

Guidelines for the use of Melatonin

Recommendation:

The UK licensed product for the short-term monotherapy of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over is Circadin®.¹

In Worcestershire, melatonin is recommended to aid sleep in the following circumstances:

- Treatment of children and adults with neurological and/or behavioural problems, including Attention Deficit Hyperactivity Disorder (ADHD) and autism.
- Treatment of older adults with dementia where alternative hypnotics have failed.
- Critical Care where use of first line hypnotics has failed. As part of the sleep Electroencephalography (EEG) procedure at Worcestershire Trusts.

Aim

These guidelines are intended to clarify the therapeutic place of melatonin in Worcestershire and support the prescribing of this product across the county.

Background

Melatonin is a naturally occurring hormone that is used as an effective sleep-initiator. Indications include conditions associated with impaired melatonin secretion, other sleep problems in which sleep-initiation is the main clinical objective, and to facilitate sleep as an adjunct to EEG investigations.

In Worcestershire Acute Hospitals NHS Trust, melatonin is used in ITU patients for direct management of sleep disturbances and extends to critically ill patients experiencing sleep disruption caused by altered diurnal rhythm from sedative use, lack of natural daylight/persistent artificial light etc. It is also used as a diagnostic tool in paediatric sleep studies. The melatonin sleep EEG forms part of an assessment process in children to help identify abnormal brain activity.

Advantages of melatonin over other hypnotic agents include:

- lack of hangover effect.
- no loss of effect or risk of tolerance with repeated dosing.
- no physical dependence (that being a state resulting from chronic use of a drug that has produced tolerance and where negative physical symptoms of withdrawal result from abrupt discontinuation or dosage reduction).
- low prevalence of unwanted effects.

Prescribing should be limited to those people where sleep problems adversely affect quality of life and where other methods of management are ineffective or impractical.

Long-term effects on endocrine systems and the long term consequences of exogenous melatonin administration are unknown.

The Children's BNF states that clinical experience suggests that '*melatonin may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, ADHD, autism and learning difficulties*'.² Its use for sleep difficulties is also supported by the National Institute for Health and Care Excellence (NICE) in the Clinical Guideline 53 on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis in adults and children.³ The NICE Evidence Summary for unlicensed or off-label medicine relating to melatonin use in children reports that there are 'no high-quality studies' to provide evidence for efficacy of the UK-licensed prolonged release product used off-label in children with sleep disorders or ADHD, but there is limited evidence for unlicensed products.⁴

Need for Treatment

Some people with learning disability have a genetic cause for their disability that also predisposes to sleep abnormalities (e.g. Smith-Magenis syndrome, Prader-Willi syndrome, Angelman syndrome and mucopolysaccharidoses). Others may have co-morbid conditions that are associated with sleep-wake cycle disruption, or have to be treated with medicine that can impair sleep (e.g. autistic spectrum disorders, overactive disorders associated with stereotyped movements and mental retardation, ADHD and the use of stimulant medicines). Some disorders (including Smith-Magenis syndrome, Rett syndrome and autistic disorders in some individuals) are associated with abnormalities in melatonin secretion. Some other mental health conditions are associated with sleep disorders, including depression, anxiety and dementia.

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Children and adults with developmental disabilities are predisposed to chronic sleep-wake cycle disturbances. Conditions such as visual or hearing impairment, autism and central nervous system disorders impair the ability to perceive and interpret cues for synchronising sleep with the environment. Such problems are often persistent and include settling difficulties and night-time waking. The literature on sleep problems in adults with learning disability is limited, but indicates a prevalence of around 15%.⁵

Sleep disturbance in children with neurological, neurodevelopmental, psychiatric and behavioural disorders is common. Disturbance of sleep pattern can have major implications for the child's development and daytime behaviour and can be very stressful for parents/carers. Disturbance includes delayed sleep induction, frequent waking, day/night reversal and early waking.

Age related physiological changes in melatonin production can lead to primary insomnia.

Circadin[®] is licensed in the UK for the treatment of primary insomnia in patients 55 years or older and limited to a fixed dose of 2mg daily for up to 13 weeks.¹

Management of Poor Sleep

General

Physiological issues such as pain and discomfort should be managed as appropriate.

The primary focus in the assessment and management of sleep disorders is usually on environmental factors and ensuring basic sleep-hygiene advice is followed. This advice includes:

- Avoid caffeine-containing drinks in the hours approaching retirement to bed.
- Avoid strenuous physical activity or exercise in the evenings/before bed.
- Avoid physical or mental arousal and excitement before bed-time.
- Keep the bed for sleeping! Reading, working, watching television in bed (etc.) stimulates the brain rather than preparing the mind for sleep.
- Avoid sources of distraction in the bedroom.
- Avoid extremes of temperature.
- Reduce light levels.

Consider the use of a sleep diary and sleep information and advice sheets prior to the use of any medicine. Psychological strategies such as relaxation training and the provision of individually tailored relaxation tapes may be used in adults.

Non-pharmacological strategies such as sleep hygiene techniques may have limited application where a patient's cognition is impaired, but these should still be explored first.

Children

Children presenting with sleep disturbance must have a careful clinical assessment including details of the sleep disturbance, the sleeping environment and the approach of parents and carers to the sleep difficulties. Consider other causes for poor sleep, including nocturnal seizures, sleep apnoea, mood disorders, pain, child abuse, depression and ADHD.

Children and those with learning disabilities may require additional support from a community nurse or psychologist to assist in assessment and management.

Children with neuropsychiatric disorders may have a lower response rate to behavioural therapy.

Mental Health and Older Adults²

Whilst attention to sleep hygiene processes and identification and treatment of co-morbid conditions remains paramount there is evidence to show that melatonin can improve the agitated and unsettled time that frequently occurs later in the day – commonly referred to as 'sundowning'. Prescription hypnotics within license remain first line pharmacology but melatonin has been found to be both safe and effective in doses of up to 10mg daily. Benefit is usually reached by 6mg daily. As with use in other patient groups there appears to be little early morning unwanted sleepiness, and tolerance and dependence with chronic dosing is not apparent.⁶

Melatonin

Unlicensed and Off-label Use

The Medicines and Healthcare Products Regulatory Authority (MHRA) recognises that melatonin use spans a wider remit than the licensed indication for Circadin[®] with regard to client groups and to formulation. Appendix 1 provides information on alternative products and formulations of melatonin that are available to meet the clinical requirements of individuals, where Circadin[®] is not considered appropriate.

For a given clinical indication, where a product is licensed for use in that indication it should be used in preference to any product that does not hold a product license for use in that indication. Where there is no licensed product for a specific clinical indication, use of an appropriate licensed product outside of its license ('off-label') is preferred to the use of a product that does not hold any product license.

For advice on the prescribing of unlicensed products or of licensed products out-side of their licensed indication please read the Medicines and Healthcare Products Regulatory Agency Drug Safety Update volume 2, issue 9: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990>.

Adverse effects

Melatonin is generally well tolerated. Reported adverse effects include: headache, dizziness, nausea and drowsiness. Further controlled trials are required to assess both short and long term side effects.

Continued monitoring of children during long term administration, particularly in the areas of growth and pubertal/sexual development is advised and is critical in those receiving melatonin for periods of a year or more.

Cautions in use

- Some reports suggest melatonin improves seizure control when used in patients with epilepsy; others indicate that it may worsen seizure control. When used in patients with epilepsy, it is important to closely monitor the effect of melatonin on seizure frequency.
- The manufacturer of Circadin[®] advises caution in patients with renal disorders and not to use melatonin in patients with liver disorders.
- The manufacturer of Circadin[®] advises melatonin should not be used in patients with autoimmune and some rare hereditary glucose tolerance disorders.
- Interactions with fluvoxamine, psoralen, cimetidine, quinolones and oestrogens are listed.
- Avoid alcohol and other sedatives.
- No evidence of safety in pregnancy or breastfeeding.
- Adults should be warned of the potential for melatonin to affect ability to drive or operate machinery.

Prescribing Points

General

Melatonin should be prescribed as a regular treatment taken up to 2 hours before bedtime.

It has no role as a daytime PRN (when required) sedative.

Children

- Melatonin for infants under 1 year of age should only be initiated by consultants.
- Initial starting dose: 2mg or 3mg given 30 – 60 minutes before bedtime.²
- Dose can be increased to 4 or 6mg after 7 -14 days.²
- Doses between 2mg and 6mg are generally effective.
- Maximum daily dose: 10mg.²
- Refer to specialist if doses above 10mg daily are considered necessary.
- If no effect has been experienced after 7-14 days then the medicine should be stopped.
- Melatonin should initially be prescribed for a 2-4 week period and be used in conjunction with behavioural advice.
- Some children may require a longer period of treatment and during this time regular medical review should focus on sleep hygiene and behavioural techniques.

- A proportion of children appear to benefit from longer term use over several years. These children need to be kept under regular (6 monthly) review.
- Tolerance does not appear to be a problem.
- It may be possible to withdraw children who have taken melatonin long term from treatment and a period of 3-4 weeks is suggested.

Adults

- Doses employed in older adults range from 2mg to 10mg daily.
- Benefit should be apparent soon after commencing treatment.
- Initial Dose: 2mg once daily.
- Titrate upwards (2mg increments) to a maximum of 10 mg daily, depending on observed response.
- If no effect has been experienced after 7-14 days then the medicine should be stopped.
- Melatonin should initially be prescribed for a 2-4 week period and be used in conjunction with behavioural advice.

Alternative licensed hypnotic agents (including short acting benzodiazepines) should be avoided in older adults with cognitive impairment as their use greatly increases the risk of falls, unwanted day time somnolence and they are associated with tolerance in continued use. Sedative antidepressants and most antipsychotics are not licensed for these circumstances and readily introduce additional unwanted effects such as postural hypotension and further cognitive decline.

Initiating Clinician

- Diagnose the condition and assess if the patient is suitable for treatment with melatonin.
- Provide patient/carer with relevant information on use, side-effects and need for monitoring of medicine.
- Explain any unlicensed uses.
- Provide treatment until stabilised including advice to patient /carer on sleep hygiene.
- If required, advise GP if the prescribing request is outside of license.
- Monitor response to treatment, side-effects etc.
- Agree to review patient's condition when requested by the patient's GP.
- Review the treatment six monthly, sending a written summary to the GP whenever the patient is reviewed.
- Advise discontinuation of medicine if no improvement is seen after a reasonable trial.
- Discontinue treatment at appropriate intervals under careful supervision – when condition stable, to assess the need to continue medicine.
- Provide any other advice or information for the GP if required, including rapid referral arrangements and contacts.

On-going Prescriber

- Ensure that he/she has the information and knowledge to understand the therapeutic issues relating to the patient's clinical condition.
- Prescribe the melatonin adjusting in line with specialist recommendations (continued prescribing is appropriate for patients attending specialist review)
- Report significant deviations from the prescribing pattern to the specialist.
- Monitor and record the therapy between specialist reviews as necessary and based on the individual.
- Refer to specialist if patient's condition deteriorates.
- Report any adverse events (e.g. to the specialist and/or MHRA).

Resources

- For further information on melatonin and other mental health medicines see www.choiceandmedicine.org.uk/worcestershire.
- A patient information leaflet (PIL) is available from Worcestershire Health and Care NHS Trust Department of Pharmacy and Medicines Management.

References

- 1) Flynn Pharma Ltd. Summary of Product Characteristics: Circadin[®]. Last updated 2/9/13. Available at: <http://www.medicines.org.uk/emc/medicine/25643/SPC/Circadin/> <accessed 3/12/13>
- 2) Paediatric Formulary Committee. British National Formulary for Children 2013-14. *BMJ Group, RPSGB and RCPCH Publications Ltd*, London; 2013.
- 3) NICE Clinical Guideline 53. August 2007. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). *National Institute for Health and Care Excellence*, London.
- 4) *National Institute for Health and Care Excellence*. Evidence Summary: Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin; Available at: <https://publications.nice.org.uk/esuom2-sleep-disorders-in-children-and-young-people-with-attention-deficit-hyperactivity-disorder-esuom2/> <accessed 5/11/13>.
- 5) Sajith, SJ, Clarke D. Melatonin and sleep disorders associated with intellectual disability: a clinical review. *Journal of Intellectual Disability Research*, 2007; 51(1): 2-13.
- 6) Olde Rikkert MG, Rikkaut M S. Melatonin in elderly patients with insomnia a systematic review. *Arch Gerontol Geriatr*, 2001 Dec; 34 (6): 491-7.

APPENDIX 1

Choice of Melatonin Product

To ensure the desired product is dispensed prescribers must be precise, e.g. prescribe as 'Circadin[®] MR 2mg tablets.'

Circadin[®] is the only melatonin product with a UK product license and is licensed for the short-term (up to 13 weeks) treatment of primary insomnia in patients over the age of 55. However, where there is no licensed product for a specific clinical indication, use of an appropriate licensed product outside of its license ('off-label') is preferred to the use of a product that does not hold any product license. The prescribed preparation should take into account the need for a sustained release preparation.

Melatonin 5mg/5ml oral solution and 5mg/5ml oral suspension are included in the Drug Tariff Part VIII B (arrangements for payment for Specials and Imported Unlicensed Medicines). This ensures consistent pricing/reimbursement of specials. However, prescribers should be aware that the solution is a cheaper option, but to obtain this product a prescription must state 'solution' rather than 'liquid'.

Formulation	Name	Manufacturer
Licensed product but unlicensed use Preferred choice unless clear reasons why this product would be unsuitable. NB: Circadin [®] can be crushed to aid administration (unlicensed and removes modified release function)		
2mg modified release tablet	Circadin [®]	Flynn Pharma Ltd Tel. 01438 727822 medinfo@flynnpharma.com
Licensed in country of origin but not UK, unlicensed use		
3mg tablet	Bio-melatonin	Pharma Nord (UK) Ltd Tel. 01670 519989
Unlicensed under Medicines Act, but with a manufacturer's licence		
1mg, 2mg, 3mg, 5mg, and 10mg capsules	Generic [must specify 'Penn product' or 'Special']	Penn Pharmaceuticals Services Ltd Tel. 01495 711222 Special Products Ltd Tel. 01932 690325
1mg/ml solution (orange flavour; sugar, colour and alcohol free)	Available as Kidnap [®]	
Note: There should be no need to prescribe imported melatonin.		

Circadin[®] is a modified release tablet. Breaking or crushing the tablet removes the modified (slow) release function. Circadin[®] can be administered after breaking or crushing, but this is unlicensed and release of the drug is similar to other immediate release preparations; however, where patients have swallowing difficulties crushing/breaking Circadin[®], using a liquid formulation or emptying capsule contents into food might be required.