PrescQIPP Community Interest Company

Melatonin (SPOT-List)

Unlicensed melatonin products (tablets/capsules/oral solution) contribute to high spend in the NHS. The net ingredient cost in England for all melatonin products is over £22.6 million. Of this about £8.9 million is for the licensed product Circadin®, £11.9 million is for the unlicenced special order products (both Drug Tariff and non Drug Tariff) and £1.8 million is for unlicenced supplements (ePACT April to June 2015).

QIPP projects in this area are aimed at reviewing the continued need for melatonin treatment and (if there is a continued need) prescribing licenced products before an unlicenced medicine as appropriate.

Recommendations

- Non-drug measures such as good sleep hygiene should be considered before a sleep aid such as melatonin.
- Melatonin has limited clinical evidence to support its use. If melatonin is prescribed, a 'special' is often required so it is not a cost effective treatment choice.
- If a sleep aid is needed, consider if melatonin is an appropriate choice of drug, and for what condition it is being used.
- When initiating treatment with melatonin ensure there is ongoing monitoring of the patient, review if there is clinical benefit and discontinue treatment in the absence of any benefit.
- If melatonin is required, consider the off label use of Circadin® as the first line treatment option, under a shared care agreement with the specialist.
- Develop a local shared care guideline (template available at http://www.prescqipp.info/resources/viewcategory/391-melatonin-spot-list). Specialists should be involved in the development of this local guideline.
- Agree an appropriate treatment dose (or limited range of doses) to prevent confusion/variation if doses are being prescribed and transferred out of secondary care.
- If patient has swallowing difficulties, consider crushing and dispersing Circadin® or consider the Drug Tariff melatonin oral solution (unlicensed medicine).
- Melatonin as a liquid formulation should be used as a last resort. If a liquid formulation is required, prescribe the oral solution as a cost-effective alternative to the oral suspension.
- Review treatment regularly. Ideally the maximum treatment period should be two months.

Background

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep. There is only one form of melatonin (Circadin® 2mg prolonged-release tablets) currently licensed in the UK for the short term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over. Its use outside of this indication, including use in children and young people under 18 years, is 'off label'.[1] It is used for sleep onset insomnia, delayed sleep phase syndrome, sleep disorders in children and young people with attention deficit hyperactivity disorder (ADHD), jet-lag and other sleep related disorders.

The Children's BNF states that melatonin is not licensed for use in children. The recommended dose for sleep onset insomnia and delayed sleep phase syndrome for children aged one month to 18 years is 2–3mg daily before bedtime initially, increased if necessary after one to two weeks to 4–6mg daily before bedtime; max 10mg daily.[2]

Evidence

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

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 are:[1]

- 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.

In summary

The evidence to support the use of melatonin in children and young people with ADHD is very limited.

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.[3] 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 or prescribe 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.[4]

Melatonin is not licensed for use in shift work disorders in the UK, and CKS considers that there is insufficient evidence to recommend its use.[4]

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 nine 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.[5]

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.[6]

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 versus unlicensed

Circadin® is the only licensed melatonin preparation available in the UK, licensed for the short term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over.[1] Flynn Pharma, the manufacturers of Circadin®, have submitted a licence extension for sleep disorders in children, which is expected in 2016. It is expected that it will be secondary care initiated, and then continued in primary care.[7]

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 widely used.[8]

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 either of these options. However, as Circadin® is a licensed product, its use outside of licence (in so far as the tablet is broken or crushed) is considered preferable to using an unlicensed presentation of melatonin.[8] The clinical effect of this is not known.

There is an MHRA licensed controlled release melatonin tablet available in the UK, however it is recognised that unlicensed immediate release products, liquids and capsule preparations may be needed for the special needs of individual patients for whom the UK licensed product is unsuitable. There is at least one pharmaceutical immediate release product available within Europe, however, other unlicensed melatonin products are frequently notified for import. These products may be classified as supplements, not pharmaceuticals in their country of origin and may not be made under pharmaceutical good manufacturing practices. They should therefore only be used as a last resort. Importers must ensure customers are advised accordingly.[9]

Table 1 on page 4 on the following page show the varying licensing statuses of different presentations of melatonin and which products are most commonly prescribed.

Table 1: Licensing status of melatonin

Presentation and use	Licensing
Circadin® for monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over	Licensed use of Circadin®
Circadin® use for a diagnosis outside its licensed indication	Unlicensed use of Circadin®
Circadin® used in patients under 55 years	Off-label use of Circadin®
Circadin ® tablets crushed	Off label use of Circadin®
Circadin® given at dose greater than 2mg	Off-label use of Circadin®
Melatonin standard release tablets/capsules	Unlicensed
Melatonin PR / modified release tablets/capsules with exception of 2mg	Unlicensed
Melatonin oral solution / liquid	Unlicensed

Costs and savings

The annual spend in England for melatonin products is over £22.6 million of which approximately £8.9 million is for Circadin®, £11.9 million is for the unlicenced special order products (both Drug Tariff and non Drug Tariff) and £1.8 million is for unlicenced supplements (EPACT April to June 2015). A 50% reduction in all melatonin prescribing (reviewing treatment and discontinuing therapy that is no longer appropriate/using non drug measures first line) **could release savings of over £11.3 million per year in England. This equates to £19,801 per 100,000 patients.**

Where treatment is appropriate, a switch to unlicenced or off label use of the licenced product Circadin will also release significant savings. Table 2 below highlights the top five liquid preparations of melatonin prescribed and the proportion of savings which can be achieved by switching to an equivalent dose of tablets.

Table 2: The top five most commonly prescribed melatonin products in England

Top five commonly prescribed melatonin products	Total items (Jul 14-Sep 14)	Total actual cost (Jul 14-Sep 14)	Average cost per item (Jul 14-Sep 14)	Circadin® average cost/ month (for same dose - half tablets may be used)	Potential saving per month (assuming one item per month for unlicenced preparation)	% Saving if using Circadin® instead of unlicensed medicine
Melatonin capsule 3mg	8312	£716,748	£86.23	£63.28	£22.95	27%
Melatonin capsule 2mg	8016	£622,726	£77.69	£62.39	£15.30	20%
Melatonin tablet 3mg	3436	£274,895	£80.00	£57.05	£22.95	29%
Melatonin capsule 5mg	3067	£220,136	£71.78	£33.53	£38.25	53%
Melatonin oral solution 5mg/5ml	8095	£774,499	£95.68	£70.03*	£25.65	27%

*Assuming a 5mg dose, total of 100ml volume

The data above is based on switching like for like dosing. In practice, it is important to review the continued need and the dose being prescribed. Ideally only two months treatment should be prescribed as a maximum. It is important to discontinue any ineffective treatment.

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Additional PrescQIPP resources

 Data pack  Template

Available here: http://www.prescqipp.info/resources/viewcategory/391-melatonin-spot-list

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Contact help@prescqipp.info with any queries or comments related to the content of this document.

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