Melatonin September 2017

Prescribing...

- Prescribing of unlicensed melatonin / biomelatonin products contribute to a large spend in the Bailiwick.
- Many are for children with ADHD and similar disorders.
- Insomnia and sleep disturbances are common in this group and are a source of great distress in families.
- This bulletin discusses the costs involved, the evidence to support the use of melatonin, what the options are and makes suggestions for prescribers to consider.

What are the costs?

The cost of prescribing of all unlicensed melatonin / biomelatonin products and the licensed product Circadin® was approximately £14,000 in June 2017, equating to an annual spend of £168,000. There were 65 prescriptions for Circadin® 2mg MR tablets at a cost of £1,714, or £26 per item. There were 291 prescriptions for unlicensed melatonin and biomelatonin products costing £13,040 per month or £44.81 per item. There is significant variability in prices. In June 2017 the lowest priced item was £3.75 and the highest £248.07. The only unlicensed melatonin product with a set price at present is Melatonin 5 mg / 5ml oral solution which costs £49.95 for a 200ml bottle.

There is at least £50,000 of savings to be made each year if better value standard-priced formulations and products are prescribed where feasible.

The Evidence

1. **Sleep disorders in children and young people with attention deficit hyperactivity disorder (ADHD)**

The BNF-c states that melatonin is unlicensed for use in children. NICE published an evidence summary on the use of melatonin in children and young people with attention deficit hyperactivity disorders with sleep disorders in January 2013. The key points from the evidence summary are as follows

- No high-quality studies were identified that provided evidence for the efficacy of prolonged-release melatonin tablets (licensed in the UK) used off-label in children with sleep disorders and ADHD.
- Limited evidence for unlicensed melatonin products was identified from two small (n=105 and n=19) short term randomised controlled trials (RCTs) and one small, long term follow-up study (n=94).
- The evidence suggests that unlicensed melatonin products, taken for ten days to four weeks, may reduce sleep onset latency (the time taken for a child to go to sleep) in children with sleep onset insomnia and ADHD by approximately 20 minutes.
- In addition, melatonin may improve average sleep duration by 15 to 20 minutes. However, there are limitations to these small studies, and longer term efficacy is unclear.
- These RCTs included stimulant and non-stimulant treated children aged six to 14 years with ADHD and suffering from sleep onset insomnia. The studies used daily doses of between 3 and 6mg of unlicensed melatonin described as 'fast-release' or 'short-acting', administered shortly before bedtime.
- Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.
- Unlicensed melatonin used in the RCTs appeared well tolerated in the short to medium term with only transient mild to moderate adverse effects reported.

The evidence to support the use of melatonin in children and young people with ADHD therefore is very limited, but it is of course widely used and other treatment options are limited.

2. **Jet lag and shift work**

A Cochrane systematic review on melatonin for the prevention and treatment of jet lag concluded that melatonin is "remarkably effective" in preventing or reducing jet lag, and occasional short term use appears to be safe. The Cochrane review recommends it for adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. In the USA melatonin is considered a health supplement and promoted for improving sleep and for use in jet lag as part of self-care. As melatonin is not available as a health supplement in the UK, it would be inappropriate to recommend it to prevent jet lag.

A Clinical Knowledge Summary (CKS) on management of jet lag and shift work states that the American Academy of Sleep Medicine (AASM) reviewed the literature on shift work disorders which included two high quality randomized controlled trials (both simulation studies), and five field studies (one high, three moderate, one low quality) and concluded that melatonin improved sleep in some of the workers but did not increase night time alertness. Melatonin is also not licensed for use in shift work disorders in the UK, and CKS considers that there is "insufficient evidence" to recommend its use.

3. Insomnia

The Midlands Therapeutic Review and Advisory Committee (MTRAC) summarised the evidence for efficacy of prolonged release (PR) melatonin for treatment of primary insomnia in October 2013. The evidence is based on three randomised, placebo-controlled trials with highly subjective outcomes. Two of the trials showed that PR-melatonin shortened sleep latency times by 9 and 15 minutes respectively compared to placebo. None of the trials showed a significant effect on total sleep time. There were no comparisons with other treatments for insomnia, giving PR-melatonin a low place in therapy.

A CKS also reviewed the evidence for melatonin use for long-term (>four weeks) insomnia. The CKS suggests there is some evidence to suggest that melatonin may improve some sleep-related parameters in older people with insomnia. When used at the dose and duration of PR melatonin licensed for use in the UK, three randomized controlled trials demonstrated an improvement in quality of sleep and morning alertness, although the clinical significance of the improvement is unclear. In two of the studies, a small improvement in sleep-onset latency (the time taken to get to sleep) was also noted with melatonin. CKS identified no studies comparing PR melatonin with hypnotics for the treatment of insomnia.

Overall, there is limited evidence for use of melatonin. Prescribing use to prevent jet lag is inappropriate, in other clinical conditions review the necessity of melatonin and ensure all other options have been exhausted. If the patient is started on melatonin, review the continued need for treatment at regular intervals.

Licensed vs Unlicensed

Circadin® is the only licensed melatonin preparation available in the UK. It is licensed for the short term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over. Flynn Pharma, the manufacturers of Circadin®, has submitted a licence extension for sleep disorders in children, which was expected in 2016, but did not materialise. The manufacturers of Circadin® do not recommend that patients break or crush Circadin® as this may impact the intended release characteristics. However, a number of patients experience difficulties in swallowing and tablet breaking or sub-division and crushing are commonly used methods to aid dosing in practice. Unlicensed liquid preparations of melatonin are also used.

If the tablet is crushed, the manufacturers have advised that the release characteristics are approximate to an immediate release dose form. From a practical standpoint therefore, wherever possible, the patient should be encouraged to swallow the tablet whole. Where this is not possible, halving or quartering the tablet, to aid administration might be expected to have some, but limited impact on its intended characteristics. The in-vitro release from a crushed or powdered tablet is expected to provide an immediate release profile similar to that from an unlicensed immediate release tablet or (unlicensed) oral liquid and as such provides a viable alternative to other option. However, as Circadin® is a licensed product, its use outside of licence (in so far as the tablet is broken or crushed) should be considered preferable to using an unlicensed presentation of melatonin.

In view of the very high costs involved, prescribers are earnestly requested to review patients in the community prescribed melatonin immediate release tablets, capsules or liquid as follows:

- If the patient has swallowing difficulties and/or a rapid onset of effect is needed, consider crushing and dispersing Circadin®. As stated above, the manufacturers state that when the tablet is crushed it becomes immediate release and this is recommended by many primary care organisations in the UK.
- As a last resort e.g. for children or adults in whom the oral route is not feasible or available at all, Melatonin 5 mg / 5ml oral solution should be prescribed first line as its cost price is set.

References : Prescquipp Bulletin 108/ September 2015, EPACT data, Medicines.org , BNFC 2017, Drug Tariff September 2017

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