

# Melatonin



is it worth losing  
any sleep over?

*Modified-release melatonin is an unsubsidised medicine that is approved for, and moderately effective at, improving sleep quality in adults with insomnia; other formulations of melatonin are unapproved. Shift-workers or people concerned about jet lag may wish to discuss the “off-label” benefits of melatonin treatment. Melatonin also may be used in specialist situations, such as in children or adolescents with neurodevelopmental disorders and sleep disturbances. Prescribers should be mindful that melatonin must be dosed at the correct time in order to be effective for assisting sleep. Due to a lack of studies on the potential adverse effects of the long-term use of melatonin, prescribing for prolonged periods should be approached with caution, particularly in children and adolescents.*

#### Key messages

- Non-pharmacological interventions remain the first-line treatment for patients with insomnia
- There is only one approved formulation of melatonin in New Zealand (not subsidised), which is indicated for treating adults aged over 55 years with insomnia
- Melatonin may be useful “off-label” for treating sleep disturbances in children with neurodevelopmental disorders, for preventing or reducing jet lag and improving sleep in shift-workers
- There is a lack of studies on the potential adverse effects of prolonged melatonin use, particularly in children and adolescents

## Melatonin: “Nature’s most versatile biological signal”

Melatonin is regarded as a hormone which regulates the circadian rhythm of sleep. It is synthesised from the amino acid tryptophan and then released from the pineal gland; the process is controlled by a biological clock in the suprachiasmatic nucleus located within the hypothalamus.<sup>1</sup> An adult produces 20 – 60 micrograms of melatonin every 24 hours.<sup>1</sup>

The release of melatonin from the pineal gland is suppressed by ocular light at the retina.<sup>1</sup> In a person with a normal sleep-wake cycle melatonin is released at night, typically beginning 14 hours after spontaneous awakening, i.e. at 9 pm in a person who wakes up at 7 am.<sup>2</sup> Melatonin release therefore provides time-of-day information, i.e. onset of darkness, to various organs and tissues throughout the body. During a normal circadian cycle, melatonin reaches a peak concentration at approximately 2 – 3 am.<sup>1</sup> Melatonin secretion then decreases

and due to its relatively short biological half-life of 15 – 30 minutes is undetectable in the bloodstream by approximately 7 am.<sup>1,3</sup>

People who work night-shifts have a delayed peak in melatonin secretion, the degree of which is influenced by their level of night-light exposure and number of nights worked.<sup>4</sup> In people who live in extreme northern or southern latitudes the duration of melatonin secretion is increased during the longer winter nights.<sup>1</sup> As children enter puberty the rhythm of melatonin release is delayed resulting in later onset of sleepiness and a later natural wake time.<sup>5</sup> The secretion of melatonin decreases in later adulthood and by the age of 70 years it is reported that a person’s nocturnal melatonin concentration may be less than a quarter of what it was when they were younger.<sup>6</sup>

Melatonin is reported to have a range of actions in the human body, other than just regulating sleep (see: “Melatonin does more than regulate sleep”, Page 21).

## Melatonin as a medicine

The majority of the evidence relating to the therapeutic use of melatonin involves treating people with insomnia. This is because the nightly melatonin peak may be altered in people who report problems with the quality or quantity of their sleep.<sup>10</sup> When given as a treatment for insomnia melatonin is referred to as a chronobiotic, i.e. it alters the timing of sleep, as opposed to hypnotic medicines, e.g. zopiclone, which act to rapidly initiate and prolong sleep.<sup>1</sup>

There is evidence that melatonin can be effective in treating people with other forms of circadian disturbances, such as sleep disturbances in children or adolescents with neurodevelopmental disorders, the reduction or prevention of jet lag (when taken at the right time) and for sleep disturbances in people with vision abnormalities (Page 24).

## Modified-release and immediate-release melatonin

Melatonin is available in modified and immediate-release formulations. Modified-release melatonin causes the blood concentration over time to more closely mimic a naturally occurring melatonin profile (Figure 1). Immediate-release melatonin results in a relatively rapid increase in melatonin levels.<sup>2</sup> Although large head-to-head trials are lacking, there is limited evidence that the initial rise in melatonin levels provided by either formulation may be sufficient to induce sleep, and in addition the length of sleep may also be improved by modified-release melatonin.<sup>2</sup>

## Melatonin in New Zealand

In New Zealand melatonin is a prescription only, unsubsidised medicine. A 2 mg modified-release formulation of melatonin is approved for the treatment of primary insomnia in adults aged over 55 years (Page 23); all other formulations of melatonin are unapproved\* and all other uses for melatonin are “off-label”.<sup>11</sup> This means that modified-release melatonin is the only formulation of melatonin in New Zealand that has undergone Medsafe’s regulatory approval process. Therefore if prescribers are considering initiating melatonin treatment, modified-release melatonin is the only formulation that

Medsafe has assessed as being safe, under the conditions set out in the Medicine Data Sheet.

\* Section 29 of the Medicines Act specifies that a person or company who supplies this medicine must notify the Director-General of Health (via Medsafe) of the supply and record the name of the prescribing practitioner

Generally, modified-release melatonin taken one to two hours before sleep onset is desired is a reasonable dosing regimen. It is recommended that modified-release melatonin be taken with, or just after, food.<sup>11</sup> Patients should be advised to avoid drinking alcohol before bedtime as this may increase the speed of melatonin release into the blood stream, effectively turning the modified-release formulation into an immediate-release medicine.<sup>12</sup> Patients should not drive or operate machinery for the rest of the evening once they have taken melatonin.

Note that crushing or halving of tablets is not recommended by the manufacturer, as this alters the release profile of the medicine. However, if immediate-release melatonin is required, crushing of the approved modified-release formulation may be appropriate, e.g. for the treatment of jet lag off-label (Page 26). If the patient is unable to swallow tablets, modified-release

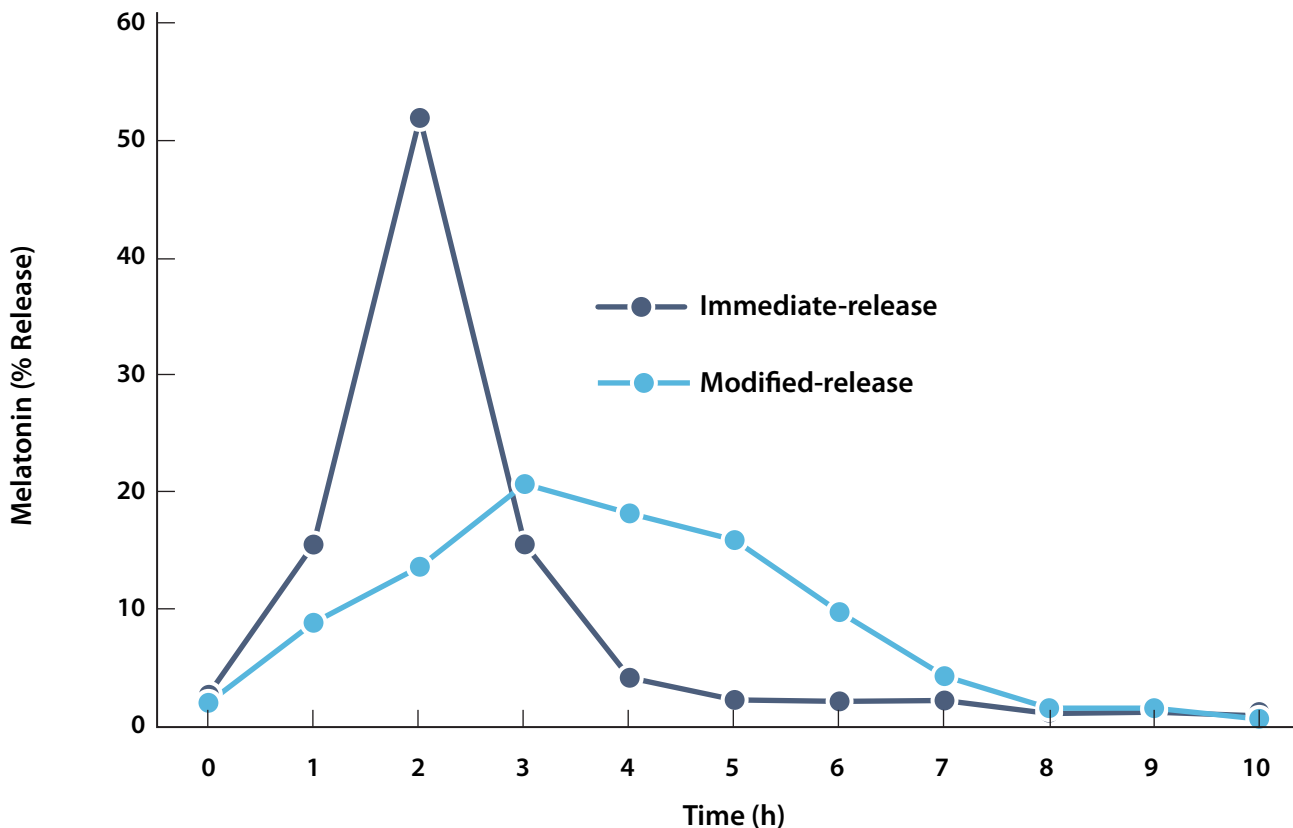


Figure 1: Pharmacokinetics of immediate-release melatonin and modified-release melatonin. Adapted from Zisapel, 2010<sup>2</sup>

melatonin tablets may need to be crushed or halved; careful halving of tablets may retain some of the delayed release profile.<sup>13</sup> Crushed melatonin tablets should not be stored, but can be mixed with cold food or drinks to aid digestion.<sup>13</sup>

If a patient taking immediate-release melatonin would like to switch to modified-release melatonin, it is reasonable to take the same dose of modified-release melatonin one to two hours earlier than they had been taking the immediate-release formulation.

### The adverse effects of melatonin treatment

The timing of melatonin administration is important when treating people with circadian disorders as delays in sleep onset may be experienced if melatonin is taken between six and 15 hours after a person's endogenous levels of melatonin begin to rise (usually around 9pm in a person who wakes at 7am).<sup>14</sup>

The adverse effects associated with melatonin use are diverse but relatively uncommon. The rate of adverse events in patients taking short courses of modified-release melatonin are reported to be similar compared with placebo, and include: asthenia (weakness), headache, respiratory infections and back pain.<sup>15</sup> It is recommended that melatonin be avoided in patients with hepatic impairment.<sup>11</sup>

### Interactions with other medicines

Melatonin is mainly metabolised by CYP1A enzymes therefore if it is taken concurrently with other substances that interact with this class of enzyme its metabolism may be affected.<sup>12</sup> Examples of medicines that may increase the plasma concentration of melatonin include: citalopram, cimetidine and quinolones (e.g. norfloxacin, ciprofloxacin).<sup>12</sup> Carbamazepine and rifampicin may cause plasma concentrations of melatonin to be reduced.<sup>12</sup>

It should also be noted that children may have reduced CYP1A2 levels compared to adults, which in addition to the above potential drug interactions, may expose children to higher concentrations of melatonin than anticipated.<sup>16</sup>

Whether or not medicines that affect the endogenous production of melatonin interact with melatonin taken orally is unknown.<sup>12</sup> There is some evidence that beta blockers may reduce melatonin levels.

### Melatonin compared with hypnotics

Melatonin may be preferable to zopiclone and benzodiazepines for the short-term treatment of insomnia because

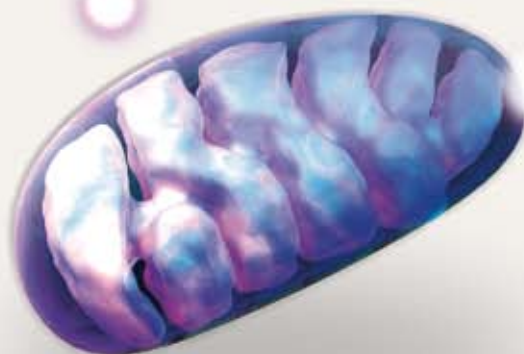
## Melatonin does more than regulate sleep

Due to its diverse range of biological functions melatonin is sometimes referred to as "Nature's most versatile biological signal".<sup>7</sup> As well as being present in the nervous system, melatonin receptors are distributed throughout the human body. Melatonin receptors in arteries are known to be involved in thermoregulation.<sup>8</sup> The coronary arteries, aorta and left ventricle have melatonin receptors and depending on which subset of receptor is present activation can lead to vasodilation or vasoconstriction.<sup>8</sup> Melatonin can also regulate haematopoiesis via receptors on bone marrow cells.<sup>8</sup> The body's immune function is influenced by melatonin, which is able to stimulate production of the cytokine interleukin-2 and its receptor, which in turn regulates leukocyte activity.<sup>8</sup> Melatonin has been demonstrated to have an inhibitory effect on carcinomas *in vitro* and *in vivo*.<sup>9</sup>

### Melatonin is a powerful antioxidant

Melatonin is an "old" molecule in an evolutionary sense and is produced in a variety of different organisms; as well as being a hormone it is a free radical scavenger, due to its antioxidant properties, and is produced by single cell organisms.<sup>7</sup> Melatonin readily penetrates cellular membranes and can therefore provide antioxidant protection to mitochondria and DNA.<sup>7</sup> Studies have shown that melatonin may have a protective effect against the development of skin cancer, both by eliminating free radicals produced by ultraviolet radiation and promoting DNA repair.<sup>7</sup>

Novel derivatives of melatonin are being synthesised and there is interest in their potential role in treating or preventing a diverse range of diseases involving oxidative stress including Alzheimer's disease, rheumatoid arthritis and cancer.<sup>3</sup>



it does not cause adverse effects such as excessive daytime sleepiness, vertigo and muscle weakness.<sup>15</sup> There is no evidence that modified-release melatonin causes tolerance, dependence, withdrawal or rebound insomnia.<sup>15</sup> There has been no reported increased risk of cognitive impairment or falls, fractures or motor vehicle accidents associated with the use of melatonin in older patients.<sup>15</sup>

**More studies on the long-term safety of melatonin are needed**

The safety of long-term melatonin use has not been widely studied and there are concerns that the long-term use of melatonin may have unforeseen consequences.<sup>1</sup>

The major safety concern with melatonin is what is not known about its long-term use, particularly among children and adolescents. In animals that are seasonal breeders variations

in melatonin production causes seasonally-appropriate changes,<sup>17</sup> e.g. oestrus in females and increasing testosterone production in males. A formulation of melatonin is used in some countries to enhance fertility in sheep.<sup>1</sup> It is uncertain if melatonin taken as a medicine may have adverse effects on human reproductive physiology. However, precocious puberty has been associated with abnormalities in melatonin rhythms and the possibility has been raised that the long-term use of melatonin in children may postpone the onset of puberty.<sup>17</sup> This concern has been partially allayed by a relatively small study which found no detectable disruption to pubertal development and mental health in 51 children aged between six and 12 years who had taken doses ranging from 0.3 mg of melatonin daily to 10 mg melatonin daily, for 1 – 4.6 years.<sup>17</sup> The New Zealand Formulary for Children recommends that melatonin should be initiated and supervised by a specialist and reviewed every six months.<sup>18</sup>

**Table 1: Causes of insomnia<sup>10,11</sup>**

Environmental	Medicines/substances	Conditions	Psychological
<ul style="list-style-type: none"> <li>■ Change in sleeping environment, e.g. living in a new house</li> <li>■ Jet lag</li> <li>■ Daylight saving</li> <li>■ “Sunday night” insomnia after an active weekend</li> <li>■ Noise</li> <li>■ Temperature or humidity</li> <li>■ Discomfort</li> <li>■ A disruptive partner or family member</li> </ul>	<ul style="list-style-type: none"> <li>■ Alcohol</li> <li>■ Stimulants, e.g. caffeine</li> <li>■ β-agonists</li> <li>■ Bupropion</li> <li>■ Ciprofloxacin</li> <li>■ Corticosteroids</li> <li>■ Decongestants</li> <li>■ Diuretics</li> <li>■ Stimulants, e.g. modafinil</li> <li>■ Thyroid hormones</li> <li>■ Selective serotonin reuptake inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>■ Cough</li> <li>■ Dyspnoea due to lung disease or heart failure</li> <li>■ Gastro-oesophageal reflux disease</li> <li>■ Menopause</li> <li>■ Nasal congestion</li> <li>■ Nocturia</li> <li>■ Pain, e.g. dental problems, chronic back pain</li> </ul>	<ul style="list-style-type: none"> <li>■ Anxiety</li> <li>■ Conditioned insomnia</li> <li>■ Depression</li> <li>■ Grief</li> <li>■ Mania</li> <li>■ Stress</li> </ul>

# The role of melatonin in sleep disorders

## Most people will report sleep problems at some stage in their life

Dissatisfaction with sleep quality or distress from not sleeping will be experienced by most people at various times in their lives.<sup>10</sup> Sleep disturbances are reported to affect 10–50% of patients presenting to primary care clinics in New Zealand, depending on the definition that is applied.<sup>19</sup> People should expect some small changes in the amount of sleep they have as they get older, even in the absence of sleep problems. Studies show that total sleep duration decreases by approximately ten minutes per decade of age, and cohorts of adults aged 55 years and older consistently report sleeping an average of seven hours per night.<sup>20,21</sup>


## Diagnosing primary insomnia

Primary insomnia can be diagnosed if a person has a significant sleep disturbance, occurring at least three nights per week, lasting for longer than one month, and there are no other contributing health conditions or sleep disorder diagnoses.<sup>19</sup> Primary insomnia is therefore a diagnosis of exclusion once other causes of sleep disturbance have been ruled-out, e.g. restless leg syndrome, depression, anxiety and stress, sleep apnoea and long-term alcohol use.<sup>10</sup>

Patients with primary insomnia have long-term insomnia and one or more of the following symptoms:<sup>10</sup>

- Difficulty falling asleep at bedtime
- Waking frequently or having a restless sleep
- Waking during the night with difficulty getting back to sleep
- Early waking with an inability to get back to sleep

Due to age-related hormonal changes, insomnia is increasingly reported by people aged over 55 years.

 Patients who report severe insomnia or who have insomnia that is not responding to treatment are likely to benefit from referral to a sleep specialist.

## Establishing the cause of insomnia

When consulting with patients who report sleep problems, a detailed history is essential to establish patterns of insomnia, associated symptoms, as well as any underlying causal factors.<sup>10</sup> Insomnia is different to sleep deprivation caused by a lack of opportunity to sleep. People who experience

insomnia are unable to sleep despite having sufficient time and desire to sleep. In some people this desire to go to sleep produces a paradoxical alertness and arousal that counteracts somnolence.<sup>10</sup>

Insomnia may be due to one or a combination of four causes: external factors, medicines or substances, medical conditions and psychological disturbances (Table 1).<sup>10</sup> A New Zealand survey of over 1500 patients in the waiting rooms of three general practices found that mental health issues, e.g. depression and anxiety, and physical issues, e.g. pain or breathing problems, caused the majority of sleep disturbances.<sup>19</sup>

## Non-pharmacological treatment of insomnia is first-line

The first-line treatment for insomnia should always be the elimination of any underlying causes of sleep disturbance before pharmacological treatment is considered. A tailored approach is likely to be required, depending on the patient's circumstances and lifestyle. Sleep hygiene, stimulus control and sleep restriction treatment can be effective for people who are experiencing insomnia.

### Simple changes can make a big difference

Sleep hygiene refers to adopting behaviours and modifying environmental factors to increase the likelihood of sleep. Examples of sleep hygiene include ensuring light and temperature are conducive to sleep, avoiding heavy meals close to bedtime, limiting caffeine intake, restricting alcohol intake, avoiding smoking close to bedtime, avoiding napping during the day and avoiding vigorous exercise close to bedtime.<sup>22</sup>


The objective of stimulus control is to retrain the patient to associate their bed and bedroom as a place of sleep and thereby establish a normal sleep-wake cycle. This involves:<sup>22</sup>

- Only going to bed when sleepy
- Restricting the use of the bedroom to sleep and sexual activity
- Leaving the bedroom if unable to fall asleep for longer than 20 minutes, and then returning only when sleepy
- Sticking to a fixed time for getting up every morning

Sleep restriction treatment involves the clinician calculating how many hours the patient spends in bed at night and then

how many of these hours they are actually asleep. This is usually done with the use of a sleep diary. The patient then restricts their time in bed to their calculated average sleep time, with a minimum time in bed of five hours.<sup>23</sup>

There is some evidence that bright light in the morning can be used to treat patients with insomnia with delayed sleep-onset, and bright light in the evening may be effective in treating insomnia associated with early morning waking.<sup>24</sup>

 For further information see: "Managing insomnia", BPJ 14 (Jun, 2008).

## The approved use of melatonin

Modified-release, 2 mg melatonin tablets, once daily, one to two hours before bedtime is indicated for the treatment of primary insomnia in people aged over 55 years, for up to 13 weeks.<sup>11</sup> The use of melatonin in younger patients is not currently approved as the clinical trials that showed modified-release melatonin was moderately effective at treating insomnia only included patients who were aged 55 years or over.<sup>6</sup>

It is important that patients who are prescribed melatonin take the medicine as directed. If melatonin dosing occurs at times of the day other than when treatment is recommended sleep patterns could be disrupted even further.

### How much improvement in sleep can patients expect?


In patients aged over 55 years it is reported that melatonin produces meaningful improvements in both quality of sleep and morning alertness in 32% of patients.<sup>15</sup> However, there is likely to be a significant placebo effect involved in treatment success as 19% of patients treated with placebo also experienced meaningful improvements in sleep.<sup>15</sup> In two clinical trials patients treated with modified-release melatonin had a time to sleep onset of approximately ten minutes compared to approximately twenty minutes for patients taking placebo.<sup>6</sup> There were no reported increases in sleep duration following melatonin treatment.<sup>6</sup>

## Off-label uses of melatonin

Patients may often enquire about the suitability of melatonin treatment for indications other than insomnia, e.g. for preventing jet lag or for managing sleep in shift work; or parents may enquire about melatonin treatment for their child. Melatonin should not be prescribed in primary care to children with sleep disturbances who are otherwise healthy. In general, melatonin treatment is only appropriate for children

with neurodevelopmental disorders and sleep disturbances (see below).

Patients who are prescribed melatonin for "off-label" purposes should be told that there is limited data available concerning the safety or efficacy of the medicine for this use and that the details of the prescription will be recorded on a database as requirement of the Medicines Act.<sup>25</sup> As in many cases of off-label medicine use, there is no established dosing regimen for melatonin; an appropriate protocol may be derived from clinical studies. In some situations it is not clear whether modified-release or immediate-release is the most effective treatment option as some studies do not specify which formulation of the medicine was used. Discussing the patient with a sleep specialist may be beneficial before prescribing "off-label" melatonin long-term, although this will not always be practical.

 For further information see: "Upfront: Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe", BPJ 51 (Mar, 2013)

## Melatonin in children with developmental disorders

Sleep disturbances are common in children with developmental disorders, e.g. autism and attention deficit hyperactivity disorder (ADHD), and complex neurodevelopmental disorders, e.g. visual impairment, epilepsy, cerebral palsy. These sleep disturbances are often long-term and harder to treat than in their age-matched peers.<sup>26</sup> Sleep disturbances in these children may be exacerbated by the use of stimulants, e.g. methylphenidate for ADHD. Melatonin treatment for children with neurodevelopmental disorders and sleep disturbances is initiated by a specialist, e.g. a paediatrician or a psychiatrist.

A study that included 263 children aged three to fifteen years with a history of impaired sleeping and a diagnosed neurodevelopmental disorder investigated whether immediate-release melatonin was beneficial in improving total sleep time and sleep onset. Children were initiated on 0.5 mg of immediate-release melatonin daily, or placebo, and this was titrated to effect through 2 mg, 6 mg and 12 mg during the first four weeks of treatment.<sup>26</sup> It was found that on average children treated with immediate-release melatonin went to sleep 45 minutes earlier, compared with placebo treatment, which was considered to be clinically significant.<sup>26</sup> Total time slept was increased on average by 23 minutes, compared to placebo, but this was not considered to be clinically significant.<sup>26</sup> It is not known if modified-release melatonin increases total sleep time in children with neurodevelopmental disorders as head-

to-head trials with immediate-release melatonin have not been conducted.

The recommended dose of melatonin for the treatment of sleep onset insomnia and delayed sleep phase disorder in children aged one month to 18 years is 2 – 3 mg daily, before bedtime\*.<sup>18</sup> While this can theoretically be increased to 4 – 6 mg after one to two weeks, to a maximum of 10 mg daily, due to differences in CYP1A2 activity and weight-based dosing in children, higher doses should be used with caution. In addition, given that lower doses of melatonin have been reported to be effective in other populations, e.g. 0.5 mg of melatonin for people with vision disturbances,<sup>27</sup> a lower dose may be effective and safer in children. Many experts would commence treatment with a 1 mg dose.

\* Modified-release melatonin tablets can be given one to two hours before bedtime, or if the child is unable to swallow tablets then modified-release tablets can be crushed and mixed with a drink immediately before bedtime (or administered via a gastrostomy/nasogastric tube).

### **Children with autism may have abnormal melatonin production**

Children with autism often secrete lower levels of melatonin compared with children in the general population.<sup>28</sup> Modified-release melatonin treatment does appear to be effective for children with autism with sleep disturbances in the short-term, and the effectiveness of treatment appears to be substantially increased when melatonin is combined with cognitive behavioural therapy.

A study including 134 children aged between four and ten years, with a confirmed diagnosis of autistic disorder, compared the effectiveness of 3 mg, daily, modified-release melatonin treatment with cognitive behavioural therapy, or with both treatments combined.<sup>29</sup> Children with an average reported duration of insomnia of 2.4 years were given 3 mg of modified-release melatonin at approximately 9 pm for 12 weeks.<sup>29</sup> The combined treatment approach was superior to melatonin or cognitive behavioural therapy alone and resulted in 85% of children either sleeping within 30 minutes of bedtime or reducing sleep onset by 50%.<sup>29</sup> In contrast, 40% of children treated with melatonin alone meet this criteria compared with 10% of the children who received cognitive behavioural therapy alone.<sup>29</sup>

### **Adolescents often do not get enough sleep**

Insufficient sleep and poor sleep hygiene are the most frequent reasons for sleep disturbances in teenagers.<sup>5</sup> Melatonin use

in adolescents should be reserved for those diagnosed with a specific circadian disturbance, e.g. delayed sleep phase disorder (see below).

Adolescents naturally go to bed later and sleep later due to changes in lifestyle and changes in the timing of melatonin release.<sup>5</sup> Teenagers will also often have a more variable sleep pattern across the week as they go into sleep deficit during the week, while attending school, and then recover this debt over the weekend by sleeping for longer.<sup>30</sup> These changes in sleeping patterns make it difficult to assess the prevalence of insomnia in teenagers. However, 21 studies across a range of countries found that 20–26% of teenagers regularly experienced difficulty falling asleep within 30 minutes.<sup>30</sup> In general, it appears that teenagers do not get enough sleep. Studies have shown that teenagers typically need at least 9 hours sleep a night, but often only manage 7.5 to 8.5 hours a night.<sup>5</sup>

### **Melatonin is appropriate for patients with delayed sleep phase disorder**

Delayed sleep phase disorder is a clinical term applied to people who may also be described as extreme “night owls”.<sup>10</sup> Delayed sleep phase disorder occurs when a person’s natural sleep time is mismatched with expectations of what is normal.<sup>10</sup> This disorder is estimated to have a prevalence of 2% in patients attending general practice in New Zealand.<sup>19</sup> Delayed sleep phase disorder is associated with attention-deficit/hyperactivity disorder (ADHD), increased rates of smoking, alcohol use, caffeine use and depression.<sup>10</sup> Delayed sleep phase syndrome is estimated to occur in 5–10% of adolescents.<sup>5</sup>

A meta-analysis of five trials found that melatonin could advance mean sleep onset by 40 minutes in patients with delayed sleep phase disorder.<sup>14</sup> It appears that melatonin is most effective for this patient group when given five to six hours before physiological levels of melatonin would begin to rise in a normal person, i.e. in the early to mid-afternoon.<sup>14</sup> The optimal dose for treating patients with delayed sleep phase disorder is unknown; studies have used nightly doses of melatonin ranging from 0.5 to 5 mg.<sup>14</sup> A small study involving 13 patients found that 0.3 mg of melatonin and 3 mg of melatonin daily were both equally effective in advancing sleep onset.<sup>31</sup> Another small study of 21 teenagers, aged 14 to 19 years, who reported being unable to sleep until 1 am on at least two weekdays per week with substantial daytime sleepiness found that 1 mg of melatonin taken in the late afternoon reduced sleep onset by approximately one hour and increased duration of sleep by the same length.<sup>32</sup>



## Melatonin may reduce or prevent jet lag

Most people experience jet lag when they travel across multiple time zones. Jet lag is a collection of symptoms that usually includes daytime fatigue and sleep disturbance, but may also involve reduced cognitive function, dizziness, weakness and irritability.<sup>33</sup> These symptoms occur when a person's circadian rhythm becomes desynchronised with the day-night cycle of their travel destination and it may take four to six days for synchronisation to occur.<sup>33</sup>

There is evidence that immediate-release melatonin is effective in reducing or preventing jet lag and the benefit is greater the more time zones that are crossed.<sup>33</sup> This effect seems to be strongest for people travelling across five or more time zones, particularly in an easterly direction, e.g. New Zealand to New York.<sup>33</sup> Modified-release tablets are thought to be less effective at preventing jet lag than immediate-release melatonin. Patients who want to take the approved form of melatonin may wish to crush modified-release melatonin tablets before taking them.

The optimal timing of melatonin dosing for the prevention or reduction of jet lag is important and people should take melatonin in the late afternoon or early evening at their destination.<sup>33</sup> Doses may be repeated for several days after arrival. Exposure to bright light in the morning also assists in adjusting to the new time zone.<sup>34</sup> Taking melatonin prior to departure at a time corresponding to night-time at the destination, i.e. to anticipate the change in time zone, is not recommended.<sup>33</sup>

A Cochrane review found that in eight of ten trials where melatonin was taken close to bedtime at the destination (10 pm to midnight) there was a reduction in jet lag for travellers crossing five or more time zones.<sup>33</sup> People appeared to fall asleep faster with 5 mg melatonin compared to 0.5 mg melatonin, but otherwise the effectiveness of doses between these ranges was the same and doses above 5 mg were found to be no more effective.<sup>33</sup> The only study that included modified-release melatonin found that immediate-release was more effective, suggesting that a short peak in melatonin concentration is more effective at entraining the sleep-wake cycle in people with jet lag in a new time zone.<sup>33</sup>

N.B. Patients can be advised that in countries where melatonin is available without prescription the quality and purity of the product may not meet the standards of pharmaceutical preparations. If melatonin is brought back into New Zealand it should be declared at customs where it will be held until a New Zealand prescription is obtained for it.

## Melatonin may increase sleep length for people doing shift-work

People who do shift-work may experience sleep disturbances resulting in sleepiness when working at night and reduced sleep duration and quality during the day. In patients with extreme symptoms this is termed shift-work sleep disorder.<sup>35</sup> The use of melatonin may increase the time shift-workers are able to sleep, but there is no evidence that it will reduce the time taken to fall asleep.

A 2014 Cochrane review assessed the effectiveness of melatonin for improving sleep in shift-workers and found low quality evidence from nine studies that melatonin use improved sleep duration during the day by approximately 25 minutes, and sleep length the next night that they were off shift-work by approximately 15 minutes.<sup>35</sup> In seven of the nine trials melatonin was administered in the morning, after the night shift had finished, and before the day time sleep period.<sup>35</sup> The doses used in the meta-analysis ranged from 1 mg to 10 mg, but there was no additional benefit observed at doses higher than 5 mg.<sup>35</sup>

## Melatonin is useful for treating sleeping problems in people with vision loss

People who are blind report an increased prevalence of sleeping problems compared to the general population; estimates vary, but approximately 50% report problems.<sup>36</sup> This is because the transmission of ocular light from the retina to the circadian clock is impaired and desynchronisation of the circadian clock and the external day/night cycle can occur.<sup>27</sup> In people who are totally blind this may result in a lifelong sensation of jet lag which can be improved by treatment with melatonin if it is given at the appropriate time relative to the patient's circadian clock.<sup>27</sup>

Melatonin at a daily dose of 0.5 mg has been shown to be effective at synchronising abnormal circadian rhythms in people who are either partially sighted or totally blind.<sup>27</sup> As treatment with melatonin may be lifelong for people who are blind the lowest effective dose of melatonin is preferable. One small study found that treatment with 0.3 mg of melatonin was sufficient to synchronise circadian rhythms in ten totally blind subjects.<sup>37</sup> To achieve synchronisation of abnormal circadian rhythms it is important that melatonin dosing occurs at the appropriate time for the individual. Therefore, assessment of the circadian phase of the individual patient is helpful to guide treatment before melatonin is initiated.<sup>27</sup> The degree of circadian misalignment can be determined with a combination of sleep diary and actigraphy (sleep/activity monitoring) at one of four or five sleep clinics across New Zealand.

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