Introduction

Melatonin 2 mg prolonged-release (PR) tablets are licensed as monotherapy for short-term (≤ three weeks) treatment of primary insomnia in patients aged 55 or over. Melatonin is a hormone secreted by the pineal gland. Exogenous melatonin has been used to manipulate circadian rhythm and induce sleep. Melatonin-PR releases melatonin over an 8 to 10-hour period mimicking the physiological profile of endogenous melatonin.

Evidence

Two studies conducted with the PR formulation in the licensed patient population have been published. These are randomised, double-blind, placebo-controlled trials which evaluated the use of melatonin-PR 2 mg once daily, one to two hours before bedtime, in adults aged 55 or older with a diagnosis of primary insomnia. Whilst comparing melatonin with placebo is not ideal, the authors justified it due to the different timings of taking melatonin compared to hypnotics. The primary endpoint in the first study (n = 170), although not categorically stated in the paper was judged to be the efficacy of melatonin-PR on quality of sleep (QOS) and behaviour following wakefulness (BFW). Melatonin-PR statistically significantly improved QOS compared with placebo (-22.5 mm vs. -16.5 mm, p = 0.047) and BFW (-15.7 mm vs. -6.8 mm, p = 0.002).

Important trial flaws included the lack of baseline data on the respective patient groups and the authors did not state how many patients were initially assessed, but 82 and 88 were randomised to melatonin and placebo respectively, with 78 and 86 completing the study. It
would have been useful to know how many patients did not fit the strict exclusion criteria (which included patients with anxiety or depression, and those that had taken any medications that affected the central nervous system within the previous three months).

The second study (n = 334)\(^5\), was similarly designed to the previous one. Baseline characteristics were balanced between the two groups. Of the original 1,248 patients pre-screened, only 169 and 165 were admitted to the melatonin and placebo arms respectively. There were many exclusions in the trial, including any patients who had used antidepressants or anxiolytics in the previous three months. This may explain the small number of patients actually recruited. The primary endpoint was improvement in QOS and BFW. A responder rate was demonstrated of 26% for Melatonin-PR versus 15% for placebo (odds-ratio = 1.97, 95% confidence interval (CI) 1.14, 3.41, p = 0.014).\(^5\) Melatonin-PR also demonstrated benefit in several secondary outcomes including quality of sleep (-4.0 mm, p = 0.014), morning alertness (-3.0 mm, p = 0.038) and getting to sleep (-3.3 mm, p = 0.013), but not in awakening from sleep (-2.0 mm, p = 0.16).\(^5\)

Both of these trials showed efficacy of melatonin-PR in a 3-week treatment period. Longer term safety and efficacy up to 61 weeks have been measured in an open-label study.\(^2\) Both trials did not compare melatonin with more established medications, and considering this is a new class of drug, active comparators would have been an important consideration.

Comparative data are limited to very small, short-term studies assessing the effects of melatonin-PR in healthy volunteers who did not have primary insomnia, i.e. not the intended licensed population.\(^6,7,8\)

**Safety**

Safety and withdrawal effects of melatonin-PR in adults have been evaluated by pooling data from short- and long-term studies, including exploratory trials (n = 1,281).\(^2,4,5\) The most common adverse events were headache (5.3%), pharyngitis (4.8%), back pain (3.4%) and asthenia (3.3%), occurring with similar frequency in both the melatonin-PR and placebo groups during the three week study period.\(^2\) There was no evidence of withdrawal effects following treatment discontinuation, assessed by the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ).\(^4,9\) The company have to collate post marketing reports and routine pharmacovigilance activities as part of the risk management plan.\(^2\)

Psychomotor function and performance in healthy subjects up to fifteen hours after ingestion of melatonin-PR, benzodiazepine and non-benzodiazepine hypnotics and placebo, have been assessed in two very small studies (n = 23 \(^7\) and n = 16 \(^8\)). PR-melatonin was not associated with impairment of psychomotor functions, performance, memory recall or driving skills, unlike the comparator agents.\(^7,8\)

Melatonin is metabolised mainly by the cytochrome P450 pathway. Consequently, altered melatonin levels have been demonstrated with a range of enzyme inducers and inhibitors.\(^1\) Melatonin-PR is not recommended for patients with hepatic impairment.\(^1\)

**NHS Impact**

**Place in Therapy**

Primary insomnia (sleeplessness not attributable to an underlying psychological or physical condition or drug) occurs in 30% of cases of chronic insomnia.\(^10\)

The first step of management should incorporate advice on sleep hygiene and stimulus control. If this is unsuccessful, a short-course (up to two weeks) of pharmacological treatment may be indicated.\(^10\) National Institute for Health and Clinical Excellence (NICE) guidance states there is a lack of compelling evidence to distinguish between the available shorter acting hypnotics and the drug with the lowest acquisition cost should be prescribed. (This guidance was published in 2004 and therefore did not consider melatonin).\(^11\)

It is not known whether melatonin-PR offers any clinical advantage over conventional hypnotics for the treatment of primary insomnia. In small studies it has been shown to improve sleep quality and morning alertness and shorten sleep latency compared to placebo. It has not been shown to have effects on psychomotor or cognitive functions, performance or withdrawal.\(^2,7,8\)

Although melatonin appears to be well-tolerated in short-term studies, long-term safety has not been established. Advice should be given regarding sleep hygiene and stimulus control measures before hypnotic agents are prescribed.\(^10\)

**Appendix I: Table of Clinical Trials**

- **Risk Management Issues:** None identified
Melatonin

References


6. Paul MA et al. Melatonin and zopiclone as facilitators of early circadian sleep in operational air transport crews. Aviat Space Envir MD 2004;75:439-443 (CT)


Key Abs – Abstract, CT – controlled trial, G – guidance, R – review, RCT – randomised controlled trial, U – Unpublished

Key papers are highlighted in bold
# Appendix I – Table of key clinical trials evaluating melatonin in patients aged over 55 years with insomnia

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Trial Design</th>
<th>Trial Population</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Outcomes</th>
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| 4      | Multi-centre, randomised, double-blind, parallel group, placebo-controlled study | 170 primary insomnia patients aged ≥ 55 years. 82 and 88 patients were randomised to melatonin-PR or placebo; 78 and 86 patients completed the study respectively. | **Inclusion Criteria**  
- Aged 55 years or older  
- Diagnosis of primary insomnia for at least 1 month  
- Had consistent complaints on poor sleep quality by the end of the single-blind placebo run-in  

**Exclusion Criteria**  
- Breathing related sleep disorder  
- Circadian rhythm sleep disorder  
- Dyssomnia not otherwise specified  
- Sleep disorder due to general medical condition  
- Significant psychiatric or neurological disorders  
- Use of any medication that affects central nervous system or sleep/wake function within two weeks prior to first day of placebo run-in  
- Use of psychotropic treatments in the last 3 months before the study  
- History of severe psychiatric disorders, especially psychosis, anxiety and depression | **Primary Outcomes**  
The primary outcome was not clearly stated but was judged to be the efficacy of melatonin-PR on quality of sleep (QOS) and morning alertness (BFW) compared to placebo. No confidence intervals (CI) were quoted. Six patients discontinued treatment during the randomised stage of the trial.  

<table>
<thead>
<tr>
<th>Improvement from baseline</th>
<th>Placebo (n = 86)</th>
<th>Melatonin-PR (n = 78)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>QOS (mm)</td>
<td>-16.5</td>
<td>-22.5</td>
<td>0.047</td>
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<tr>
<td>BFW (mm)</td>
<td>-6.79</td>
<td>-15.67</td>
<td>0.002</td>
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**Secondary Outcomes**  
As before, secondary outcomes were not clearly stated. Sleep quality improved significantly in the treatment group by 0.43 units over placebo, (p = 0.003). There were no significant differences between the treatments for ease of getting to sleep and hangover on awakening from sleep. |
<table>
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<tr>
<th>Ref No</th>
<th>Trial Design</th>
<th>Trial Population</th>
<th>Inclusion/Exclusion Criteria</th>
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<tr>
<td>5</td>
<td>Double-blind, randomised, placebo-controlled, parallel group trial</td>
<td>334 patients aged between 55 and 80 years, suffering from primary insomnia. (354 were eligible for inclusion and were randomised, but 8 in the melatonin group and 12 in the placebo group were withdrawn during the treatment phase, and had no outcome data).</td>
<td><strong>Inclusion Criteria</strong>&lt;br&gt;☐ Aged between 55 and 80 years&lt;br&gt;☐ Diagnosis of primary insomnia&lt;br&gt;☐ Had consistent complaints about poor sleep quality by the end of the single-blind placebo run-in</td>
<td><strong>Primary Outcomes</strong>&lt;br&gt;Concomitant improvements of 10mm or more on Quality of sleep (QOS) and Behaviour following wakefulness (BFW) in the two treatment groups. &lt;br&gt;<strong>Inclusion Criteria</strong>&lt;br&gt;☐ Psychiatric disorders or a history of, including depression, anxiety and dementia&lt;br&gt;☐ Use of psychotropic treatments in the 3 months prior to study&lt;br&gt;☐ Positive drug screen on visit 2 for benzodiazepines or morphine derivatives&lt;br&gt;☐ Use of benzodiazepine or non-benzodiazepine hypnotics within previous 2 weeks or any psychoactive treatment within previous 3 months&lt;br&gt;☐ Sleep disorders associated with a psychiatric disorder&lt;br&gt;☐ Sleep disorders secondary to another medical condition&lt;br&gt;☐ Use of prohibited concomitant medication or excessive alcohol&lt;br&gt;☐ Any chronic medical condition that was likely to cause the sleep problem or might interfere with conduct of study&lt;br&gt;☐ Lifestyle likely to interfere with sleep patterns</td>
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<td>Odds Ratio = 1.97 (95%CI 1.14, 3.41)</td>
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