

## MELATONIN - DON'T LOSE SLEEP OVER IT

- ▶ MELATONIN IS AVAILABLE ON PRESCRIPTION ONLY
- ▶ APPROVED FOR PRIMARY INSOMNIA IN THOSE OVER 55 YEARS
- ▶ CONSIDERED USEFUL FOR JET LAG
- ▶ LONG-TERM SAFETY AND INTERACTION DATA ARE LACKING
- ▶ CAN CAUSE DAYTIME DROWSINESS AND IMPAIRED CONCENTRATION
- ▶ SAFETY IN CHILDREN HAS NOT BEEN ESTABLISHED

Melatonin is a hormone, structurally related to serotonin.<sup>1</sup> It is primarily produced in the pineal gland and plays a part in the regulation of biological rhythms and the timing of physiological processes.<sup>2</sup>

Endogenous melatonin secretion increases soon after the onset of darkness, peaking between 11pm and 3am; with production being suppressed by light. There appears to be an age-related decrease in endogenous melatonin production.<sup>3</sup>

### MELATONIN IS AVAILABLE ON PRESCRIPTION ONLY

Melatonin 2mg Prolonged Release tablet (CIRCADIN<sup>®</sup>) was approved in New Zealand in 2011, as monotherapy for the short-term treatment of primary insomnia in patients who are aged 55 or over.<sup>1</sup>

It is worth noting that melatonin is available in many countries (including the United States and Canada) as an over the counter 'nutritional' supplement in varying doses and compositions, some of which contain additional vitamins.<sup>2</sup> This has led to widespread unregulated and uncontrolled use. Although data is emerging, there is very little robust clinical evidence available about long-term use and there are inconsistencies between results; this makes it difficult to reach any firm conclusions about unapproved indications.

Melatonin has been extensively studied in New Zealand for sleep timing disorders in the blind and visually impaired, and has been considered very useful for this group.<sup>4</sup>

### APPROVED FOR PRIMARY INSOMNIA IN THOSE OVER 55 YEARS

Short-term use (up to 13 weeks) has demonstrated benefits in primary insomnia for those over 55 years, but these effects were not clinically significant in younger patients.<sup>1</sup>

In those over 55 years, a 2mg dose as monotherapy taken

1-2 hours before bedtime has been shown to improve quality of sleep and morning alertness.<sup>1</sup> If melatonin loses effectiveness, it may help to cease treatment for a month, and restart again at the initial dose.<sup>3</sup>

A shortened time to sleep onset (by 9 to 11 minutes) has been observed with melatonin, although in those over 55 years, time to sleep onset is usually normal.<sup>3</sup>

**Note:** Primary insomnia is sleeplessness that is not associated with another medical or psychological condition, and could arise as a result of prolonged periods of stress. Primary insomnia may not always require drug treatment and could be managed by careful assessment and 'sleep hygiene' methods<sup>5</sup> or cognitive behavioural therapy<sup>6</sup> with specialist input.<sup>7</sup> See pg 4 for definition of primary insomnia and sleep hygiene tips.

### CONSIDERED USEFUL FOR JET LAG

Melatonin may be effective in preventing or reducing jet lag especially if it has been experienced previously, and if flying across five or more time zones (particularly in an easterly direction).<sup>8,9</sup> The timing of the dose is critical (see below) and determines the effect; if it is given at the wrong time it will delay circadian adaptation to local time.<sup>10</sup>

**Note:** This indication has not been approved in New Zealand. See pg 4 for 'Requirements for unapproved indications'.

Most studies recommend that melatonin is most effective when taken as 0.5-3mg<sup>9</sup> one to two hours prior to bedtime on the day of arrival at the destination, and on the following 2-5 days at the same time. Taking melatonin before the day of travel is not recommended.<sup>8</sup> Slow release preparations may not be as useful for jet lag as normal release agents<sup>9</sup>, which are not approved in New Zealand.

Other measures to alleviate jet lag should be recommended, for example exposure to natural daylight and eating meals at regular times after arriving at the destination.

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### LONG-TERM SAFETY AND INTERACTION DATA ARE LACKING

Although occasional short-term use as monotherapy appears to be safe, there is no clear information available concerning long-term safety or interactions with other medications, so some of the following is theoretical. Melatonin should be avoided in people with epilepsy, hypertension and diabetes, and could potentially worsen symptoms of depression.<sup>1</sup> There is no evidence for use in pregnancy and breast-feeding; some studies suggest it may interfere with ovulation. There is currently no data regarding dosing in renal or hepatic impairment.<sup>1</sup>

The efficacy and safety of melatonin in combination with other agents has not been assessed. It is best to avoid combinations with benzodiazepines and other hypnotics, caffeine and alcohol.<sup>1</sup> Melatonin is likely to increase the sedative properties and side effects of hypnotics leading to a more pronounced impairment of attention, memory and coordination.

Caution should be taken in patients taking oestrogen-containing preparations, e.g. contraceptives or hormone replacements, which also increase melatonin levels. Interactions have been identified in combination with fluvoxamine, quinolones, carbamazepine and rifampicin. Melatonin could lead to an increased risk of bleeding, so caution is advised in combination with warfarin or other anticoagulants.<sup>8</sup>

### CAN CAUSE DAYTIME DROWSINESS AND IMPAIRED CONCENTRATION

Melatonin may cause minor transient adverse effects such as headache, insomnia, rash, upset stomach, and nightmares.<sup>1</sup>

One of the most common side effects of melatonin therapy is daytime drowsiness. Melatonin taken at the wrong time of the day or at excessive doses is likely to cause daytime sleepiness, particularly if combined with other medications. Melatonin has been associated with fatigue and impaired

concentration; driving or use of machinery should be avoided for 4 to 5 hours after taking melatonin.<sup>11</sup> There have also been reports of transient anxiety, irritability and confusion.<sup>1</sup>

**Note:** Melatonin used in excessive doses can lead to receptor desensitization and exacerbate the condition that is being treated.<sup>3</sup>

### SAFETY IN YOUNG CHILDREN HAS NOT BEEN ESTABLISHED

There is insufficient safety and efficacy data to recommend use in those under 18 years.<sup>1</sup> Melatonin may interfere with development during adolescence due to its effects on other hormones.<sup>3</sup>

Despite this, melatonin may be useful for children with specific sleep disturbances associated with central nervous system disorders and developmental disabilities (e.g. cerebral palsy and mental retardation) where it can help to reduce the time to sleep onset and minimise nighttime awakenings.<sup>2</sup> Melatonin has been used successfully in blind children and adults with sleep-timing disorders due to a lack of conscious light perception.<sup>4</sup>

There is little evidence to suggest it is helpful in other conditions associated with insomnia. In a small study of 19 children aged 6-14 years with ADHD presenting with initial insomnia, melatonin in combination with sleep hygiene measures improved sleep onset by 16 mins.<sup>12</sup> It is unknown if sleep hygiene measures alone would have the same effect.

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### Definition of Primary Insomnia (DSM\*-IV)<sup>13</sup>

- A** The predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month
- B** The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- C** The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia
- D** The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalized anxiety disorder or delirium)
- E** The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition

\*Diagnostic and Statistical Manual of Mental Disorders (DSM) of The American Psychiatric Association.

### Sleep Hygiene<sup>6</sup>

**ASLEEP** is a useful acronym for remembering sleep hygiene tips

**A**lcohol, caffeine and nicotine should be avoided, especially in the evening

**S**leep and sex should be the only uses of the bed; make sure your bed environment is comfortable

**L**eave laptops, TV and paperwork out of the bedroom and keep clocks out of sight; blue light from phones, computers and TV can exacerbate insomnia

**E**xercise regularly and be active during the day, spending time outdoors if possible

**E**arly rising – avoid sleeping-in or daytime naps; get up at the same time each day

**P**lan for bedtime – establish a bedtime routine to wind down such as having a warm drink or a bath; avoid going to bed until you are drowsy

Talk to your doctor about changing specific habits that may affect your sleep. It can be very helpful to learn relaxation skills or try other techniques such as sleep restriction or cognitive behavioural therapy, which may need referral to a psychologist or sleep specialist.

Adapted from Cape G BPJ 2008;14:6-11

### Requirements for unapproved indications<sup>14</sup>

Melatonin 2mg tablets are currently registered in New Zealand for primary insomnia in those over 55 years.

For other patient groups or conditions, the patient should be advised that it is an unapproved indication. Unbiased efficacy and safety information should be discussed with the patient, together with other treatment options, to be assured that it may offer benefit and not harm.

If the use of melatonin is regarded 'experimental', signed consent must be obtained from the patient, as per The Code of Health and Disability Services Consumers' Rights. Agree with the patient on how monitoring for safety and efficacy will be arranged. The unapproved use of a medicine would be considered to be experimental if there is limited documented evidence supporting its use.<sup>14</sup>

For further information on other high-risk medicines visit our website at: [www.saferx.co.nz](http://www.saferx.co.nz)

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