Guidance for use of melatonin in children and young people with severe sleep disorders

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<td><strong>Author</strong></td>
<td>Dr. Janet Butterworth</td>
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1. Introduction

Background
Sleep disturbance in children and young person is common, especially in those with neurological and/or behavioural disorders (Lin-Dyken and Dyken 2002, Ross, Davies, Whitehouse 2007). Chronic sleep loss causes poor emotional processing, impaired cognition (difficulties with executive function, attention, working memory and long term memory.). It results in poor motor performance, an increased risk of general health problems and a poorer quality of life generally. (www.innerdrive.co.uk)

Sleep disturbance may include delayed onset of sleep, frequent waking, early morning waking or day-night reversal of sleep pattern (Jan, Espezel, and Appleion, 2008). The resulting daytime sleepiness and associated cognitive impairment affects learning, behaviour and emotional regulation, it also adds considerably to the burden of care.

Melatonin is a hormone secreted by the pineal gland which has an important role in the regulation of circadian rhythm. Administration of synthetic melatonin promotes the onset of sleep and has been used for the management of sleep difficulties in adults and children.

Melatonin
Melatonin, the hormone of the pineal gland, is normally made in response to dropping light levels at night and after morning exposure to daylight. Production is affected by light exposure detected by the retina; it is thought that this rhythm is disturbed in children with brain damage, neurodevelopmental disorders such as autism or visual disturbance.

When given to humans it has a rapid half-life of half to one hour, producing transient, mild sleep inducing effects (Wassmar and Whitehouse 2006). It lowers alertness, body temperature and performance during the three or four hours after a low dose has been given. Correctly timed, it is able to shift the internal ‘body clock’ both to later and earlier times (BNF for Children 2015).

Children with Smith-Magenis syndrome have a reverse day night sleep pattern due to abnormal melatonin secretion (Boudreau et al 2009)

Children with autism have lower melatonin levels (Rossignol et al 2014)

Melatonin is a hormone reported to improve the onset and duration of sleep in people with Learning Disabilities, in particular those with cortical blindness (Antonia et Al 2017)

Although the evidence base for Melatonin is limited, it is actually more substantial than that available to support the use of any alternative hypnotic (London New Drugs Group 2008).

Melatonin brand / formulary choices

Until 2019 there were no licensed melatonin preparations in the UK for use in children. Slenyto is licenced for use in children with an Autism Spectrum Disorder and Smith- Magenis Syndrome. It is a prolonged release formulation with a tiny 3mm tablet which is easy to swallow for the paediatric population, however is not recommended to be prescribed within Shropshire as it has not been authorised by Shropshire Area Prescribing Committee.
A licensed modified release melatonin 2mg tablet (Circadin®) has been available since June 2008. Circadin® is only licensed for patients aged 55 years and over, and in response to guidance issued by MHRA on melatonin in 2008, its use in children is off-licence.

A melatonin 1mg/ml oral solution licensed for short-term treatment of jet lag in adults was also released in 2019, however safety concerns regarding its excipients mean it should not be prescribed off-license in children and young people.

Several strengths of melatonin capsules, tablets and liquids are available via Specials manufacturers. These products are unlicensed and should not be prescribed if there is licensed or off-license alternative (GMC)

**MHRA guidance**

MHRA stated that many non-pharmaceutical grade products of melatonin are being imported from countries where melatonin is classed as a food supplement and so are not required to be manufactured to the Good Manufacturing Practice (GMP) standard. The MHRA stated that there should be a special clinical need should be submitted by the imported to MHRA if imported melatonin was used, but if there was a licensed product available in the UK then that should be prescribed.

If the dosage or formulation of Circadin® is not appropriate then a melatonin product that does meet the GMP manufacturing standard could be used, but would be unlicensed.

Liquid preparations should only be prescribed for selected patients that cannot tolerate solid dosage form, have swallowing difficulties, or because of the drug release characteristics.

**Shropshire melatonin formulary**

Melatonin formulary choices within Shropshire are;
- First line: Circadin MR 2mg Tablets - off-license
- Second line: melatonin 10mg/5ml oral solution - unlicensed

**2. Purpose**

The purpose of these guidelines is to provide clinicians with
- Guidance to the medical management of children and young people aged 2-18 years old with sleep disorders within Shropshire Community Health Trust (SCHT).
- Recommendations on the cost-effective, evidence based prescribing of melatonin by considering product formulations and brand.

**3. Definitions and Glossary**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>BNFC</td>
<td>British National Formulary for Children</td>
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<td>CAMHS</td>
<td>Child and Adolescent Mental Health Services</td>
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<tr>
<td>CHM</td>
<td>Commission on Human Medicines</td>
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<td>CYP</td>
<td>Cytochrome P450</td>
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<td>MHRA</td>
<td>Medicine and Healthcare Products Regulatory Agency</td>
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<tr>
<td>Off-licence</td>
<td>A licensed medication has been assessed for efficacy, safety and quality and is manufactured to appropriate quality standards. Age-appropriate formulations are difficult to develop so are used off-licence. (<a href="http://www.gov.uk">www.gov.uk</a>)</td>
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<tr>
<td>SCHT</td>
<td>Shropshire Community Health Trust</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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4. Duties

4.1 Chief Executive
The Chief Executive has ultimate accountability for the strategic and operational management of the Trust, including ensuring there are effective and appropriate processes in place for the medical management of children.

4.2 Director of Nursing & Medical Director
The Director of Nursing & Medical Director has responsibility for ensuring that Children are offered appropriate medical management.

4.3 Service Managers
Service Managers are responsible for the day-to-day operational management and coordination of the medical management.

4.4 All Clinical Staff
Clinical staffs are key members in ensuring that children with sleep difficulties are managed appropriately. All clinical staff who prescribe Melatonin are required to comply with this guideline and report any adverse care related issues to their line manager and report any adverse reactions.

5 Management of poor sleep in Children

5.1 Indications for Therapy
Randomized-controlled trials and clinical experience suggests that it may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, epilepsy, autism, and learning difficulties.

Melatonin will only be initiated where standard non pharmacological behavioural modification methods have failed, and other medical causes of sleep disturbance such as sleep apnoea, have been excluded i.e., Patients should first receive sleep hygiene advice.

5.2 Treatment Aims
The aim of treatment is to establish a regular nocturnal sleep pattern. This treatment is of particular benefit when behavioural modification has been unsuccessful or very difficult to achieve, especially in children with severe sleep disturbance.

5.3 Non-pharmacological Therapy
Non-pharmacological measures take precedence in the management of most disorders. These interventions stated below should be initiated by the clinician before considering any form of medication to treat the sleep difficulties.
Before starting melatonin treatment consider the use of a sleep diary; the use of sleep diary is crucial in establishing the sleep routine and in determining the pattern of sleep difficulties.

Signposting to the relevant sleep management websites for Information regarding sleep is essential. Parents should be provided with sleep information and advice sheets and signposting to the children sleep charity website www.childrensleepcharity.org.uk  See Patient resources.
Traditional non-pharmacological sleep hygiene methods must have been tried and failed:

- Behavioural interventions like good sleeping hygiene and managing sleep difficulties. See Patient resources.
- Cognitive behavioural therapy (CBT) may be more effective than hypnotics in improving sleep in the longer term. Reduced hypnotic use and improved quality of sleep has been shown with CBT.

5.4 Pharmacological Treatment with Melatonin

Consider initiating treatment with Melatonin when non-pharmacological measures have failed. Behavioural therapies should be continued alongside medication as the combination has been found to be more effective than medication alone.

Problems with sleep initiation
Standard release melatonin is indicated for children and adolescents who have problems with sleep initiation. The starting dose is usually 2mg mg given 30-60 minutes before bedtime. If there is no response or insufficient response after a minimum of 3 days therapy the dose is increased to 6mg. In certain circumstances the dose can be increased up to a maximum dose of 10mg.

Problems with both sleep initiation and sleep maintenance/fragmental sleep/early morning awakening
Ideally Circadin tablets should be swallowed whole when their long acting properties will be at their best Circadin can be crushed. This reduces its delayed absorption. They can however be cut in half and swallowed without chewing, which will cause them to retain their slow release characteristics.

A time period of 7-14 days is usually sufficient to determine if a specific dose is effective, and if ineffective, melatonin can be stopped without the need for gradual withdrawal

5.4.1 Dosage (by mouth)

Child 1 month–18 years:
- Initially 2 mg
- Dose may be doubled after 1-2 weeks of insufficient benefit
- Maximum daily dose 10 mg
- If no benefit is seen after 2 weeks, melatonin treatment should be stopped

The dose should be given 30-60 minutes prior to bedtime.
In sleep phase disorders, lower doses (0.5 to 1.0 mg) may be employed initially.

Change of formulation
If needing to change from immediate release (unlicensed) melatonin capsule to Circadin Tablets then this can be done on a like for like basis
- 3x2mg melatonin capsule = 3x2mg MR tablet (Ciracdin)

For patients not on an equivalent Circadin dose, the melatonin dose can be change to the nearest dose
• 2.5mg melatonin capsule = 2mg MR Circadin or 3mg MR Circadin (Circadin can be halved whilst retaining slow release properties)

Swallowing difficulties or feeding tubes administration
Circadin® is a modified-release tablet, and is not licensed to be given through enteral feeding tubes. However the manufacturers state that if necessary it can be crushed (note – this would change it from a modified-release tablet to an immediate-release one) and mixed in 15-30mL of water for administration through enteral feeding tubes. The tube should be flushed well after administration (NEWT guidelines, 2020).

Telford and Wrekin CCG have a PID (Prescribing information document) which we currently use across the two CCGs

5.4.2 Contra-indications
Hypersensitivity to the active substance or excipients in each preparation

5.5 Cautions
There is no convincing evidence that melatonin adversely affects seizure control, indeed improved sleep often improves common forms of However when used in patients with epilepsy, it is important to monitor seizure frequency.

The manufacturer of the UK licensed product advises caution in patients with renal disorders and not to use melatonin in patients with liver disorders some rare hereditary glucose tolerance disorders (due to it containing lactose).

5.5.1 Side Effects
Melatonin is generally well-tolerated. Sedation and fatigue, headaches, skin disorders, restlessness, increased pulse, itching and nausea have all been reported as side effects associated with melatonin use.

Melatonin has no predictable effect upon seizure control (see above).

There is no safety data for long term use but it has been used in some patients with learning disability throughout their childhoods. (P.Gringas et al 2012, 2017, A.Maras 2018)

The above details are not a complete list and the BNF and the summary of product characteristics (SPC) remain authoritative. Full list of side effects is given in the Melatonin (Circadin) SPC, available from Circadin - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

5.5.2 Interactions
Fluvoxamine and cimetidine has been shown to increase melatonin levels by inhibiting cytochrome P450 (CYP), isoymes CYP1A2 and CYP 2D respectively and these combinations should be avoided. There is a theoretical risk that any CYP1A2 inhibitors could cause an increase in melatonin levels (e.g. oestrogens, quinolones). CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin. Alcohol should be avoided as it reduces the effect of melatonin on sleep.

Melatonin may enhance the effects of sedatives and hypnotics (e.g. benzodiazepines).
On initiation of melatonin the specialist will be responsible for checking interactions and making necessary alterations in treatment.

The above details are not a complete list and the BNF and the SPC remain authoritative.

5.5.3 Pregnancy /Lactation
No clinical data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic /foetal development, parturition or postnatal development. In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. There are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Breast-feeding is not recommended in women under treatment with melatonin.

5.6 Monitoring
During initiation of treatment, sleep patterns should be documented in a sleep diary to monitor efficacy.

In people with epilepsy, monitoring of seizure frequency is advised.

Review patients after four weeks to ensure that continued treatment with Melatonin is appropriate and effective. Six monthly reviews should then take place to review the need for ongoing treatment.

There should be at least an annual trial of cessation of treatment, a drug holiday of four to six weeks, to assess if continued treatment is indicated. Timing of such a trial must take into account individual circumstances where the impact of potential sleep disruption can be minimised.

A drug holiday may also be indicated if melatonin stops working. Melatonin can then be restarted at a lower dose after the wash out period.

Patients on long term treatment should be reviewed every 6 months to reduce the dose and aim for withdrawal of treatment

5.6.1 Toxicity
It has been suggested that melatonin may affect the reproductive system by inhibiting the hypothalamic-pituitary- gonadal axis. Growth and sexual development monitoring is advisable, especially with long-term melatonin use.

This is primarily the responsibility of the Consultant clinician but any concerns from the primary care clinician should be reported to the Consultant clinician.

(Melatonin is monitored intensively by the Commission on Human Medicines (CHM) and MHRA - Please report any adverse reaction to the CHM, using the yellow card system available online at Yellow Card Scheme - MHRA

6. Review and Compliance Monitoring
Compliance to guidelines can be audited through the audit cycle within the Children, Young People and Families Service
SCHT Medicines Management Team monitors all prescribing individuals within the trust via ePact2.

Prescription costs are monitored within each department for as part of their budgeting responsibilities.

7. Consultation
Consultation with Community Paediatric team; Dr M Ganesh, Dr S Buch, Dr G Minnaar, Dr S Ogilvie, Dr S Postings, Dr D Short, Dr H Unsworth, Mrs N Kular Nurse consultant, and Specialist Registrar Doctors.
Expert opinion from Diane Kitching (Lead Pharmacist for Children’s’ Community Services)
Susan Watkins (Chief Pharmacist)

8. Dissemination and Implementation
Dissemination to all Community Paediatric Clinicians who prescribe Melatonin within SCHT

9. References
BNF for children 2020


Prescribing unlicensed medicines - GMC (gmc-uk.org)

10. Useful patient resources

10 Steps to a Quiet Night available from "Ten Steps to a Quiet Night" (cchp.nhs.uk)

Healthy sleep tips for children www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tips-for-children/

Taking Melatonin information leaflet download from medicines for children https://www.medicinesforchildren.org.uk/melatonin-sleep-disorders

Sleep advice websites- www.cerebra.org.uk
www.thesleepcharity.co.uk

Good sleep habits booklet can be downloaded at:
www.autism.org.uk

11. Appendices

Appendix 1

What is enough sleep?

Below are the approximate hours of sleep needed by children of different ages (How much sleep do children need? - NHS (www.nhs.uk)).

Babies 4 to 12 months old

• 12 to 16 hours including naps

Toddlers 1 to 2 years old

• 11 to 14 hours including naps

Children 3 to 5 years old

• 10 to 13 hours including naps

Children 6 to 12 years old

• 9 to 12 hours

Teenagers 13 to 18 years old

• 8 to 10 hours

Sleep hygiene in children and young people | Great Ormond Street Hospital (gosh.nhs.uk)

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Shared Care Agreement
Agreement to transfer of prescribing to GP

Patient details

Name:
Address:
Date of Birth:
NHS number:

Drug name, dose and manufacturer: (NB for unlicensed formulations please remember to specify manufacturer – Special Products Ltd should be the first line choice):

Drug: Circadin MR Dose: 2mgs Manufacturer: 

Consultant: Dr
Address: Coral House, Longbow Close, Shrewsbury, SY1 3GZ

Contact number:

GP:
Email:
Contact number:

Main carer: parent/guardian
Name:
Contact number:

Agreement to shared care, to be signed by GP and Consultant before prescribing is transferred to GP

Consultant Signature:
Date:

GP Signature:
Date:

This shared care agreement outlines suggested ways in which the prescribing responsibilities can be shared between the specialist and GP. GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient’s mental health remains with the specialist. If a specialist asks the GP to prescribe, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between specialist, GP and patient. The prescriber of the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Nuala O’Kane – Chair
Patricia Davies – Chief Executive

Appendix 2
Circadin MR tablets (melatonin)

Advice for crushing

Circadin tablets may require to be crushed for ease of consumption. If so, the following advice may be beneficial.

1. Tablet can be crushed by the use of the tablet crusher or between two metal spoons.
2. The crushed border should be added to 15 to 30 ML of water and mixed well.
3. The mixed solution should be drawn into an oral syringe.
4. The dose can then be administered to the child.
5. The tablet crusher should be rinsed with water and this should also be administered.

Alternatively, powder may be mixed with soft food.

Tablets should not be crushed in plastic containers, other than commercially available tablet crushers, due to the possibility of the medicine sticking to the plastic container.

Boiling water should not be used.

Medicine should not be left unattended in syringes.

Medicine which has been prepared by someone else must not be administered.

Tablet crushers are inexpensive and can be purchased from your local community pharmacy. They can be washed and dried after use.

If using two metal spoons, two spoons of similar size should be taken, sitting one spoon inside the one below.

A small gap must be made between the spoons, and one tablet must be placed between these surfaces and the spoons should be gently squeezed together.

The tablet should break up without shooting out. Further crushing will make a finer powder.

Even if tablet is roughly crushed, it will offer "immediate release" characteristics as desired.

Information from the manufacturer states that crushing a Circadin® tablet will not damage the active ingredient (melatonin). There are no safety concerns with crushing Circadin®, however it will affect prolonged-release properties of the product.

As long as the tablet is swallowed whole, the prolonged-release properties are maintained.

The prolonged-release properties will be maintained to some extent if the tablet is halved or divided into 4 quarters.

For further queries, please speak to your prescriber or pharmacist.

Ref: www.newtguidelines.com