

## **Melatonin for insomnia**

**DTB 2009;47:74-77**

*'But doctor, all my friends in the States use Melatonin...so it must be safe!'*

*I was tempted to reply 'Oh well, if all your friends use, that's OK, I'll do you a prescription now...' But I resisted the urge, despite the fact she was my last patient on Friday evening, the sun was shining and I was looking forward to supper and a glass of wine in the garden. She wanted melatonin to help with her insomnia, experienced on overnight hotel stays related to her work. When I arrived home that evening I found this Drugs and Therapeutics Bulletin review on melatonin lying on my door mat. I sent her a copy in the post and she was intrigued to read it – with the evidence far more eloquently expressed than I had managed in the consultation.*

**If you think melatonin isn't a big issue, remember this...last year 94 000 scripts were issued by GPs for melatonin. This cost the NHS £6.5 million!**

- Melatonin is available as a standard release preparation or as a slow release preparation (Circadian - 2mg).
- The slow release preparation is licensed for use in the UK.
- It is licensed only for short term use in those aged 55 or over with insomnia characterised by poor quality of sleep. It should be used for periods of 3 weeks or less.

*A bit of physiology...*

*Melatonin is a hormone produced in the pineal gland in the brain, which has an important role in regulating circadian rhythms, particularly the sleep-wake cycle. It is released after the onset of darkness and secretion peaks between 2-4am and then levels start to fall.*

### **What is the evidence for melatonin for insomnia?**

- Much of the data considered in DTB is not helpful to us as it does not include Circadian – the preparation licensed for use in the UK.
- A small meta-analysis of 279 patients included very heterogenous data with different doses and drug preparations. It showed **no clinically significant benefit of melatonin.**

### **Evidence relating to Circadian (slow release melatonin, 2mg)**

- There are only two published trials RCT comparing Circadian with placebo.
- There are no published trials compare it with any drugs currently used for sleep, although one such trial has been done but the drug company has not published it in a peer reviewed journal (I wonder why?!).
- Both placebo controlled trials were done on primary care populations, which is good, but both included only people over 55 (why?!), and both were small (<350) and included a methodology that would exaggerate the effect of the drug over the placebo. The trials do not relate to jet lag, just ordinary insomnia without underlying causes.

**In summary the evidence is poor!**

*Here is the story of how the drug got its licence...*

In 2002 the European Medicines Agency (EMA) advised that new studies of efficacy needed to be done, before a licence would be granted. They suggested that a 3 armed trial would best answer the question as to whether Circadian was effective. This would involve a Circadian arm, a placebo arm and a third 'active control' arm where a drug currently used for sleep, such as zopiclone was used.

However the manufacturers did not follow this advice and performed an RCT comparing Circadian with zolpidem 10mg, with no placebo arm. This has never been published, but was submitted to the EMEA as part of the licensing process!

The licence was granted but the EMEA commented 'the product is efficacious with a small effect size and in a relatively small fraction of patients' ie. it works a bit on a few patients! However, because it was not harmful a licence was granted.

#### ***The bottom line?***

- ***All the trials of Circadian are small but do show a marginal benefit for a small group of people. However the published trials of Circadian contain methodological flaws that exaggerate the benefit of the drug over placebo.***
- ***To paraphrase the licensing authority 'it works a but on a few patients!'***
- ***The good news? It doesn't seem to be harmful.***

#### **Other things you ought to know about Circadian**

- **Circadian should be taken 1-2 hours before bedtime after a small amount of food.**
- **Side effects resulting in discontinuation were comparable with placebo in clinical trials (30-40% of people stop it).** Commonest side effects were headache, pharyngitis, back pain (?!) and weakness – these occurred in between 1 in 10 and 1 in 100 people. Rarer side effects were reported which were *probably* related to melatonin included restlessness, irritability, bad dreams, somnolence and insomnia(!), dry mouth, hyperhidrosis, constipation and weight gain. *(I am sure if I had known these side effects when I saw my patient, a simple listing of common side effects would have been enough to put her off!)*
- **Dependency:** there was no evidence of dependency over the 3 weeks of the trials.
- **The licence is only for 3w use at a time, in those aged ≥55y.**  
It is not licensed (and should not be used) in those <18y due to lack of safety data.  
In the UK melatonin is classed as a drug – in the US it is considered a food supplement!

- **Safety and interactions**

Use cautiously in renal impairment (reduced excretion).

Not recommended in pregnancy or breast feeding.

Potential interactions: fluvoxamine (and presumably therefore other SSRIs) cimetidine, oestrogen, quinolones increase the concentration of melatonin through enzyme induction. Smoking, carbamazepine and rifampicin reduce the plasma levels of melatonin.

**Melatonin can cause drowsiness, so caution with driving and heavy machinery.**

#### **The DTB concluded that:**

- **The limited and unconvincing evidence, in particular lack of evidence that it is effective when compared with currently available preparations for insomnia, and it should not be recommended.**

### **What about melatonin for jet lag?**

**Cochrane 2002;2008 CD001520**

A Cochrane review of the literature (10 placebo controlled trials) showed that, for jet lag:

- Melatonin is effective if taken before going to bed at around the 10pm-midnight **local time** (ie. when it is 10pm- midnight at your arrival destination) (NNT 2).
- Used incorrectly (ie. not taken around bedtime local time) it will increase jet lag!
- Benefits were greatest in those crossing  $\geq 5$  time zones, especially going eastward.

#### **What dose?**

- 0.5-5mg doses were all effective. The higher dose resulted in falling asleep quicker. Doses  $>5$ mg were no more effective than 5mg.
- Slow release melatonin (Circadin) was relatively **ineffective** suggesting that a surge in melatonin may be important in jet lag.
- There were no significant side effects in the trials however, there are case reports of interactions with warfarin and it should not be used in those with epilepsy.

#### *CPD Ideas:*

*See the GP Update Revalidation Action Plans sent with this update update: designed to help you record your learning ready for your next appraisal and your revalidation folder.*

### **Take home messages: Melatonin for insomnia**

- **For non-travel related insomnia, the evidence for melatonin is weak – in a few people it has a small benefit compared with placebo. There are no published trials showing effect compared with drugs currently used for insomnia.**
- **Time to stop prescribing it for insomnia unrelated to jetlag?**
- **The evidence for use in jet lag is good in those crossing more than 5 time zones, especially in an eastward direction, but only if taken correctly (at bedtime local time). Do not use slow release preparations in this settling (and remember that this would need to be a private script).**

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