

Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin

Evidence summary

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[nice.org.uk/guidance/esuom2](https://www.nice.org.uk/guidance/esuom2)

Key points from the evidence

The content of this evidence summary was up-to-date in January 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep.

Only 1 form of melatonin (prolonged-release tablets) is currently licensed in the UK for the short-term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over. Additional melatonin products are available from special-order manufacturers or specialist importing companies, or can be purchased directly online.

No high-quality studies were identified that provided evidence for the efficacy of prolonged-release melatonin tablets (licensed in the UK) used off-label in children with sleep disorders and attention deficit hyperactivity disorder (ADHD).

Limited evidence for unlicensed melatonin products was identified from 2 small (n=105 and 19) short-term randomised controlled trials (RCTs) and 1 small, long-term follow-up study (n=94). The evidence suggests that unlicensed melatonin products, taken for 10 days to 4 weeks, may reduce

sleep onset latency (the time taken for a child to go to sleep) in children with sleep onset insomnia and ADHD by approximately 20 minutes. In addition melatonin may improve average sleep duration by 15 to 20 minutes. However, there are limitations to these small studies, and longer term efficacy is unclear.

These RCTs included stimulant and non-stimulant treated children aged 6 to 14 years with ADHD and suffering from sleep onset insomnia. The studies used daily doses of between 3 and 6 mg of unlicensed melatonin described as 'fast-release' or 'short-acting', administered shortly before bedtime.

Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.

Unlicensed melatonin used in the RCTs appeared well tolerated in the short to medium term with only transient mild to moderate adverse effects reported.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle^[1].

Regulatory status of melatonin

Melatonin (Circadin, Flynn Pharma Ltd) is currently licensed in the UK for the short-term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over^[1]. It is a prescription-only medication available as 2 mg prolonged-release tablets (also referred to as modified-release)^[1]. Its use outside of this indication, including use in children and young people under 18 years, is 'off-label'.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using melatonin outside its authorised indications.

Additional melatonin products, including liquid, tablet and capsule preparations, are available from special-order manufacturers or specialist importing companies, or can be purchased directly online^{[2],[3]}. In the USA for example, melatonin products are classed as supplements and are not made under the [pharmaceutical good manufacturing practices](#)^[2]. One melatonin product (Bio-Melatonin, Pharma Nord) is licensed in Europe (Hungary) but is not licensed in the UK^[4]. Use of any of these melatonin products in the UK is unlicensed. [Guidance from the GMC](#) states that, to prescribe an unlicensed medicine, the prescriber must be satisfied that it would better serve the patient's needs than an appropriately licensed alternative.

The sole UK licensed melatonin product (Circadin, Flynn Pharma Ltd) is referred to in this document as 'licensed prolonged-release melatonin'; all other melatonin products are referred to as 'unlicensed melatonin'.

Evidence statements

- No high-quality evidence was identified relating directly to the efficacy of the licensed prolonged-release melatonin in children with sleep disorders and ADHD (an off-label use).
- Two small [RCTs](#) and 1 long-term follow-up study provided limited evidence on the safety and efficacy of unlicensed melatonin in stimulant and non-stimulant treated children with ADHD experiencing sleep problems.
- The evidence is applicable to children aged 6 to 14 years with ADHD and sleep onset insomnia, using unlicensed melatonin (3–6 mg daily) shortly before bedtime.

- The evidence indicates that unlicensed melatonin used in these small RCTs may reduce sleep onset latency by approximately 20 minutes and may improve average sleep duration by 15 to 20 minutes when taken for between 10 days and 4 weeks. The longer term efficacy is unclear.
- Unlicensed melatonin appeared well tolerated in the RCTs in the short and medium term with only mild and transient adverse effects (for example, headache or dizziness) reported. This included data from children treated for an average of 18 months (range of 1–57 months).
- Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.
- Discontinuation of unlicensed melatonin led to relapse of sleep onset insomnia in most of the cases where it was used for more than 30 days.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

No RCTs of sufficient size to provide high-quality evidence were identified that assessed the use of licensed prolonged-release melatonin in children with sleep disorders and ADHD.

Limited evidence from 2 small RCTs^{[5],[6]} (see table 1) and 1 small, long-term follow-up study^[7] suggests that short-term treatment (10 days or 4 weeks) with unlicensed melatonin (3–6 mg daily) taken just before bedtime may improve sleep onset, sleep onset latency and sleep duration in children (aged between 6 and 14 years) with ADHD experiencing sleep onset insomnia. The efficacy past 4 weeks is unclear.

The larger of the 2 RCTs included children who were not taking stimulant medication for their ADHD; treatment lasted for 4 weeks^[5]. The smaller, lower quality RCT was in children taking stimulant medication for their ADHD who had previously had a 10 day sleep hygiene intervention that had not worked^[6]. These studies were not carried out in the UK. No robust evidence was identified indicating that melatonin-related improvement in sleep onset or sleep onset latency led to a subsequent improvement in daytime ADHD behaviour, cognition or quality of life.

Table 1 Summary of the trials

	Unlicensed melatonin	Placebo	Analysis
van der Heijden et al. 2007^d (the Netherlands) RCT (3 or 6 mg daily for 4 weeks)			
Completed and analysed	n=53	n=52	n=105
Primary sleep outcomes			
Actigraph-derived sleep onset ^a (±SD)	-26.9±47.8 minutes mean change compared with baseline	+10.5±37.4 minutes mean change compared with baseline	p<0.0001 between groups; no mean difference reported
Actigraph-derived total time asleep (±SD)	+19.8±61.9 minutes mean change compared with baseline	-13.6±50.6 minutes mean change compared with baseline	p=0.01 between groups; no mean difference reported
Parent-reported difficulty falling asleep (averaged over 7 days on a scale of 1 [not difficult] to 5 [very difficult])	-1.2±1.3 points (35% of baseline)	-0.1±0.8 points (4.3% of baseline)	p<0.0001 between groups; no mean difference reported
Other outcomes Actigraph-derived sleep latency ^b (±SD)	-21.3±33.0 minutes mean change compared with baseline	+3.0±31.7 minutes mean change compared with baseline	p=0.001 between groups; no mean difference reported
Dim light melatonin onset (±SD)	-44.4±67.9 minutes mean change compared with baseline	+12.8±60.0 minutes mean change compared with baseline	p<0.0001 between groups; no mean difference reported
Weiss et al. 2006^e (Canada) 10-day sleep hygiene followed by <u>crossover</u> placebo controlled trial (5 mg daily for 10 days)			

Analysed	n=19	n=19 (same 19 as melatonin group because of crossover trial design)	
Primary outcome Sleep onset latency ^c (±SD) (measured by parent-completed somnolog)	Mean 46.4±26.4 minutes	Mean 62.1±26.6 minutes	Effect size 0.6 Absolute difference 15.7 minutes (p<0.01)
Secondary outcome Sleep onset latency (±SD) (measured by actigraph)	Not reported	Not reported	Melatonin reduced sleep onset latency by 16 minutes compared with placebo (p<0.01)
Abbreviations: n, number of patients; RCT, randomised controlled trial; <u>SD, standard deviation</u> .			
^a Sleep onset is the clock time at the point when the child falls asleep.			
^b Sleep latency is the time from lights out until sleep onset.			
^c Sleep onset latency is the time from when the child was put to bed until sleep onset.			
^d van der Heijden KB, Smits MG, Someren EJ et al. (2007) <u>Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia</u> . Journal of the American Academy of Child and Adolescent Psychiatry 46: 233–41			
^e Weiss MD, Wasdell MB, Bomben MM et al. (2006) <u>Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia</u> . Journal of the American Academy of Child and Adolescent Psychiatry 45: 512–9			

Safety

Unlicensed melatonin used in the RCTs was well tolerated in children during short-term (up to 4 weeks) and medium-term (average 18 months) use^{[5],[7]}. Only mild transient adverse effects were reported throughout. The most common adverse events reported in the melatonin group of the larger 4-week RCT were headache (n=3; 5.7%), hyperactivity (n=3; 5.7%), dizziness (n=2; 3.8%) and abdominal pain (n=2; 3.8%)^[5].

Cost effectiveness and cost

No cost-effectiveness analyses were identified. Prescription Cost Analysis in England shows that, over the last year (July 2011 to June 2012) in general practice, licensed prolonged-release melatonin accounted for around 44% of total melatonin prescribed items (for all indications) and around 16% of the cost (£2,850,038), whereas unlicensed melatonin accounted for around 56% of all prescribed items and around 84% of the cost (£17,295,385)^[8]. In addition, in terms of both spending and prescribing volume, unlicensed special order melatonin products are listed among the top 5 of all special order products prescribed in the last quarter (July to September 2012)^[9].

^[1] Flynn Pharma Ltd (2012) [Circadin summary of product characteristics](#)

^[2] MHRA (2012) [Importing unlicensed medicines](#)

^[3] [British national formulary for children \(2012\)](#)

^[4] Burrill P (2009) [Prescribing and clinical effectiveness newsletter](#)

^[5] van der Heijden KB, Smits MG, Someren EJ et al. (2007) [Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41

^[6] Weiss MD, Wasdell MB, Bomben MM et al. (2006) [Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 45: 512–9

^[7] Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research* 47: 1–7

^[8] Personal communication. NHS Business Services Authority (November 2012)

^[9] NHS Business Services Authority. (2012) [Volume and cost of special order products](#)

Relevance to NICE guidance programmes

Licensed prolonged-release melatonin and unlicensed melatonin have not been appraised through the NICE technology appraisal work programme and are not currently planned into the technology

appraisal or any other work programme. Unlicensed and off-label medicines are not considered for the NICE technology appraisal work programme.

Personal accounts of parents regarding the prescription of melatonin for treating sleep disorders in children with ADHD are described in the [Attention deficit hyperactivity disorder \(ADHD\) full guideline](#) (NICE clinical guideline 72). These accounts do not specify whether they refer to the use of prolonged-release melatonin or unlicensed melatonin and NICE make no recommendations about its use.

Intervention and alternatives

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is part of the body's sleep-wake cycle. Specifically, it is associated with the control of circadian rhythms and the synchronisation of the body to the light-dark cycle. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks between 2 a.m. and 4 a.m., and diminishes during the second half of the night^[10].

Condition

Sleep disorders may affect 20–30% of children aged 1 to 5 years and can often persist in later childhood. Disorders include problems getting to sleep (dyssomnias) or undesirable phenomena during sleep (parasomnias), such as sleep terrors and sleepwalking. Children with neurodevelopmental or psychiatric comorbidities are at greater risk of sleep disorders^{[11],[12]}.

ADHD is characterised by inattention, hyperactivity/impulsivity, or both and is 1 of the most common psychiatric disorders of childhood^[13].

The reported prevalence of sleep problems in children with ADHD varies. It has been estimated that approximately 50–60% of children with ADHD experience sleep problems^[11], and that approximately one-third of children who are not taking any medication (including stimulants) for their ADHD experience chronic sleep onset insomnia^[13].

Alternative treatment options

First-line treatments for children with sleep problems and ADHD include ensuring good sleep hygiene and behavioural therapy^[11]. It has been suggested that in some patients sleep disturbances may be related to pre-existing ADHD symptoms that could respond to dose adjustment or switching to a stimulant agent associated with fewer sleep difficulties^[11].

^[10] Flynn Pharma Ltd (2012) [Circadin summary of product characteristics](#)

^[11] Bendz LM, Scates AC (2010) [Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder](#). *Annals of Pharmacotherapy* 44: 185–91

^[12] Bruni O, Novelli L (2010) Sleep disorders in children. *Clinical Evidence*

^[13] van der Heijden KB, Smits MG, Someren EJ et al. (2007) [Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41

Evidence review: efficacy

Evidence assessing the efficacy of unlicensed melatonin to treat sleep disorders in children with ADHD was identified from 2 small RCTs^{[14],[15]}, 1 small, long-term follow-up study^[16] and 1 non-systematic narrative review that reviewed these 3 studies^[17]. The RCTs used unlicensed melatonin formulations described as 'fast-release' and 'short-acting'.

A small RCT (n=42) examined prolonged-release melatonin in children with neurodevelopmental difficulties but this was excluded from this evidence summary because only a small minority of participants (7% of 42 children) also had ADHD^[18].

A recently published UK RCT that used unlicensed melatonin for 12 weeks to treat sleep disorders in 146 children with neurodevelopmental disorders was also identified^[19]. The efficacy data from this trial has not been included in this evidence summary because it did not focus on children with ADHD. However, safety data have been included.

Parallel randomised trial

The larger of these small RCTs (van der Heijden et al. 2007^[14]) recruited 107 non-stimulant treated children aged 6 to 12 years in the Netherlands diagnosed (by a psychologist and a psychiatrist) with ADHD and sleep onset insomnia. Children were excluded if they had previously been on melatonin, or had taken neuroleptics, benzodiazepines, clonidine, antidepressants, hypnotics or beta-blockers within 4 weeks of enrolment. Other exclusion criteria included pervasive developmental disorders, epilepsy or an IQ of less than 80. Participants were randomised to receive either unlicensed melatonin tablets (n=54) or placebo (n=53) for 4 weeks. Two participants, 1 from each group, withdrew from the study before treatment had started. Dosage was 3 mg daily when body weight

was less than 40 kg (n=44), or 6 mg daily when body weight was greater than 40 kg (n=9). The average age of children given melatonin was 9 years; 66% of them were male. 'Fast-release' melatonin tablets were used and administered at 7 p.m. each night. Children were allowed to go to bed whenever they felt tired.

Primary sleep outcomes included actigraphy-derived sleep onset, actigraphy-derived total time asleep, and difficulty falling asleep reported by parents (averaged over 7 days on a scale of 1 [not difficult] to 5 [very difficult]). Other outcomes included salivary dim light melatonin onset (DLMO), sleep latency, problem behaviour, cognitive performance and quality of life. DLMO is the time at which there is a rise in endogenous melatonin secretion in dim light settings, which is related to sleep onset. Sleep latency is the time from lights out until sleep onset.

At 4 weeks, the melatonin group showed statistically significant improvements in sleep onset, total time asleep, parent-reported difficulty falling asleep and DLMO compared with the placebo group.

Sleep onset advanced by a mean of 26.9 ± 47.8 minutes with melatonin compared with a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$). Total time asleep increased with melatonin ($+19.8 \pm 61.9$ minutes) compared with a decrease with placebo (-13.6 ± 50.6 minutes, $p = 0.01$). The mean score on parent-reported difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < 0.0001$). There was an advance in DLMO of 44.4 ± 67.9 minutes in those given melatonin and a delay of 12.8 ± 60.0 minutes for those given placebo ($p < 0.0001$). Sleep latency improved by 21.3 ± 33.0 minutes with melatonin compared with a worsening of 3.0 ± 31.7 minutes with placebo ($p = 0.001$).

There was no significant effect on behaviour, cognition and quality of life^[14]. At the end of the trial period, all participants were offered melatonin treatment in the context of regular care by specialised physicians^[16].

Long-term follow-up

The long-term follow-up study (Hoebert et al. 2009^[16]) obtained data on 94 of the 105 (89.5%) participants who received unlicensed melatonin or placebo during the study by van der Heijden et al. (2007)^[14]. The mean follow-up time was 3.7 years. Mean age at the start of melatonin treatment was 8.7 years and 12.4 years at follow-up. After the RCT by van der Heijden et al. (2007), all children were offered melatonin, breaking the randomisation. At follow-up, 61 (64.9%) children used melatonin daily, 11 (11.7%) used it occasionally (in most cases only using melatonin when they could not sleep), and 22 (23.4%) were not using melatonin. Parental satisfaction with melatonin

was high with 87.8% of parents expressing the opinion that "melatonin is an effective therapy for the sleep onset problems of my child", 70.8% that "melatonin improved daytime behaviour of my child" and 60.9% that "melatonin improved the mood of my child". During the treatment period, 67 children (71.3%) temporarily discontinued melatonin. The effect of this in most of the cases (92.3%) was a delay in sleep onset time.

Crossover randomised trial

The smaller of the RCTs (Weiss et al. 2006^[15]) recruited 33 children aged 6 to 14 years with initial insomnia and ADHD in Canada. Initial insomnia was defined as an average sleep onset latency of more than 60 minutes during a 10 night period. Sleep onset latency was defined as the amount of time between when the child was put to bed and when they fell asleep. Before randomisation, all children received a 10-day sleep hygiene intervention. If the intervention did not work, the child progressed to the randomised crossover trial. In this trial, 22 participants were randomised to receive unlicensed melatonin treatment or placebo for a 10-day period followed by a 5-day washout period before crossing over to the other treatment arm for 10 days. 'Short-acting' pharmaceutical grade melatonin (5 mg) was used and administered 20 minutes before bedtime. This study also required the child to have been taking stimulant medication (for example, methylphenidate) for at least 2 months before the trial and to continue doing so throughout the trial duration. The primary outcome was mean sleep onset latency measured by parent-completed somnolog. Sleep onset latency measured by actigraphy was 1 of the secondary endpoints and was used to provide an objective measure of sleep.

Three participants had protocol violations and were excluded. A total of 19 children were available for final analysis, of which 91% were male with an average age of 10 years (range 6.5–14.7 years). Mean parent-completed somnolog sleep onset latency was statistically significantly shorter for children receiving melatonin (46.4±26.4 minutes) compared with children receiving placebo (62.1±26.6 minutes, $p<0.01$); giving an absolute difference of 15.7 minutes and an effect size of 0.6. Sleep onset latency measured by actigraphy was also shorter by 16 minutes with melatonin than with placebo ($p<0.01$).

When measured by somnolog, melatonin increased total time asleep by a mean of 15 minutes compared with placebo ($p<0.01$). However, no significant difference was found when this was measured by actigraphy (no p value reported). There was no significant change in ADHD symptoms (assessed by Conners Attention Deficit Scale, Parent version) between baseline and completion of the study in those receiving melatonin or placebo.

Seventeen children reported as having received 'substantial benefit' (undefined in the study) from melatonin continued into an open-label follow-up for 90 days. Mean sleep onset latency at the end of the open-label follow-up was 31 minutes. This was lower than, but not significantly different from, the end of the crossover trial. By contrast, sleep duration continued to improve by 23 minutes ($p < 0.01$) during the 90-day period after the crossover trial^[15].

^[14] van der Heijden KB, Smits MG, Someren EJ et al. (2007) [Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41

^[15] Weiss MD, Wasdell MB, Bomben MM et al. (2006) [Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 45: 512–9

^[16] Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research* 47: 1–7

^[17] Bendz LM, Scates AC (2010) [Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder](#). *Annals of Pharmacotherapy* 44: 185–91

^[18] Jan JE, Hamilton D, Seward N et al. (2000) Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *Journal of Pineal Research* 29: 34–9

^[19] Gringras P, Gamble C, Jones AP et al. (2012) [Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial](#). *BMJ* 345: e6664

Evidence review: safety

The larger of the RCTs in 105 children (van der Heijden et al. 2007^[20]) reported no statistically significant differences between the number of adverse events in the unlicensed melatonin and placebo groups, and for the different doses of melatonin given (3 mg and 6 mg). No adverse events were reported in the placebo group compared with 16 events in the melatonin group reported about 10 children. The most common adverse events reported in the melatonin group were headache (3 children, 5.7%), hyperactivity (3 children, 5.7%), dizziness (2 children, 3.8%) and abdominal pain (2 children, 3.8%). No adverse events caused withdrawal from the study and none needed further treatment.

Approximately 20% of the 94 children in the long-term follow-up study (Hoebert et al. 2009^[21]) experienced adverse events which they or their parents attributed to melatonin. Mean follow-up time was 3.7 years and mean treatment time was 18 months (range of 1–57 months). No serious adverse events were reported or treatment-related comorbidities. The most common adverse events reported were dizziness (4 children, 4.3%), sleep maintenance insomnia (3 children, 3.2%) and bedwetting (3 children, 3.2%). Of the 94 children, 3 (3%) discontinued melatonin because of adverse events: 1 experienced profuse perspiration; 1 persistent dizziness, visual disturbances, headache and daytime laziness; and 1 headache, abdominal pain, nausea and excessive morning sedation. These adverse events resolved spontaneously after melatonin was stopped.

The small Canadian study (19 children evaluated) by Weiss et al. (2006)^[22] found that 20% of all adverse events were reported during melatonin treatment and 23% during placebo treatment. All adverse events were mild or moderate except 1 case of migraine, which was rated as severe.

Overall, the unlicensed melatonin used in these studies (3–6 mg daily) appeared to be well tolerated with only temporary mild to moderate adverse effects reported in the short (up to 4 weeks treatment) and medium term (mean treatment 18 months). No severe adverse effects were attributable to treatment^{[19],[20],[21]}. The safety of long-term melatonin use in children with ADHD is unclear.

In an RCT carried out in the UK (Gringras et al. 2012^[23]), 146 children aged from 3 years to 15 years 8 months with neurodevelopmental delay and other conditions (epilepsy or autistic spectrum disorder, or both) were randomised to receive treatment with unlicensed melatonin or placebo for 12 weeks. No children were reported as having ADHD but comprehensive safety data are available. More headaches were recorded as adverse events (14.3% on melatonin compared with 9.2% on placebo) than those recorded in the ADHD trials. The most common adverse events in the melatonin group were: coughing (31.4%), mood swings (22.9%), vomiting (21.4%) and increased excitability (18.6%), which were reported in similar frequencies in the placebo group (no statistical test was undertaken). A weekly seizure diary was completed for children with a pre-existing diagnosis of epilepsy. This showed no deterioration in frequency or severity of seizures. No child without epilepsy developed seizures or had a new diagnosis of epilepsy. Of the 7 serious adverse events, 2 (1 in the melatonin group and 1 in the placebo group; not described) were considered related to the study drug.

The British National Formulary for children (BNFC) states that unlicensed melatonin preparations are available. It indicates that the manufacturer of such products should be specified and recorded as part of the care of the patient because of variability in clinical effect of unlicensed formulations^[24].

In a UK survey of 148 paediatricians, 27 (18%) reported observing adverse events associated with melatonin treatment^[25]. These were new onset of seizure activity (n=2), increased seizure frequency (n=3), hyperactivity (n=5), agitation or behaviour changes (n=6), worsening sleep pattern (n=6), nightmares (n=2) and constipation (n=2).

^[20] van der Heijden KB, Smits MG, Someren EJ et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 46: 233-41

^[21] Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. Journal of Pineal Research 47: 1-7

^[22] Weiss MD, Wasdell MB, Bomben MM et al. (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 45: 512-9

^[23] Gringras P, Gamble C, Jones AP et al. (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. BMJ 345: e6664

^[24] British national formulary for children (2012)

^[25] Waldron DL, Bramble D, Gringras P (2005) Melatonin: prescribing practices and adverse events. Archives of Disease in Childhood 90: 1206-7

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies were identified.

Cost

No standard UK cost data were identified for the unlicensed melatonin products used in the RCTs.

Prescription Cost Analysis in England shows that, over the last year (July 2011 to June 2012) in general practice, licensed prolonged-release melatonin accounted for around 44% of total melatonin prescribed items (for all indications) and around 16% of the cost (£2,850,038), whereas unlicensed melatonin accounted for around 56% of all prescribed items and around 84% of the cost (£17,295,385)^[26]. In addition, in terms of both spending and prescribing volume, unlicensed special order melatonin products are listed among the top 5 of all special order products prescribed in the last quarter (July to September 2012)^[27].

In addition, the BNFC provides dose information for using oral melatonin in children with sleep onset insomnia and delayed sleep phase syndrome. It states that children (1 month to 18 years old) should start off at a dose of 2–3 mg daily before bedtime and increase, if necessary, after 1–2 weeks to 4–6 mg daily, up to a maximum of 10 mg daily^[28]. This is broadly in line with the small RCTs in children with ADHD which used doses of between 3 mg and 6 mg daily^{[29], [30]}.

The cost of a 30 tablet pack of 2 mg licensed prolonged-release melatonin is £15.39 (excluding VAT; costs taken from MIMS, December 2012). A low-end monthly cost estimate would therefore be £15.39 (2 mg daily for 30 days) compared with a high-end monthly cost of £76.95 (10 mg daily for 30 days), based on the regimens described in the BNFC.

The BNFC notes that other formulations of melatonin (other than Circadin) are available from special-order manufacturers or specialist importing companies. It states that there is possible variability in clinical effect of these unlicensed formulations.

Current drug usage

An anonymous survey of 148 paediatricians in Britain (published in 2005) indicated that 98% were currently prescribing or had prescribed melatonin in the previous year^[31]. The survey had a low response rate of approximately 15%. Data were obtained on 1918 children. Autism (68%) and ADHD (44%) were the most frequently reported diagnoses associated with melatonin prescription. Other less common diagnoses included learning difficulties (40%), visual impairment (13%) and specific sleep disorders (5%).

The most common formulations of melatonin reportedly prescribed at the time of the survey (around 2005) were 'immediate-release' preparations (68.5%). 'Slow-release' prescriptions were less common (2.3%), although a significant proportion of paediatricians described prescribing both formulations (29.2%). The dose prescribed varied widely (from 0.5 mg to 24 mg)^[30]. Importantly, this survey was undertaken before prolonged-release melatonin was licensed in the UK (2007). Figures from July 2011 to June 2012 show that, in general practice in England, licensed prolonged-release

melatonin accounted for around 44% of total prescription items, with unlicensed melatonin accounting for the remaining 56%^[25].

^[26] Personal communication. NHS Business Services Authority (November 2012)

^[27] NHS Business Services Authority. (2012) Volume and cost of special order products

^[28] British national formulary for children (2012)

^[29] van der Heijden KB, Smits MG, Someren EJ et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 46: 233–41

^[30] Weiss MD, Wasdell MB, Bomben MM et al. (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 45: 512–9

^[31] Waldron DL, Bramble D, Gringras P (2005) Melatonin: prescribing practices and adverse events. Archives of Disease in Childhood 90: 1206–7

Evidence strengths and limitations

Strengths

Strengths of the larger study (van der Heijden et al. 2007^[32]) included the objective and subjective outcome measures, allocation concealment and a 2-year safety follow-up. Safety data were further strengthened by the 3-year follow-up study by Hoebert et al. (2009)^[33].

The small study (Weiss et al. 2006^[34]) provided unique information on the efficacy of melatonin in children with ADHD receiving stimulant drugs and in whom sleep hygiene intervention was ineffective. The crossover study design also limited the effects of between child variability in sleep patterns.

Limitations

Interpretation of the evidence is limited by the fact that the 2 RCTs had relatively few participants^{[31],[33]}, especially the smallest study (only 19 children evaluated)^[33]. In addition, neither of them were carried out in the UK.

In the larger RCT (van der Heijden et al. 2007^[31]), high levels of missing data limited the analysis, including 24% of data missing for the primary outcome actigraphy-derived sleep onset. The generalisability of this study was limited by the exclusion of children using stimulant drugs for their ADHD and the diagnosis of insomnia was based on Dutch criteria, which may not be applicable in other countries. Also, children that were excluded included those with an IQ less than 80, a pervasive development disorder or epilepsy, as well as those receiving certain other medications. There are, therefore, questions about the generalisability of this study's findings to a wider population of children with ADHD. Additionally, this study may have been too small to detect anything but large differences in adverse events between the treatment and placebo groups. Furthermore, it is not known whether children had previously tried sleep hygiene methods before entry into the trial, which would more accurately reflect the population of children with ADHD who might be given melatonin in practice.

Limitations of the follow-up study (Hoebert et al. 2009^[32]) included using a subjective measure of efficacy (based on the opinion of parents) and reporting of adverse events, which may have been confounded by recall bias. There was also no untreated control group for this follow-up study.

The smallest study (Weiss et al. 2006^[33]) was particularly limited by its very small sample size, its sample characteristics (91% male), and a relatively short-term assessment of insomnia for inclusion in the study (based on somnologs over 10 nights). This study was sponsored by Circa Dia B.V. which manufactures melatonin tablets. The role of sponsor in the RCT was not clearly reported. In addition, parents evaluated sleep by checking on their children every 15 minutes. It is possible that this in itself could have affected sleep onset reported in the trial. Also, it was not reported whether or not allocation was concealed.

When considering the limited evidence available from these small RCTs, it is important to note that any reported benefits of melatonin on sleep in children with ADHD have not been associated with improvements in ADHD symptoms, behaviour, cognition or quality of life^{[31],[33]}.

^[32] van der Heijden KB, Smits MG, Someren EJ et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41

[33] Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research* 47: 1-7

[34] Weiss MD, Wasdell MB, Bomben MM et al. (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *Journal of the American Academy of Child and Adolescent Psychiatry* 45: 512-9

Summary for patients

A summary written for patients is available on the NICE website.

References

Bendz LM, Scates AC (2010) Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Annals of Pharmacotherapy* 44: 185-91

British national formulary for children [online; accessed 20 November 2012]

Bruni O, Novelli L (2010) Sleep disorders in children. *Clinical Evidence* (Online)

Burrill P (2009) Prescribing and clinical effectiveness newsletter. Derby: Derbyshire County PCT [online; accessed 19 November 2012]

Flynn Pharma Ltd (2012) Circadin summary of product characteristics [online; accessed 20 November 2012]

Gringras P, Gamble C, Jones AP et al. (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 345: e6664

Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research* 47: 1-7

Jan JE, Hamilton D, Seward N et al. (2000) Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. *Journal of Pineal Research* 29: 34-9

MHRA (2012) [Importing unlicensed medicines](#) [online; accessed 19 November 2012]

NHS Choices (2012) [Insomnia - Treatment](#) [online; accessed 20 November 2012]

NHS Business Services Authority. (2012) [Volume and cost of special order products](#)

Personal Communication. NHS Business Services Authority (November 2012)

Tjon Pian Gi CV, Broeren JP, Starreveld JS et al. (2003) Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. *European Journal of Pediatrics* 162: 554–5

van der Heijden KB, Smits MG, Someren EJ et al. (2007) [Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41

Waldron D, Bramble D, Gringas P (2005) Melatonin: prescribing practices and adverse events. *Archives of Disease in Childhood* 90: 1206–7

Weiss MD, Wasdell MB, Bomben MM et al. (2006) [Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia](#). *Journal of the American Academy of Child and Adolescent Psychiatry* 45: 512–9

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [interim process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

The sources are:

1. [NHS Evidence](#) (including guidelines)
2. [NICE](#)
3. Broad internet search: [Google](#), for example, melatonin child* OR pediatric OR paediatric OR infant OR newborn OR neonat* OR adolescen* "guideline" -"annual -report" filetype:pdf

Medline & Embase (via Ovid)

1. exp review/ (1746567)
2. (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or pubmed or medline).ti,ab,sh. (68617)
3. ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6081)
4. ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (13323)
5. (pooling or pooled or mantel haenszel).ti,ab,sh. (44999)
6. (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2598)
7. or/2-6 (118425)
8. 1 and 7 (53235)

9. Meta Analysis/ (36882)
10. (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (64847)
11. ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (51214)
12. (integrative research review\$ or research integration).ti,ab,sh. (83)
13. or/9-12 (100398)
14. 8 or 13 (127821)
15. clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (236757)
16. (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (862629)
17. 15 or 16 (957894)
18. (animal\$ not human\$).sh. (3703261)
19. 17 not 18 (854555)
20. 19 and 14 (47702)
21. *Melatonin/ (10961)
22. (Melatonin\$ or circadin or MEL or MLT or N-acetyl-5-methoxytryptamine or Pineal Hormone or Mela-T or Melatol or Melatonex or Melovine or MT6 or Nature's Harmony or Night Rest or Vivitas or Revital Melatonin or Rx Balance or Sleep Right).tw. (20059)
23. 73-31-4.rn. (14308)
24. or/21-23 (21479)
25. (pediatric\$ or paediatric\$ or child\$ or adolescen\$ or teenager\$).tw. (1082669)
26. exp Child/ (1464136)
27. Adolescent/ (1506532)
28. exp Infant/ (889269)

29. (infant? or newborn or neonate?).tw. (353228)
30. or/25-29 (2984777)
31. exp *Sleep Disorders/ (43294)
32. (sleep\$ adj2 disorder?).tw. (8525)
33. (insomnia? or night terror? or dyssomnia? or parasomnia?).tw. (11338)
34. or/31-33 (51160)
35. 24 and 30 and 34 (326)
36. limit 35 to english language (297)
37. 14 and 36 (16)
38. 19 and 36 (83)
39. (economic? or cost?).tw. (364466)
40. 36 and 39 (2)

CRD HTA, DARE and EED database

(child*) AND (melatonin or circadin):TI AND (sleep)

Cochrane CENTRAL

#1 sleep:ti,ab,kw (11489)

#2 MeSH descriptor:[Melatonin] this term only (621)

#3 melatonin or circadin:ti,ab,kw (916)

#4 child* or adolescen* or pediatric* or paediatric* or infant:ti,ab,kw (137454)

#5 #2 or #3 (916)

#6 #4 or #5 (160)

#7 #1 or #6 (108)

Euroscan

Melatonin

Grey literature and ongoing trials

1. [FDA](#)
2. [EMA](#)
3. [MHRA](#)
4. [Scottish Medicines Consortium](#)
5. [All Wales Medicine Strategy Group](#)
6. ~~Manufacturers' websites as applicable~~
8. [ClinicalTrials.gov](#)

Manufacturers' websites

[Circadin](#)

[Flynn Pharma Ltd](#)

Evidence selection

Studies were included based on predetermined criteria for relevance to the question set at scoping. The highest quality research was selected as the basis for answering the questions set on efficacy, safety and cost. Two RCTs (van der Heijden et al. 2007^[35] and Weiss et al. 2006^[36]) and a long-term follow-up of participants in the van der Heijden et al. (2007) RCT (Hoebert et al. 2009^[37]) provided the core evidence for this evidence summary. Preliminary open-label safety studies such as Tjon Pian Gi et al. (2003)^[38] were excluded because of their open-label design and the presence of more robust evidence identified above.

A study by Gringas et al. (2012)^[39] was excluded from the efficacy review but included in the safety section as it did not focus on children with ADHD. Jan et al. (2000)^[40] was excluded as it contained too few children with ADHD.

^[35] van der Heijden KB, Smits MG, Someren EJ et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 46: 233–41

^[36] Weiss MD, Wasdell MB, Bomben MM et al. (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. Journal of the American Academy of Child and Adolescent Psychiatry 45: 512–9

^[37] Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. Journal of Pineal Research 47: 1–7

^[38] Tjon Pian Gi CV, Broeren JP, Starreveld JS et al. (2003) Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. European Journal of Pediatrics 162: 554–5

^[39] Gringras P, Gamble C, Jones AP et al. (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. BMJ: 345: e6664

^[40] Jan JE, Hamilton D, Seward N et al. (2000) Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. Journal of Pineal Research 29: 34–9

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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