresses endogenous production of the hormone.

Answer: 'c' There has been no long term safety testing of melatonin in children, especially reproductive safety, but also with respect to other endocrine and immune effects in patient populations. 'a' is incorrect because all melatonin preparations are chemically synthesised; content of animal pineal glands is extremely low and would be impossible to incorporate into tablets. 'b' and 'd' are incorrect as there is no evidence that melatonin causes dependence or that it suppresses endogenous production.

Colourful creatures by Zara Wyatt (5) from Operation Art 2014.