

# Graylands Hospital Drug Bulletin

## Melatonin Melodrama

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### Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a naturally occurring hormone that can be found in a number of plants (fruits, vegetables and wheat) and organisms (bacteria and fungi).<sup>1</sup> In humans melatonin is created by the pineal gland, retina, bone marrow<sup>2</sup> and gastro intestinal tract.<sup>3</sup> Changes in light directly influence the creation and secretion of melatonin. A reduction in light increases melatonin production. The pineal gland is the only endocrine gland directly stimulated by the retina in response to a stimulus originating outside of the body.

There is evidence melatonin plays a crucial role in sleep wake cycle regulation, development through puberty and seasonal adaptation. Melatonin has also been linked to memory consolidation, body posture, balance and a number of other physiological processes.<sup>4</sup>

Studies into the administration of melatonin and its effects on the brain in the early 1970s, have led to further research of its hypnotic and sedative effects and the role it could play in sleep disorders.<sup>5</sup>

It is estimated that at least 10% of the population suffers from a sleep disorder that is deemed clinically significant.<sup>5</sup> Sleep disorders are often associated with other comorbid health conditions such as psychiatric disorders, neurological and cardiovascular diseases and have been linked to an increase in mortality, hospitalisations and traffic accidents.<sup>6</sup> Current pharmacological treatments of sleep disorders often come with unwanted side effects ranging from day time sedation to dependence.<sup>6</sup> Melatonin on the other hand has a relatively insignificant side effect profile.<sup>7</sup>

Given its apparent beneficial effects and benign side effect profile, it has been widely utilised in the United States and Australia. Melatonin is more expensive than most other medications used for sleep. The cost to Graylands Hospital was \$7512.25 over the past 12 months. Melatonin may cost an individual greater than \$33 a month, and when put in the context of conflicting clinical evidence, benefits may not necessarily outweigh the cost.

Many trials have been done to assess the effectiveness of melatonin in treating primary and secondary sleep disorders. These trials have resulted in a mass of conflicting data. The widely differing interpretation of this data by sleep specialists and health professionals has led to varying opinions regarding its place

### Melatonin Summary

**Recommended Dose:** 2mg once daily, 1-2 hours before bedtime after food

**Cost:** \$32.99 per month\*

**Evidence:** *Primary sleep disorders:* Small non-clinically relevant benefit

*Sleep disorder related to intellectual disability:* Safe and effective treatment

*Secondary sleep disorders:* No evidence for use as treatment

**Common Side Effects:** Headache, pharyngitis, back pain and asthenia

**Availability:** 2mg modified release tablet - Circadin®

in therapy e.g. despite the positive recommendation from sleep physicians, the West Australian Drug Evaluation Panel (WADEP) did not include melatonin in the state-wide formulary for general use. The purpose of this bulletin is to look at what the evidence supports about melatonin's place in the current treatment model for sleep disorders.

## Mechanism of Action

The mechanism by which melatonin brings about its action is proposed to be through a number of different pathways.<sup>8</sup>

1. Binding to Melatonin, G-protein coupled receptors MT<sub>1</sub> and MT<sub>2</sub> as well as human quinone reductase 2 (MT<sub>3</sub> receptor)
2. Binding to intracellular proteins: tubulin, calmodulin and calreticulin
3. Binding to the retinoid –related orphan nuclear hormone receptor family (RZR/ROR)
4. Antioxidant effects

The role of melatonin in the sleep wake cycle is thought to be due to its action on the MT<sub>1</sub> and MT<sub>2</sub> receptors in the suprachiasmatic nucleus (SCN) of the hypothalamus.<sup>9</sup> This proposed mechanism is supported by the efficacy of ramelteon, a MT<sub>1</sub> and MT<sub>2</sub> melatonergic receptor agonist that has specific effects on MT<sub>1</sub> and MT<sub>2</sub> receptors in the SCN, to promote sleep.<sup>9</sup>

The binding of melatonin to intracellular proteins and the antagonism of Ca<sup>2+</sup> binding to calmodulin are likely to be responsible for some of the physiological effects of melatonin, although these effects are yet to be isolated.<sup>4</sup>

It is thought that melatonin also produces many effects by binding to RZR/ROR receptors. It has been shown to enhance interleukin-2 and interleukin-6 production and have oncostatic and anti-proliferative effects.<sup>4</sup>

## Pharmacokinetics

The only licensed melatonin product in Australia is Circadin® which is a modified release tablet. The pharmacokinetics of Circadin® have not been well reported. Assessment of other oral formulations suggest that the absolute bioavailability of melatonin is in the order of 15% (though it is highly variable due to first pass metabolism).<sup>10</sup>

The pharmacokinetics of melatonin between doses of 2 and 8 milligrams have shown to be linear in formulations other than Circadin®.<sup>11</sup> Melatonin pharmacokinetics are affected by age, caffeine intake, smoking status, oral contraception, diet and Cytochrome P450 (CYP) inhibitors (e.g. fluvoxamine).<sup>12</sup> It is primarily metabolised to inactive metabolites by the CYP1A1, CYP1A2 enzymes and potentially CYP2C9. The terminal half-life (t<sub>1/2</sub>) of melatonin is 3.5 to 4 hours. Elimination of the drug occurs largely through renal excretion of metabolites.<sup>11</sup>

There are a number of formulations of melatonin, most of which are available to the Australian population via the internet. These formulations range in excipients, quality of formulation and dose (0.3mg-8mg). In a systematic review that included 22 studies, doses ranged from 0.3mg to 100mg and the maximum plasma concentrations (C<sub>max</sub>) ranged from 72 to 163 pg/ml. The time to maximum concentration (T<sub>max</sub>) ranged between 15 and 210 minutes. The overall bioavailability of melatonin preparations ranged between 9 and 33%. The presence of food delays the absorption of melatonin increasing average T<sub>max</sub> from 1.6 hours to 2.6 hours. Advancing age has also been shown to affect the absorption of oral melatonin. Clinical data shows a reduction in oral absorption by up to 50% in elderly patients. The variations in pharmacokinetics due to differing formulations and dosing across different clinical trials, make it difficult to compare results from trials.

## Administration

Melatonin, in the Circaden® formulation, is recommended to be given 1-2 hours before bedtime.<sup>10</sup>

When treating delayed sleep phase disorder (estimated to be present in 10% of patients with chronic insomnia<sup>13</sup>), the use of melatonin should be aimed at advancing the circadian clock. It has been reported that the largest advancement has been seen when melatonin is given so that the peak in plasma levels occurs 5 hours prior to the DLMO (the “dim light melatonin onset”).<sup>13</sup> The DLMO is normally between 19:30 and 21:30 in adults suggesting dosage of melatonin should be timed so that the peak is attained between 14:30 and 16:30.

As light can have a significant effect on melatonin production, it is advisable for patients using melatonin for sleep to reduce exposure of light, particularly blue light in the evenings.<sup>14</sup>

## Prescribing Patterns

The TGA licensed indication is “Monotherapy for the short term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over”<sup>11</sup> and the WADEP recommendation is “For use under the direction of a Neurologist for refractory insomnia in patients with neurological co-morbidity where melatonin was initiated in the Child and Adolescent Health Service (CAHS)” for a limited period of six months.<sup>15</sup> So it would be logical to assume the majority of patients prescribed melatonin were either under the age of 18.5 or older than 55 years.

Of the patients prescribed melatonin only 34.4% met the TGA or WADEP restrictions (just by age with no regard for indication). This data shows that in the majority of cases neither the TGA nor the WADEP recommendations are followed.

## Evidence

Published studies expressed conflicting opinions regarding the effectiveness of melatonin for treating sleep disorders. There seems to be some narrowing of opinion in

recent large meta-analyses although these studies were limited by the lack of consistency in melatonin trials when it came to formulation and dosing schedule.<sup>6, 16-19</sup> A summary of the conclusions made for each condition can be found in Table 1.

### Evidence for melatonin in secondary sleep disorders and sleep disorders accompanying sleep restriction:

Secondary sleep disorders were characterised as sleeping disorders that are associated with a medical condition, substance use or comorbid psychological condition.<sup>19</sup>

In 2006, a large meta-analysis showed melatonin had no effect on the time it took to get to sleep in people with secondary sleep disorders or people who had sleep disorders with accompanying sleep restriction, but they concluded melatonin is safe in short-term use (under three months). The authors concluded that there is no evidence melatonin is effective in treating either secondary sleep disorders or sleep disorders accompanying sleep restriction such as jet lag and shift work disorder.<sup>19</sup>

### Evidence for melatonin in primary sleep disorders:

Primary sleep disorders were characterised as sleeping disorders that are not associated with a medical condition, substance use or comorbid psychological condition.<sup>6</sup>

A meta-analysis done in 2005 pooling 17 studies with a combined 284 subjects, reported primary outcomes of sleep onset latency (time it took to get to sleep), sleep efficiency (ratio of total sleep time to time in bed) and total sleep duration. Sleep onset latency time was reduced significantly by 4.0 minutes (95% CI of 2.5, 5.4 minutes). Sleep efficiency was increased by 2.2% (95% CI of 0.2, 4.2%). Sleep duration was increased significantly by 12.8 minutes (95%CI 2.9, 22.8). This meta-analysis also performed an evidence of heterogeneity test on their primary outcomes. The evidence of heterogeneity was significant solely for the

outcome measure of sleep onset latency, which is indicative of widely varying results. The authors concluded that exogenous melatonin may have some role in the treatment of insomnia, especially in aged individuals with night time melatonin deficiency.<sup>18</sup>

Another 2005 meta-analysis investigated the effectiveness of melatonin in primary sleep disorders. This study produced different results. Sleep onset latency was significantly reduced by 11.7 minutes (CI 18.2, 5.2 minutes) but sleep efficiency was not significantly improved. This study also showed large heterogeneity between results. The authors concluded that there is no evidence that melatonin is effective in managing primary sleep disorders but qualified their negative finding by calling for large additional randomised control trials before any firm conclusions were made.<sup>16</sup>

A more recent (2013) meta-analysis investigating the efficacy of melatonin in primary sleep disorders showed significant results. The meta-analysis included 19 studies with a total population of 1683 subjects. The two primary outcomes were sleep onset latency which showed a reduction of 7.06 minutes (95% CI 4.37, 9.75 minutes  $p < 0.001$ ) and sleep duration which was improved by 8.25 minutes (95% CI. 1.74, 14.75 minutes  $p = 0.013$ ). It was also reported that melatonin dose and the duration of melatonin use caused no significant effects on sleep quality. It was concluded that melatonin appears to have a modest effect on sleep that does not dissipate with continued melatonin use and that melatonin may play a role in treatment of insomnia given its relatively benign side-effect profile compared to other agents.<sup>6</sup>

### **Evidence for melatonin in elderly patients with melatonin deficiency related sleep disorder**

A trial including 354 patients aged over 55 years showed a reduction in baseline adjusted sleep onset latency of 8.8 minutes (95% CI 1.0, 16.7 minutes) and no significant difference in overall sleep time. The study did show small significant improvements in

quality of life measures and concluded that melatonin reduced sleep onset latency to the same extent as some frequently used medications for sleep.<sup>20</sup>

### **Evidence for melatonin in Delayed Sleep Phase Disorder:**

Delayed sleep phase disorder is characterised by dysfunction of the body's natural circadian sleep-wake cycle. It manifests as sleeping and waking outside of societal norms.<sup>21</sup>

A meta-analysis investigating the effects of melatonin in delayed sleep phase disorder concluded that melatonin was effective in advancing sleep-wake rhythm. It reported a reduction in sleep onset latency of 23.27 minutes (95% CI: 4.83, 41.72 minutes) and an improved sleep time of an overall of 16.23 minutes although there was extreme variation in the results.<sup>21</sup>

One possible reason for the variation is that circadian timing of the melatonin dose was not always taken into account.<sup>13</sup>

### **Evidence for melatonin in individuals with intellectual disability related sleep disorders**

A meta-analysis looking into the effectiveness of melatonin in the treatment of sleep problems in individuals with intellectual disability showed significant changes in sleep onset latency, total sleep time and the number of wakes per night. Melatonin reduced sleep onset latency by a mean of 34 minutes and increased total sleep time by 50 minutes. The authors also stated that it reduced wakes per night ( $p < 0.05$ ) but did not enumerate the reduction in number of wakes per night.

It was concluded that melatonin is a safe and effective treatment for sleep disorders in individuals with intellectual disability.<sup>22</sup>

### **Place in therapy**

Melatonin is licensed by the Therapeutics Good Administration (TGA) for short term (up to 3 weeks) treatment of primary insomnia in patients who are aged 55 or older.

Following review by the WA Drug Evaluation Panel (WADEP), melatonin was included in the state-wide formulary with a restricted listing. It is restricted to use under the direction of a Neurologist or Sleep Physician for refractory insomnia in patients with neurological co-morbidity where melatonin was initiated in the Child and Adolescent Health Service (CAHS). Supply is limited to a period of six months following the patient's transition from CAHS to an adult service.<sup>15</sup>

WADEP also considered melatonin for REM sleep behaviour disorder or circadian rhythm disorder but did not list melatonin on the formulary for these indications because of concerns about the strength of the evidence. This decision was made even though the Sleep Expert Advisory Group made a positive recommendation for inclusion of melatonin.

From the large pool of research that has been published investigating the effects of melatonin in sleep disorders (both primary and secondary) there seems to be very little clinical benefit outside of specific sleep disorders (Intellectual disability and delayed sleep phase disorder). Meta-analyses of literature for secondary sleep disorders resulted in no supporting evidence for the use of melatonin. Meta-analyses of previous studies in primary sleep disorders seemed to consistently show small but clinically insignificant changes in sleep onset latency and overall sleep time, among other outcomes. There does not appear to be supporting evidence for the prescription of melatonin outside of the WADEP recommendations. The cost incurred for off-label prescribing in 2016 at Graylands Hospital is estimated to be around \$4928, and this figure most likely a fraction of the amount people spend on melatonin in the community.

## Availability

The only TGA licensed melatonin product in Australia is Circadin® CR 2mg tablets. There are a large number of different formulations available over the internet including immediate and normal release tablets and even liquid formulations of melatonin.

**Table 1.** Summary of conclusions.

Sleep Disorder	Conclusions
Secondary Sleep Disorders	No evidence to support the use of melatonin in secondary sleep disorders or sleep disorders related to sleep restriction (shift work, jetlag).
Primary Sleep Disorders	Small statistically significant effect on sleep in primary sleep disorders that is clinically insignificant. Melatonin is not an appropriate treatment for the majority of primary sleep disorders give its cost.
<i>Delayed Sleep phase disorder</i>	There is small positive evidence for melatonin in children with delayed sleep phase disorder, but this positive relationship does not extend to adults.
<i>Sleep disorder related to intellectual disability</i>	Seems to be a safe and effective treatment in sleep disorders related to intellectual disability.
<i>Melatonin deficiency related sleep disorder (&gt;55 years)</i>	Small clinically insignificant effect on sleep that does not warrant the use of melatonin.


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