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# Melatonin in the treatment of insomnia in children and adolescents

### AIMS AND METHOD

To review the efficacy and safety of melatonin in the treatment of insomnia in children and adolescents, through a Medline search covering the years 1966 to November 2003.

### RESULTS

Five placebo-controlled studies and several case series were identified. Melatonin reduces sleep latency, but does not consistently improve other aspects of sleep disturbance. Safety, particularly in the medium- and long-term, is poorly evaluated; short-term concerns include exacerbation of epilepsy and asthma.

### CLINICAL IMPLICATIONS

Melatonin might be effective in the short-term treatment of sleep onset insomnia. The optimal dose is unknown. It cannot currently be recommended for the treatment of other forms of sleep disturbance or for routine long-term use. Melatonin is not a licensed medicine in the UK.

From early childhood onwards, the cycle of wakefulness and sleepiness is regulated by a circadian 'clock' in the suprachiasmatic nucleus (SCN) of the hypothalamus. This clock is regulated (reset) by various cues, including that of the light–dark cycle of day and night.

In the neonate, there is little entrainment of the sleep–wake cycle to the light–dark cycle (Garcia *et al*, 2001). By the age of 6 months, circadian rhythms have become established and sleep patterns have taken on a roughly 24 hour cycle of nocturnal sleep plus daytime naps. By the age of 6 years, most children sleep only at night. Total sleep time gradually decreases with age and by adolescence has stabilised to a daily average of about 8 hours and the sleep–wake cycle to slightly more than 24 hours. This cycle is reset daily by the SCN.

Insomnia is a common problem in children with sensory deficits and some learning disability syndromes. It is also a symptom of childhood psychiatric disorders such as depression and attention-deficit hyperactivity disorder. Persistent sleep disturbance in a young child can adversely affect family life. Mothers of learning-disabled children with severe sleep problems have been reported to be more irritable and less affectionate towards their children than mothers of such children without sleep problems (Quine, 1992). Successful treatment of the child's sleep problems generally leads to improvements in the mother's mental state, confidence and relationship with the child, as well as in the child's behaviour (Minde *et al*, 1994).

In adolescence, delayed sleep phase syndrome, in which the sleep–wake cycle may be particularly prolonged, is common. About 10% of otherwise normal

children (Smits *et al*, 2001) and up to 80% of children with developmental disorders (Jan & O'Donnell, 1996) are affected.

### The role of melatonin

Melatonin is an endogenous hormone chemically related to serotonin. It is produced by the pineal gland in the midbrain. Body levels follow a circadian course, being stimulated by the evening onset of dim light and suppressed by bright light. The evening rise in melatonin precedes the rise in sleepiness by about 1.5–2 hours (Tzischinsky & Lavie, 1994). The circadian rhythm of sleep consolidation (the ability to stay asleep) may also be related to melatonin levels, but this has yet to be demonstrated. Melatonin acts by resetting any disruption of SCN rhythms. Given its association with circadian rhythms, oral melatonin could be expected to treat sleep disturbances. Many case studies, case series, open and controlled studies have been published. These are summarised below.

### Case series

Jan & O'Donnell (1996) gave melatonin (2.5–25 mg) to 100 children with developmental disorders, half of whom were visually impaired or blind. Benefits including fewer tantrums, better attention and improved socialisation were noted in 80%. In a further case series, Palm *et al* (1997) gave melatonin (0.5–4 mg) 30–60 min before the scheduled bedtime to eight children and young adults. All



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the children were learning-disabled and blind, and four also had hearing impairments. All improved in terms of sleep–wake timings.

In a case series of two children with Rett syndrome, a dramatically beneficial effect on the regulation of the sleep–wake cycle was seen in one child, with the other child showing marginal benefit (Miyamoto *et al*, 1999). Jan (2000) gave melatonin (3 mg) to 10 children with developmental disorders and severe sleep disorders: 8 of the 10 improved with respect to delay of sleep onset, early morning waking, duration of unbroken sleep and total duration of sleep. In the most recent case series, Ivanenko *et al* (2003) gave melatonin (average dose 2 mg) an hour before bedtime to 32 children with chronic sleep problems. Partial or complete resolution of sleep problems was achieved in 29. Some children (number unstated) were receiving other unspecified medical and behavioural interventions.

## Controlled studies

Five placebo-controlled studies have been published. Camfield *et al* (1996) gave melatonin (0.5 mg or 1 mg) or placebo in 2-week alternating phases at 18.00 to six children with fragmented sleep and developmental disorders, none of whom showed any significant improvement in sleep patterns. McArthur & Budden (1998) gave nine children with Rett syndrome variable doses of melatonin or placebo for a 4-week period with a 1-week drug wash-out period between the treatment and placebo phases. Sleep latency was reduced significantly in the treatment phase, although individual response varied greatly. Dodge & Wilson (2001), in a 6-week double-masked, placebo-controlled study, compared melatonin with placebo in 20 children with developmental disorders. Significant reductions in sleep latency were observed, but sleep duration and number of awakenings did not change.

Smits *et al* (2001) gave 40 children with sleep onset insomnia either 5 mg melatonin or placebo once daily at 18.00 for 4 weeks. Children with developmental disorders were excluded. Melatonin was significantly better than placebo with respect to lights-off time, sleep onset and sleep duration, but not sleep latency or wake-up time. Two children had mild headache during the first 2 days of treatment with melatonin, and one child developed mild generalised epilepsy while taking open-label melatonin 4 months after the start of the trial. On 18-month follow-up, 13 children were able to stop taking melatonin without further sleep disturbance.

In a further similar study (Smits *et al*, 2003), 62 children with idiopathic chronic sleep-onset disorder were given melatonin 5 mg or placebo for 4 weeks after a 1-week baseline period. The active group improved significantly in measures of general health, sleep onset time and sleep offset time. There was no change in lights-off time or total sleep time. Children with comorbid psychiatric illness were excluded from this study, with the exception of those treated with methylphenidate. The active and placebo groups contained markedly different numbers of children prescribed methylphenidate (22% v. 54%). This could have biased

the result, as methylphenidate is independently associated with insomnia.

Melatonin is widely prescribed by child psychiatrists in the UK, although it is not a licensed medicine.

## Side-effects

Since melatonin is a natural substance, it is often assumed that its side-effect profile is benign. However, most other endogenous hormones produce considerable adverse effects in high or inappropriately phased doses and it should be anticipated that melatonin might behave similarly. Many of the published reports involved children with developmental abnormalities, which limited the scope for detection of subtle adverse effects. Most studies involved short-term use of melatonin and did not systematically inquire about side-effects.

Sheldon (1998) reported that melatonin increased seizure frequency in neurologically disabled children, an effect that disappeared when melatonin was discontinued and reappeared on further challenge. Also, Smits *et al* (2001) reported the development of mild epilepsy in one child. Whether seizure threshold is affected in the general population is unknown.

Melatonin raises levels of inflammatory cytokines such as interleukins 1 and 6 and tumour necrosis factor alpha (Maestroni, 1993), and this effect may have adverse consequences for people with inflammatory-mediated conditions such as asthma. Sutherland *et al* (2003) and Sutherland *et al* (2002) reported that peak endogenous levels of melatonin were elevated in people with nocturnal asthma and were inversely correlated with measures of respiratory function; they concluded that the 'avoidance of exogenous melatonin supplementation by persons with asthma might be warranted'.

Melatonin has contraceptive properties and can affect the onset of puberty (Weaver, 1997). It also has antioxidant (Pieri *et al*, 1994) and cytostatic (Brzezinski, 1997) properties. These effects are minimal at physiological levels, but may become more apparent when synthetic melatonin is taken in supraphysiological doses: the cut-off point between physiological and pharmacological levels in adults is estimated to be produced by doses of 500 µg, and this is likely to be less in children.

In clinical depression in adults, there is evidence that the risk–benefit ratio for melatonin may be adverse. Carman *et al* (1976) found that melatonin exacerbated symptoms of dysphoria, reduced sleep and led to weight loss in a small, double-blind, cross-over study in moderately to severely depressed adult patients. It has been suggested that seasonal affective disorder might respond to propranolol through the suppression of endogenous melatonin production (National Institute of Mental Health USA, 2003).

## Overview

Five placebo-controlled trials in children have been identified. Most of the published literature consists of case reports and case series, which used a variety of doses



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and formulations of melatonin. The nature of the populations treated is diverse, and most studies report short-term use in which the placebo effect would be highest. Oral melatonin may reduce sleep latency, but its effects on other aspects of sleep are inconsistent between studies. The optimal dosages and duration of treatment are unknown. Side-effects have been poorly evaluated to date, although worsening of seizures and asthma have been reported in the short term. Long-term side-effects are not established, although melatonin is known to have significant effects on many body systems. Melatonin is not a licensed medicine in the UK and the prescriber is fully accountable for any problems that might result from its use.

## Declaration of interest

None.

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