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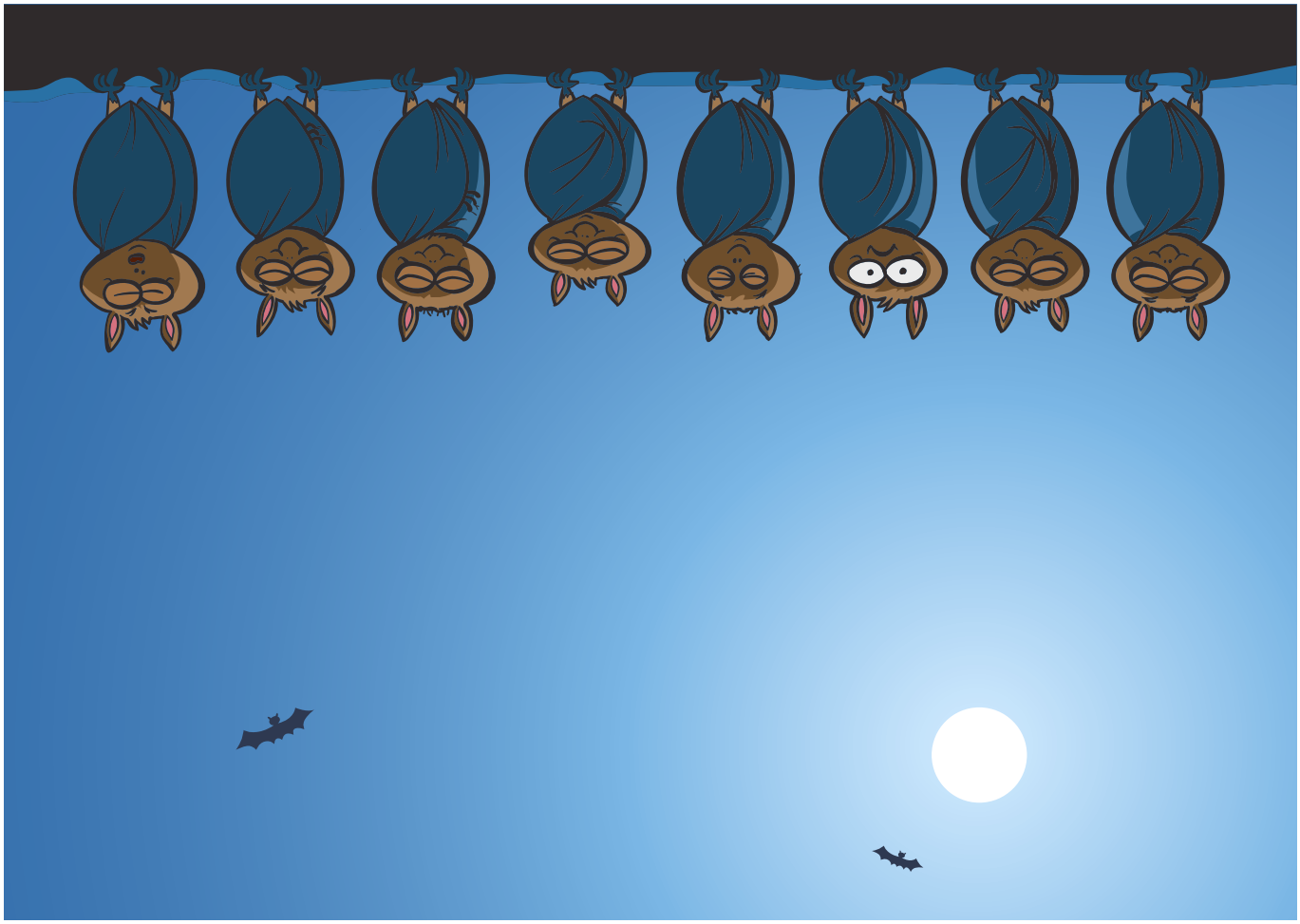

abstract

Objective: To develop a synthesis of the evidence on the efficacy and safety of melatonin use in the management of sleep disorders in children and adults. **Methods:** We carried out an analysis of systematic reviews of clinical trials, evidence-based clinical practice guidelines, and of more-recently published randomised controlled trials. Bibliographical research was carried out through Pubmed and Trip database (last update 14/1/2014). **Results and conclusions:** Melatonin is marketed both as a drug and a dietary supplement. Its indication as a drug is for insomnia in patients over 55. Trials indicate efficacy of questionable clinical relevance (sleep latency is reduced by 8 minutes). There is no evidence that melatonin is effective in reducing sleep latency in adults with circadian rhythm disorders. Evidence of efficacy is scarce and inconsistent with regard to use in children with delayed sleep disorders or attention deficit and hyperactive disorder. In children with disorders affecting neurological development, modest efficacy has been observed. It is not clear what the most appropriate dose is.

Melatonin for sleep disorders

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Introduction

Melatonin is a hormone produced in the pineal gland. At nightfall, neuronal signals connecting the retina and the central nervous system with the gland produce a release of norepinephrine that triggers the transformation of serotonin into melatonin, which is then released into blood and spinal fluid. Being liposoluble, it easily travels across the blood brain barrier. Most circulating melatonin is metabolized in the liver via P450 cytochrome enzymes and it is eliminated through urine as inactive metabolites.

In humans, melatonin receptors have been identified in the membrane and cell nucleus of many tissues and systems where it exercises diverse actions, including the regulation of circadian rhythms.[1,2] The rhythmic pattern of melatonin secretion is important because it provides important information to the organism regarding time, which allows for adjustments of some physiological functions according to daily and seasonal variations.[3] Other physiological functions of melatonin are not well known.[4] It reduces the levels of sexual hormones (GnRH, LH, FSH),[2] and thus it has been suggested that melatonin can alter the onset of puberty.[5]

The aim of this article is to provide a synthesis of the evidence on the efficacy and safety of melatonin for the management of sleep disorders in adults and children. Selected studies include those that evaluate the efficacy of melatonin at well defined doses in adults and children with primary insomnia or insomnia associated with other problems. Accepted comparators were placebo, no treatment, non-pharmacological therapies and hypnotics. Results on time to sleep onset, sleep duration and quality of sleep are discussed.

Information sources included systematic reviews of clinical trials, evidence based clinical practice guidelines, and also randomised clinical trials published after the systematic reviews and guidelines. Bibliographical research was carried out through Pubmed and Trip database (last update 14 January 2014).

Rather odd regulation of marketing

Although generally the use of hormones requires a medical prescription, the regulation of melatonin is unusual and quite diverse. In the USA it is considered a dietary supplement. In Australia it is regarded as a prescription-only medicine. In Europe it is commercialised both as a prescription medicine and as a dietary supplement to reduce sleep onset latency. A review by the European Food Safety Authority (EFSA) concluded that 1 mg of melatonin should be consumed at bedtime to obtain the desired effect.[6] There are also 1.95 mg tablets available on the market.

On the other hand, as a medication there is a prolonged-release melatonin 2 mg formulation (Circadin®), with the approved indication, as monotherapy, of management of primary insomnia in cases of poor quality sleep in patients over 55.[7] A medical prescription is required. It is not reimbursed by Spain's National Health Service.

Sleep disorders

In a simple manner sleep disorders can be classified as **primary insomnia** or **secondary insomnia**. The latter can also be classified into *circadian rhythm disorder*, (which includes *delayed sleep,* jet lag type, and that originating from shift work disorder), or insomnia due to organic disease, mental disorder, or substance-induced.[8]

Melatonin has been studied in all of these types of sleep disorders in both adults and children.

The most frequently used outcome in clinical trials is *sleep latency* or time from which the patient tries to sleep up to the point when she actually falls asleep. This can be subjective, measured by registration in the patients sleep diary, or objective, measured through polysomnography or actigraphy. In addition, total sleep time and sleep quality are also measured through questionnaires.

Primary insomnia

The Clinical Practice Guidelines of Spain´s National Health Service on the management of patients with insomnia in primary care conclude that there is insufficient evidence to recommend the use of melatonin in either the management of insomnia or for withdrawal from long-term benzodiazepine use. However these conclusions are based on systematic reviews that did not include the more recent clinical trials that are currently available.[8]

Efficacy evidence for the marketed drug

The European Public Evaluation Report (EPAR) released by the EMA on prolonged-release melatonin 2 mg includes two main randomized double-blind, placebo-

controlled clinical trials (Neurim VII and IX) and a preliminary study. Included patients were over 55 years old, and diagnosed with primary insomnia. Patients with depression, anxiety or dementia and those taking benzodiazepines or antipsychotics were excluded. There was a run-in single-blind phase with placebo, after which those patients who responded to placebo were excluded. Treatment duration was 3 weeks.

Another trial (Neurim VIII) was prematurely discontinued due to problems with patient inclusion, as an inspection detected that 35% of those included did not really suffer from primary insomnia. Data from this trial were only used for the safety analysis.

The EPAR includes a meta-analysis of the two main trials and one preliminary study that measured the endpoint *response of clinical relevance in relation to sleep quality and day time awakeness*, defined as improvements of at least 10 mm in the QOS and BFW scales from the Leeds Sleep Evaluation Questionnaire (LSEQ) (table 1). As the previous exclusion of patients who responded to placebo could have introduced biases, an analysis was made including patients excluded in the run-in phase and for whom data were available (table 1).[3]

A more recent double-blind trial included patients with primary insomnia between 18 and 80 years of age. There was a run-in phase lasting 2 weeks on placebo, after which 791 patients were randomised to receive prolonged-release melatonin 2 mg or placebo for three weeks. The primary endpoint was *change in sleep latency* recorded in the patient's sleep diary. No significant differences were found in the overall population (difference melatonin – placebo: - 4 minutes [95% CI, -10 to 1 min]). In the subgroup of patients over 55 years of age there were statistically significant differences although of scarce clinical relevance (-8 min [-14 to -2 min]). An extension of the trial was carried out for 26 weeks in which patients on placebo were re-randomised to melatonin or placebo, whereas those patients on melatonin continued treatment. During the extension phase the differences in efficacy were maintained[9].

Drug, supplement... melatonin is a hormone

Meta-analysis of the clinical trials

A meta-analysis was carried out on the efficacy of melatonin *vs* placebo in the management of primary sleep disorders in adults and children. It included 19 trials with 1683 patients in total. The studies were very diverse with regard to age, doses used and design. This meta-analysis included studies on primary insomnia, delayed sleep disorder and one trial on REM behaviour disorder (table 2). There was no evaluation of the risk of bias in the studies. Melatonin was effective in reducing sleep latency *vs* placebo by 7 minutes (-4 to -10 min), increasing sleep duration by 8 minutes (2 to 15 min) and improving sleep quality (figures 1 to 3). No evidence of publication bias was found. These findings are of limited clinical relevance[10].

A small study did not find a difference between melatonin and placebo as supportive therapy for benzodiazepine withdrawal.[11]

Table 1. Meta-analysis carried out by the EMA published in the EPAR.[3]

	Placebo	Melatonin	Difference (95%CI)	NNTB* (95%CI)
Response of clinical significance				
N	322	308		
% Responders	18%	29%	11% (4% to 18%)	10 (6 to 24)
Sleep latency				
N	165	169		
Sleep latency	-12.9 min	-24.3 min	-8,8 min (-16.7 to -1.0)	

*NNTB: number needed to treat to obtain an additional response

Table 2. Trials included in the meta-analysis by Ferracioli-Oda.[10]

Author / year	n / design	Population	Condition	Daily dose	Duration
Wade AG 2011	746/parallel	Adults	PI	2 mg	21 d / 182 d
Kunz D 2010	8/crossover	Adults	REM-SBD	3 mg	28 d
Luthringer R 2009	40/parallel	Adults	PI	2 mg	56 d
Garzón C 2009	22/crossover	Adults	PI	5 mg	126 d
Lemoine P 2007 (Neurim VII)	170/parallel	Adults	PI	2 mg	21 d
Wade AG 2007 (Neurim IX)	354/parallel	Adults	PI	2 mg	21 d
Mundey K 2005	13/parallel	Adults	DS	0.3 mg or 3 mg	28 d
Almeida Montes LG 2002	10/crossover	Adults	PI	0.3 mg, 1 mg	21 d
Kayumov L 2001	22/crossover	Adults	DS	5 mg	28 d
Zhdanova IV 2001	30/crossover	Adults	PI	0.1 mg, 0.3 mg, 1 mg	28 d
Dawson D 1998	12/crossover	Adults	PI	0.5 mg	8 d
Nagtegaal JE 1998	25/crossover	Adults	DS	5 mg	28 d
Ellis CM 1996	15/crossover	Adults	PI	5 mg	7 d
Haimov I 1995	26/parallel	Adults	PI	2 mg	7 d
Dahlitz M 1991	8/crossover	Adults	DS	5 mg	28 d
James SP 1989	10/crossover	Adults	PI	1 mg, 5 mg	14 d
Van Geijlswijk IM 2010	70/parallel	Children	DS	0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg	7 d
Smits MG 2003	62/parallel	Children	DS	5 mg	28 d
Smits MG 2001	40/parallel	Children	DS	5 mg	28 d

PI: primary insomnia. DS: Delayed sleep phase syndrome. REM-SBD: REM sleep behaviour disorder.

Insomnia due to delayed sleep phase syndrome

A systematic review included trials on patients with delayed sleep disorders in which melatonin was administered according to the circadian clock (table 3). In adults, melatonin led to earlier sleep, although no statistically significant differences in sleep latency or total sleep time were found (table 4).[12]

Disorders affecting circadian rhythm: jet lag and shift work disorder

The regulating action of melatonin on the biological clock raised great interest concerning its possible usefulness for disorders of the circadian rhythm produced by time maladjustment.

A Cochrane systematic review (Herxheimer 2009) evaluated the effectiveness of melatonin to alleviate jet lag after airplane trips through various time zones. The results measured were subjective score of time maladjustment or related components such as wellbeing, tiredness during the day, onset and quality of sleep, psychological performance, duration to return to normal or indicators of circadian rhythms. It includes 10 clinical trials with a total of 954 patients, although only 4 trials provided information on the primary endpoint (table 5).

The results showed that melatonin, administered just before sleeping at the patient's destination (from 10 pm to midnight) reduced time maladjustment for flights that crossed over 5 or more time zones. Daily doses of melatonin between 0.5 mg to 5 mg were equally effective except that people went to sleep faster and slept better on a 5 mg daily dose. Doses of more than 5 mg daily did not prove more effective. The lower effectiveness of prolonged-release melatonin 2 mg daily suggests that the higher peak of melatonin works better.[13]

Another systematic review (Buscemi 2006), evaluated the efficacy of melatonin on sleep restriction disorders such as those produced by jet lag or shift work disorder. The primary endpoint was sleep latency. Melatonin did not differ from placebo (table 5). Nor were there differences in the efficiency or quality of sleep. Total sleep time was greater with melatonin by 18 minutes (8 to 28 min). Nor were there differences in adverse effects

Table 3. Studies in adults with delayed sleep phase disorder.[12]

Author /year	n / design	Daily dose	Duration
Dahlitz 1991	8/crossover	5 mg	28 d
Laurant 1997	25/crossover	5 mg	14 d
Nagtegaal 1998	25/crossover	5 mg	14 d
Kayumov 2001	22/crossover	5 mg	28 d
Mundey 2005	11/parallel	0.3/3 mg	28 d

Table 4. Melatonin efficacy on delayed sleep phase disorder in adults.[12]

Primary endpoint	No studies / patients	Melatonin *vs* placebo
Sleep latency	4/111	-30 min (-63 to 3)
Time to sleep	5/111	-42 min (-62 to -22)
Total sleep time	3/67	1 min (-34 to 35)

Table 5. Clinical trials included in the systematic reviews on time maladjustment.[13-15]

Author /year	Condition	n /design	Daily dose	Duration
Beaumont* 2004	Jet lag	18/parallel	5 mg	5 d
Suhner* 1998	Jet lag	234/parallel	0.5 mg; 5 mg; 2 mg PR	4 d
Suhner* 2001	Jet lag	74/parallel	5 mg	4 d
Folkard* 1993	Shift work	7/crossover	5 mg	6 d
James* 1998	Shift work	22/crossover	6 mg	4-6 d
Jockovich* 2000	Shift work	19/crossover	1 mg	3 d
Jorgensen* 1998	Shift work	18/crossover	10 mg	Not fixed
Wright* 1998	Shift work	15/crossover	5 mg	3 d
Waldhause* 1990	Privation	20/parallel	80 mg	1 d
Arendt † 1988	Jet lag	59/crossover	5 mg	4 d
Claustrat† 1992	Jet lag	30/parallel	8 mg	3 d
Nickelsen† 1991	Jet lag	36/parallel	5 mg	5 d
Arendt† 1987	Jet lag	17/parallel	5 mg	4 d
Edwards 2000	Jet lag	31/parallel	5 mg	3 d
Nickelsen 1991	Jet lag	36/parallel	5 mg	5 d
Petrie 1989	Jet lag	20/crossover	5 mg	3 d
Petrie 1993	Jet lag	52/parallel	5 mg	5 d; 8 d
Spitzer 1997	Jet lag	257/parallel	5 mg; 0.5 mg	6 d
Sharkey 2001	Shift work	21/crossover	1.8 mg PR	2 d
Yoon 2002	Shift work	12/crossover	6 mg	2 d

* Provide data in the primary endpoint of Buscemi meta-analysis[14]. † Provide data in the primary endpoint of Herxheimer meta-analysis[13]. PR = Prolonged-release.

in comparison to placebo.[14] The most frequent dose used in the clinical trials was 5 mg daily.

How can the differences between the two reviews be explained? The reviews evaluated different endpoints: subjective evaluation of jet lag in Herxheimer´s review and sleep latency in the case of Buscemi (table 6). Nor were the same studies included in the reviews.

The *American Academy of Sleep Medicine* recommends the use of melatonin to help shift workers to sleep. This recommendation is judged to have moderate strength of evidence[16] despite the fact that in its review, the Academy admits that the evidence is discordant and the variety of management regimens and doses make it difficult to reach conclusions. In reality, the recommendations are based on theoretical reasons rather than the results (table 7).[15]

These guidelines strongly recommend melatonin use for jet lag.[16] This is based on the same studies included in the Hexheimer systematic review.

Insomnia secondary to other diseases

A systematic review did not find that melatonin had any effect on sleep latency in cases of insomnia originating from other problems (tables 8 and 9).[14] Later, a small trial in patients with schizophrenia did not show efficacy in reducing sleep latency.[17]

Sleep hygiene should always be a priority

The clinical efficacy of melatonin is questionable

The *American Academy of Sleep Medicine* concludes that melatonin is not indicated in elderly patients with dementia and irregular sleep-wake rhythms, as no studies have shown any efficacy.[16]

Effects of melatonin in children

The presumed benign profile of melatonin has raised interest in use in children despite the fact that safety evidence is limited.

Table 6. Efficacy of melatonin for time maladjustment.

Review	Condition	Primary endpoint	No trials/ patients	Melatonin *vs* placebo (95% CI)
Herxheimer[13]	Jet lag	Difference in jet lag score*	4/142	-19.5 (-28.1 to -10.9)
Buscemi[14]	Jet lag	Sleep latency	3/326	-4.7 min (-12.6 to 3.1)
	Shift work	Sleep latency	5/162	-0.8 min (-1.9 to 0.3)
	Overall	Sleep latency	9/508	-1.0 min (-2.3 to 0.3)

*Flights towards the East. On a 100-point scale.

Table 7. Trials on shift work disorder with sleep outcomes included in the review.[15]

Author /year	Result
Sharkey 2001	Only improved sleep on the first day and no improvement on night alertness.
Folkard 1993	Improved the quality and duration of self-evaluated sleep.
James 1998	No differences observed under placebo with regard to sleep or the alert state.
Jorgensen 1998	No differences observed under placebo with regard to sleep or the alert state.
Yoon 2002	Increase sleep duration

Table 8. Trials on secondary insomnia with sleep outcomes.[14,17]

Author/ year	Condition	n /design	Daily dose	Duration
Serfaty 2002	Dementia	25/crossover	6 mg PR	14 d
Serfaty 2003	Major depression	31/parallel	6 mg PR	14 d
Shamir 2000a	Shizophrenia	19/crossover	2 mg PR	21 d
Shamir 2000b	Shizophrenia	14/crossover	2 mg	21 d
Singer 2003	Alzheimer	151/parallel	2.5 mg PR; 10 mg	56 d
Suresh Kumar 2007	Shizophrenia	40/parallel	3 to 12 mg	15 d

PR: prolonged-release.

Table 9. Efficacy of melatonin in reducing sleep latency in secondary insomnia.

Condition	No trials/patients	Melatonin *vs* placebo (95%CI)
Depression[14]	1/31	-14 min (-33 to 6)
Shizophrenia[14]	2/66	-5 min (-30 to 21)
Overall[14]	**3/97**	**-7 min (-25 to 11)**
Schizophrenia[17]	1/40	-17 min (-55 to 21)*

*95%CI calculated for this article (see note).

Children with insomnia due to delayed sleep

Data from studies in children from the meta-analysis carried out by Ferracioli-Oda show a sleep latency reduction of 17 minutes (6 to 28 min) (table 10 and figure 4).

The review published by *Clinical Evidence* that includes two trials by Smits MG (102 children between 6-12 years of age), in which 5 mg daily doses were used, concluded that the evidence is very limited and that the differences in sleep latency are of questionable clinical relevance. Although no differences were found compared to placebo in reported adverse effects, hardly anything is known about long-term effects.[5]

The posology in children is not clear, as in the clinical trials the doses used were higher than the recommended ones in adults. Moreover, there are indications of receptor saturation at high doses.[5] It is surprising that the most recent trial in children is a dose-ranging study, whereas earlier trials used high doses without considering which dose might be most appropriate. Studies in children to establish the most appropriate dose should have been carried out first, to avoid exposing children to unnecessarily high doses.[18]

Children with Attention Deficit Hyperactivity Disorder (ADHD)

The UK Agency NICE has carried out a review on the use of melatonin for children with ADHD, an unapproved indication. The limited evidence included 2 small, short-term clinical trials (table 11) and one small study following up the patients from one of the trials over a 2-year period (n=94). The studies included children 6 to 14 years old. The larger study included only children not treated with stimulants; the other study only children on stimulants. Doses of fast-release melatonin of 3 to 6 mg/d were never tested in clinical trials in children.

Some children with neurological development disorders had shorter sleep latency, but the response should be evaluated

The evidence suggests that melatonin taken between 10 days and 4 weeks can reduce sleep onset latency in children with ADHD and insomnia at sleep onset by about 20 minutes. Moreover, melatonin can improve average

Table 10. Trials in children with delayed sleep.

Author /year	n /design	Age	Daily dose	Duration
Smits 2001	40/parallel	6-12 years	5 mg	28 d
Smits 2003	62/parallel	6-12 years	5 mg	28 d
Van Geijlswijk 2010	70/parallel	6-12 years	0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg	7 d

Figure 1. Efficacy of melatonin in reducing sleep latency in children with delayed sleep.

Study or Subgroup	Weight	Mean difference IV, Fixed, 95% CI
Smits MG 2001	24.8%	15.10 (-6.50 - 36.70)
Smits MG 2003	63.3%	14.00 (0.49 - 27.51)
Van Geijilswijk IM 2010	12.0%	36.33 (5.24 - 67.42)
Total (95% CI)	**100.0%**	**16.94 (6.19 - 27.69)**

Heterogeneity: $Chi^2 = 1.70$ / df = 2 (P = 0.43) / I2 = 0%
Test for overall effect: Z = 3.09 (P = 0.002)

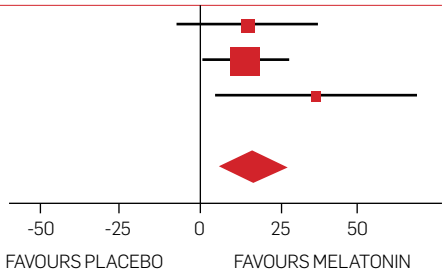

Table 11. Efficacy of melatonin in children with ADHD.

Study	Population	Dose	Duration	Sleep latency Melatonin *vs* placebo (95%CI)	Total sleep time Melatonin *vs* placebo (95%CI)
Weiss 2006	Treated with stimulants (n=19)	5 mg	10 d	-16 min (-33 to 1)	
Van der Heijden 2007	Not treated with stimulants (n=105)	3/6 mg	28 d	-24 min (-37 to -12)	33 min (12 to 55)

sleep duration by 15 to 20 minutes. In none of the studies were there differences in ADHD symptoms. These small studies have limitations and it remains unclear whether melatonin's efficacy continues in the long term.[19]

Children with neurological development disorders

Autism spectrum disorder

A systematic review including five clinical trials with daily doses between 1 and 10 mg found statistically significant differences compared to placebo in the reduction of sleep latency (39 min [31 to 47 min]), duration of sleep (44 min [20 a 68 min]), but no difference in the number of night awakenings, in children with autism spectrum disorders. These studies had limitations, including the small size, and differences in design.[20] In another clinical trial including 134 patients with a follow-up of 12 weeks, controlled-release melatonin 3 mg was used alone or in combination with behavioural cognitive therapy and showed a positive effect on *sleep latency, total sleep time and night time awakenings*[21] (table 12).

General neurological development disorders

A meta-analysis on individuals with intellectual disability, the majority children, found that melatonin reduced sleep latency by 34 minutes (25 to 43 min) compared to placebo, increased sleep duration by 50 minutes (34 to 65 min) with no statistically significant differences in night time awakening.[22]

A clinical trial was published on children with neurological development disorders, commissioned by the *UK National Institute of Health Research.* Melatonin at daily doses between 0.5 mg and 12 mg was used for 12 weeks. The minimum differences for clinical relevance were specified: 1 hour in total sleep time and 30 minutes in duration of sleep latency. In comparison with placebo, melatonin increased total sleep time by 22 minutes (1 to 44 minutes) and reduced sleep latency by 37 minutes

Table 12. Efficacy of melatonin in children with neurological development disorders.

Study	Condition	Dose	Sleep latency		Total sleep time	
			No trials/ patients	Melatonin *vs* placebo (95%CI)	No trials/ patients	Melatonin *vs* placebo (95%CI)
Rossignol 2011[20]	Autism	2-10 mg	5/57	-39 min (-47 to -31)	5/57	44 min (20 to 68)
Cortesi 2012[21]	Autism	3 mg PR	1/134	-36 min (-45 to -27)*	1/134	61 min (46 to 76)*
Braam 2009[22]	Intelectual disability	0.5-9 mg	7/273	-34 min (-43 to -25)	7/257	50 min (34 to 65)
Appelton 2012[23]	Neurological development disorders	0.5-12 mg	1/113	-37 min (-55 to -20)	1/110	22 min (1 to 44)

PR: prolonged-release. *numerical data calculated for this article (see note).

(20 to 55 min),[23] thus clinical relevance was not attained in regard to total sleep time and was uncertain for sleep latency.

What do other sources say?

Even with limited evidence, the *Canadian Paediatric Society* considers that melatonin can be useful in certain sleep disorders affecting children, especially in those secondary to other diseases. It should only be considered after carrying out interventions on sleep hygiene.[24]

Clinical Evidence states that melatonin's risk–benefit balance is favourable for insomnia in healthy children or in those with ADHD, epilepsy or neurological development disorders. The effectiveness of other pharmacological interventions is still unknown.[5]

Is melatonin really as safe as it appears?

The regulation of melatonin as a dietary supplement makes the evaluation of its safety profile somewhat difficult as there is no obligation to report adverse effects to a regulatory agency.

In the clinical trials included in the EPAR on prolonged-release melatonin 2 mg, 37% of the patients on melatonin reported adverse effects, in comparison with 31% on placebo. A total of 1.3% patients discontinued treatment due to adverse events on melatonin and 3.6% on placebo. The drug´s risk management plan reports visual alterations, infections, immune based disorders, loss of consciousness, pharmacological interactions and withdrawal symptoms as factors to monitor. It is not recommended in cases of liver failure, pregnancy or lactation.[3] The possible interaction with warfarin detected in one study[13] is not commented in the drug's monograph.

In the reviews melatonin is described as a very safe treatment with no differences compared to placebo in the incidence of adverse events.[14,20,25] However, these reviews also point out that in those trials not submitted to the EMA, there was often no systematic recording of adverse events.[13,22]

Adequate posology is still uncertain

Melatonin affects the secretion of sexual hormones (GnRH, LH, FSH)[2] and it has been suggested that it can alter the onset of puberty[5]. In one extension clinical trial, 16 boys and 30 girls were evaluated and no evidence of changes in puberty were found compared to population based data.[26]

In trials on children, headache, dizziness, cold sensation, depressed mood, and decreased appetite have been reported. One case of elevated alkaline phosphatase and another case of epilepsy have also been described.[12] A proconvulsant effect had previously been reported.[5] A recent review has not shown any evidence that there is any effect on seizures, although it does admit that the data are too limited to draw solid conclusions.[27]

It is worth pointing out that most of the research in children has been carried out in patients with attention disorders or disabilities, and some adverse effects could have been missed, others masked by clinical manifestations of the diseases and by the difficulty these patients may have to express themselves.[5]

A lot of confusion

What is the most appropriate dose? In the majority of the studies, melatonin was tested at doses of 5 mg/d

or more. However, the EPAR on Circadin® indicates that the safety profile at doses between 4 and 8 mg daily has not been established.[3] In a dose-ranging study in elderly patients with insomnia no differences were found between the 0.3 mg and 3 mg daily dose.[28] In another trial on jet lag, the prolonged-release 2 mg/d dose was less effective than 5 mg/d.[13]

The posology in children is even less clear, given that the clinical trials used higher doses than those recommended for adults. Moreover there is some evidence of receptor saturation at high doses.[1,5] In this sense it is surprising that one of the recent trials is aimed at dose finding.[18]

In which patients does melatonin work? One systematic review concluded that melatonin showed a greater reduction of sleep latency in patients with delayed sleep disorder compared to patients with primary insomnia. The former was the only outcome presenting data of clinical relevance.[25] In a later meta-analysis, differences versus placebo in adults with delayed sleep did not reach statistical significance.[12]

In the case of primary insomnia effectiveness has been shown only in patients over 55 years old.

How does one know if melatonin works? Better scores on sleep quality scales in primary insomnia or jet lag do not clearly correlate with a reduction in sleep latency, and results are of limited magnitude and may be clinically irrelevant.

Points for reflection

Melatonin is a hormone with effects on a variety of tissues that are still not well understood. Just like other hormones, it can have therapeutic effects. Well-designed clinical trials are needed to assess the real risk-benefit balance and learn about the most appropriate doses to be used. Melatonin's approval as a dietary supplement is not justified.

We would be naive to think that a hormone with effects on various organs would not produce any adverse effect.

In the case of patients with ADHD it is important to distinguish between insomnia related to the disorder and insomnia as an adverse effect of stimulants. For the latter situation, adding melatonin is an example of a 'prescription cascade' in which adverse effects lead to prescribing of additional medication use rather than reconsidering the initial treatment decision.

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Conclusions

When addressing insomnia, the first thing to evaluate is the possible causes, and initiate management with sleep hygiene interventions.

Drugs should only be used for altered sleep when there is substantial discomfort or if quality of life is negatively affected.

The efficacy of melatonin for sleep disorders is at best only modest. Its use has been justified by its safety profile and although this profile appears better than that of other hypnotics, still very little is known, especially concerning longer-term effects.

Available evidence is derived in general from small and short-term studies.

Melatonin has not proven effective for sleep disorders affecting patients with dementia. There is no evidence that melatonin improves sleep in shift workers. It seems to improve symptoms in jet lag. In any case the evidence on effectiveness is of low quality.

The use of melatonin for insomnia in children with neurological disorders can be considered given the absence of evidence on other alternatives; it is prudent to always carry out a trial of therapy and monitor the response.

Note: The 95% confidence interval of the results of the trials by Suresh Kumar 2007 and Cortesi 2012 was calculated according to the method described in the Cochrane Handbook (sec. 16.1.3.2), assuming, just like Buscemi 2005, a correlation coefficient of 0.5. The groups with or without Cognitive Therapy in Cortesi 2012 were combined using a fixed-effect model meta-analysis. The calculations were carried out in Review Manager and Microsoft Excel.

REFERENCES

1. Wurtman R. Physiology and clinical use of melatonin. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA. (Acceso: 26 diciembre, 2013). http://www.uptodate.com/contents/physiology-and-clinical-use-of-melatonin

2. Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol Cell Endocrinol 2012;351:152-66. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288509/#R185

3. CHMP Assesment Report for Circadin INM: melatonin. London (UK): European Medicines Agency; 2007. Procedure No. EMEA/H/C/695. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000695/WC500026808.pdf

4. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev 2005;9:11-24.

5. Bruni O, Novelli L. Sleep disorders in children. Clin Evid (Online) 2010:2304. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217667/#BMJ_2304_I1181726699032

6. European Food Safety Authority. Scientific opinion on the substantiation of a health claim related to melatonin and reduction of sleep onset latency (ID 1698, 1780, 4080) pursuant to article 13(1) of regulation (EC) No 1924/2006. EFSA Journal 2011;9:2241. http://www.efsa.europa.eu/en/search/doc/2241.pdf

7. Circadin (melatonin) summary of product characteristics. RAD Neurim Pharmaceuticals EEC Limited. Jun 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000695/WC500026811.pdf

8. Grupo de Trabajo de la Guía de Práctica Clínica para el Manejo de Pacientes con Insomnio en Atención Primaria. Guía de Práctica Clínica para el Manejo de Pacientes con Insomnio en Atención Primaria. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Unidad de Evaluación de Tecnologías Sanitarias. Agencia Laín Entralgo. Comunidad de Madrid; 2009. Guías de Práctica Clínica en el SNS: UETS Nº 2007/5-1. http://www.guiasalud.es/egpc/insomnio/completa/index.html

9. Wade AG, Crawford G, Ford I, et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. Curr Med Res Opin 2011;27:87-98.

10. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One 2013;8:e63773. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656905/

11. Vissers FH, Knipschild PG, Crebolder HF. Is melatonin helpful in stopping the long-term use of hypnotics? A discontinuation trial. Pharm World Sci 2007;29:641-6. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2039831/

12. van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep 2010;33:1605-14. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2982730/

13. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002:CD001520.

14. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 2006;332:385-93. http://www.bmj.com/content/332/7538/385?view=long&pmid=16473858

15. Sack RL, Auckley D, Auger RR, et al. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. An American Academy of Sleep Medicine review. Sleep 2007;30:1460-83. http://www.aasmnet.org/Resources/PracticeParameters/Review_CircadianRhythm.pdf

16. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. Sleep 2007;30:1445-59. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082098/

17. Suresh Kumar PN, Andrade C, Bhakta SG, Singh NM. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. J Clin Psychiatry 2007;68:237-41.

18. van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl) 2010;212:379-91. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952772/

19. National Institute for Health and Care Excellence. Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin (ESUOM2) 2013. http://publications.nice.org.uk/esuom2-sleep-disorders-in-children-and-young-people-with-attention-deficit-hyperactivity-disorder-esuom2

20. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol 2011;53:783-92. http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2011.03980.x/full

21. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21:700-9. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2869.2012.01021.x/full

22. Braam W, Smits MG, Didden R, Korzilius H, Van Geijlswijk IM, Curfs LM. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. Dev Med Child Neurol 2009;51:340-9. http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2008.03244.x/full

23. Appleton RE, Jones AP, Gamble C, et al. The use of Melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). Health Technol Assess 2012;16:i-239. http://www.journalslibrary.nihr.ac.uk/hta/volume-16/issue-40

24. Cummings C. Melatonin for the management of sleep disorders in children and adolescents. Paediatr Child Health 2012;17:331-6. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380753/

25. Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005;20:1151-8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1490287/

26. van Geijlswijk IM, Mol RH, Egberts TC, Smits MG. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology (Berl) 2011;216:111-20. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3111733/

27. Jain S, Besag FM. Does melatonin affect epileptic seizures? Drug Saf 2013;36:207-15.

28. Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab 2001;86:4727-30. http://press.endocrine.org/doi/full/10.1210/jcem.86.10.7901

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