Melatonin Guidance for the Treatment of Sleep Disorders in Children

Background

Melatonin is an endogenous hormone produced by the pineal gland in the brain. It is important in the regulation of circadian rhythms. Inadequate or irregularities with the production of melatonin can cause sleep disturbance.

Sleep disturbance in children with neurological or behavioural disorders is common and can be a major source of distress for the patient and the family. Furthermore, sleep disturbances can have an impact on the child’s behaviour and ability to concentrate during the day. In neurodevelopmental disorders which include Attention Deficit Hyperactivity Disorder (ADHD), Autistic Spectrum Disorders (ASD) and Learning Disability (LD) most children suffer from sleep disturbances. For example in ADHD, up to 70% of children experience sleep problems and stimulant medication has been thought to contribute largely to this.

Melatonin is not recommended for the management of sleep disorder in neurotypical children.

Melatonin is available as a licensed prolonged release formulation (Circadin® 2mg tablets). It is licensed for short term use in the treatment of insomnia in patients aged over 55. Use of Circadin® in children with sleep disorders is an off-label use.

Alternative licensed formulations of melatonin include; immediate release tablets and liquid formulations.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using melatonin outside it’s authorised indications or using an unlicensed formulation. The MHRA advise that a licensed preparation should be considered first, even if it is for an off label use as the quality is then assured and this is safer than an unlicensed product.

Evidence Base

SIGN guidance (SIGN 112, 2009) on the management of ADHD, acknowledges that sleep problems are reported in up to 50% of patients with ADHD. Also the use of stimulants in ADHD may contribute to sleep problems in children.

No high-quality evidence is available for the efficacy of Circadin® in children with sleep disorders and ADHD. However, there is limited evidence, from 2 small RCTs and a long-term follow-up study on the safety and efficacy of unlicensed melatonin in stimulant and non-stimulant treated children with ADHD experiencing sleep problems. The evidence is applicable to children aged 6 to 14 years with ADHD and sleep onset insomnia, using unlicensed melatonin (3–6 mg daily) shortly before bedtime. The evidence indicates that unlicensed melatonin used in these RCTs may reduce sleep onset latency by approximately 20 minutes and may improve average sleep duration by 15 to 20 minutes when taken for between 10 days and 4 weeks. Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated. Discontinuation of unlicensed melatonin led to relapse of sleep onset insomnia in most of the cases where it was used for more than 30 days. Longer term efficacy is unclear.

SIGN guidance (SIGN 145, 2016) on the management of Autistic Spectrum Disorders, recommends that a trial of melatonin should only be considered in children and adults with ASD whose sleep difficulty has not resolved following behavioural interventions.

NICE guidance (NG11, 2015) on the management of challenging behaviour and LD recommends that melatonin should only be considered if sleep problem persists after behavioural interventions have been tried. Melatonin should be used in combination with behavioural interventions.
Children Sleep Problem Management Process in Primary Care

1. Sleep Problem Identified or Reported
   - Refer pre-school age to Health visitor for support
   - Is there any condition causing or contributing to sleep problem?
     (e.g. sleep apnoea, restless legs at night, skin problems, cough, asthma, anxiety, GORD etc.)
     - Yes: Investigate & manage primary cause.
     - No: Discuss sleep hygiene and bedtime routines with Parent/Carer/Patient
       Give sleep hygiene resources available via - Sleep Scotland (www.sleepscotland.org)

2. Does sleep problem still persist despite trial of sleep hygiene tips?
   - Yes: Clinician to use questionnaire in Appendix 1 – Section 1 to assess problem and motivation to attend sleep clinic
   - No: Parent/Carer can self refer directly to sleep clinic

3. Is the ongoing sleep problem causing significant distress for family?
   and Is the parent/ carer/patient ready to make changes?
   - Yes: Complete Fife Children's Sleep Clinic Referral Form and send to generic sleep clinic email fife-uhb.fifewidesleepclinic@nhs.net (See Appendix 1 – Section 2)
   - No: No further action at present monitor situation
Points to Consider Prior to Initiation of Melatonin

1. Clinicians are strongly advised to follow the sleep problem management pathway in primary care.

2. Melatonin is not recommended for the management of sleep disorder in neurotypical children.

3. Melatonin should only be considered after evidence of engaging in sleep counseling or sleep programme.

4. Melatonin should only be initiated by a specialist service or clinician that specialises in managing sleep problems (e.g. Paediatrician, psychiatrist within CAMHS).

5. Consider adjusting the dose of any stimulant medication if child is struggling to settle in the evening. E.g. reducing the total dose, changing the regimen or formulation so that less medication is administered later in the day or switching to an agent associated with fewer sleep difficulties (e.g. atomoxetine).

6. A sleep chart or diary should be completed by parent/carer for a minimum 2 weeks period and during school term time only, highlighting problems with sleep latency despite use of non-pharmacological measures.

7. A trial of behavioural intervention or sleep hygiene measures for a minimum of 2 months. If trial successful, measures should be continued without prescribing of melatonin. If trial fails, melatonin should be considered for prescribing along with behavioural interventions/sleep hygiene measures.

Simple non-pharmacological measures include:

- Ensuring that there is an established bedtime routine and that a realistic sleep-wake schedule has been agreed.
- Ensuring that the room conditions (temperature, light and noise) are at an optimum level to promote sleep. (e.g. minimise background noise, use of a blackout blind)
- Ensuring no late afternoon/evening caffeine consumption.
- Removing television and electronic devices from the child’s room, since it is known that the blue green light emitted by these screens can disturb sleep. Children should avoid looking at bright screens beginning 2-3 hours before bed.

8. Engagement from the family is vital and there may be instances when it is difficult or impossible to establish behavioural interventions or sleep hygiene measures because the patient and/or family are struggling to cope with the current situation. In these instances, melatonin may be initiated at the same time as behavioural interventions or sleep hygiene measures and consideration of withdrawal once the other interventions are established.

Indication

Sleep disorders in children (age 3 to 18 years) with attention deficit hyperactive disorder, autism, visual impairment, learning difficulties and developmental delay where symptoms have been present for at least 6 months or sleep disturbance is so severe that the family are heading for a crisis.

Please note that Melatonin is not recommended for use in Neurotypical children (i.e without a neurodevelopmental disorder).
NHS Fife Formulary Products

First line
- Circadin® - Melatonin m/r tablets 2mg

See up-to-date NHS Fife Formulary and Scriptswitch recommendations for preferred products and prescribing advice.

Non-formulary products
Non-formulary products should only be considered where Circadin® is not suitable. Although Circadin® and Slenyto® were not recommended by the Scottish Medicine Consortium (SMC) for use within Scotland, Circadin® is the preferred prolonged release option in Fife based on cost-effective prescribing. A PACS2 will be required to be completed prior to prescribing Slenyto.®

See Appendix 3 for comparison of melatonin products available on the market.

Prescribing Information

- Recommended starting dose of melatonin is 0.5mg to 1mg up to a maximum dose of 2mg to 3mg at night depending on formulation and increased by 2mg to 3mg depending on response every 7-14 days up to a maximum of 6mg. Higher doses above 6mg do not necessarily produce any better effect.

- Melatonin m/r tablets 2mg (Circadin®) should be taken 1-2 hours before expected bedtime and after food. Tablets should be swallowed whole but can also be halved using a tablet cutter and still maintain the controlled release profile.

- Melatonin immediate release 3mg tablets & 1mg/1ml solution should be taken 20 - 30 minutes before expected bedtime and after food.

- Immediate release effect can be achieved by crushing Circadin® MR tablets. See Crushing Melatonin Leaflet (Appendix 2).

- Some patients may require both immediate and prolonged release effect. In this case, Circadin® tablet can be taken both whole and crushed.

- If Melatonin becomes ineffective, the timing of administration should be checked. Also a trial of stopping melatonin should be considered. It is worth noting that there has been reported tolerance to long term melatonin therapy.

- Avoid giving repeated doses of melatonin overnight as this confuses the circadian rhythm.

- If melatonin has successfully established a good sleep pattern, where appropriate a trial withdrawal of melatonin over 2-3 weeks should be undertaken by the specialist 3-6 months following initiation. The continued need for melatonin should be assessed periodically every 2 to 6 months. Consider reducing or stopping melatonin for up to a minimum of 2-3 weeks every 12 months.

- Melatonin is generally well tolerated. Full adverse effect profile is unclear due to small size of trials in children. The most commonly reported side effects are: headache, dizziness, nausea and drowsiness.

- Co-prescribing of Melatonin and other agents used to promote sleep is not recommended.

- Off-label use should be discussed with patient/parent and recorded in notes before initiation.
Prescribing Unlicensed Melatonin Products

In **exceptional circumstances** there may be a need to prescribe unlicensed Melatonin (e.g. melatonin 3mg capsules). These will be initiated by the specialist and responsibility for ongoing prescribing will stay with the specialist.

Interactions

Possible interactions of melatonin with other medicinal products have not been fully characterised. Interaction of melatonin with selective serotonin re-uptake inhibitors has been observed.

Refer to BNF / SPC for full details.

Cautions

Caution is also advised in children with autoimmune, renal and hepatic disorders due to limited safety data and in those with lactose intolerance. It can affect seizure control in patients with epilepsy and should be closely monitored. Concerns have also been raised about it causing delays in the onset of puberty, based on animal studies.

Refer to BNF / SPC for full details.

Swallowing Difficulties and Feeding Tubes

- Melatonin m/r tablets 2mg (Circadin®) or melatonin 3mg tablets may be crushed to fine powder and mixed with 15-30mls of water. Tube should be flushed with 30ml water before and after medication given.

- For patients with swallowing difficulties, the liquid solution should be considered. Where this is not suitable, tablets can be crushed and sprinkled over food or alternatively mixed with small amount of soft food e.g yoghurt or Jam (immediately prior to administration), see Appendix 2.

Reference: NEWT Guidelines

Secondary Care / Managed Services Responsibilities

- Initiation of prescription and titration of dose to the optimum level using the minimum effective dose.

- Monitoring of response and adverse drug reactions (ADRs) during the titration period.

- Liaison with general practitioner (GP) when a stable dose has been achieved and proven benefit has been established.

- Provide GP with initiation letter within 14 days of seeing patient including diagnosis, dose of melatonin that patient is stabilised on, treatment plan, duration of treatment before consultant review and state whether specialist or GP to continue prescribing.

- Review patients 2-3 months after initiation, and 6 months thereafter and GP to be notified of any changes within 14 days. A trial withdrawal should be considered at each medication review.

- In the event that the patient does not attend review meetings on two consecutive occasions, the specialist will discharge the patient and advise the GP by letter that in the absence of follow up, continued supply of medication can no longer be recommended.

- Discontinuation in late adolescence (by 18 years) or if necessary, arrange transfer to adult services when child is 18.
GP Responsibilities

- Informing the secondary care / managed services clinician of any ADRs observed or any concerns regarding the child’s overall health and well being.
- Prescribe ongoing supplies of melatonin for doses up to 10mgs.

Patient / Parent Responsibilities

- Ensure that behavioural interventions/sleep hygiene measures continue to be implemented even whilst on medication.
- Ensure compliance with medication.

Further Information & Contacts

Dr Susie Gibbs, Lead clinician, Learning disability, Consultant in child and adolescent psychiatry. susie.gibbs@nhs.net

Dr Stephanie Shearer, Locum, Community Paediatrician. s.shearer1@nhs.net

Ade Deekae, Senior Clinical Pharmacist, Child & Adolescent Mental Health Service. adepeju.deekae@nhs.net

Contributors

Fife - Child & Adolescent Mental Health Service (CAMHS) Team
Fife - Community Paediatricians
School & Community Sleep Nurse Team
Health Visiting Team
Fife Children Sleep Clinic
Fife ADHD Service
Fife Learning Disability Team
Children & Young People’s Community Service
Primary Care Pharmacy Team

References.

British National Formulary (BNF) for Children online. Version 2.1.24 (2019110601)


Sleep Scotland. Supporting every child to get a good night’s sleep. www.sleepscotland.org

The NEWT Guidelines for administration of medication to patients with enteral feeding tubes or swallowing difficulties. Updated September 2017.
## Appendix 1

### Section 1

**Fife Children's Sleep Difficulty Assessment Form**

(Only complete section 1 if Clinician or Healthcare professional making referral)

### A. Sleep difficulty (Complete as applicable?)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Night Wakening</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes or more to settle</td>
<td>Less than twice a week</td>
</tr>
<tr>
<td>Less than twice a week</td>
<td>2 – 4 times a week</td>
</tr>
<tr>
<td>2 – 4 times a week</td>
<td>More than 4 times</td>
</tr>
<tr>
<td>More than 4 times</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parents out of bed</th>
<th>Children in parent’s bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than twice a week</td>
<td>Less than twice a week</td>
</tr>
<tr>
<td>2 – 4 times a week</td>
<td>2 – 4 times a week</td>
</tr>
<tr>
<td>More than 4 times</td>
<td>More than 4 times</td>
</tr>
</tbody>
</table>

### B. How long has there been a sleep difficulty?

- Less than 6 weeks
- 6 weeks – 3 months
- Over 3 months

### C. How difficult is the problem to cope with?

- 10: Very difficult
- 9: Difficult
- 8: Moderate
difficult
- 7: Slightly difficult
- 6: Marginally difficult
- 5: Not at all difficult
- 4: Not at all difficult
- 3: Not at all difficult
- 2: Not at all difficult
- 1: Not at all difficult
- 0: Not at all difficult

### D. Are you ready at this time to make changes?

- 10: Definitely
- 9: Almost definitely
- 8: Maybe
- 7: Somewhat
- 6: Not really
- 5: Not really
- 4: Not really
- 3: Not really
- 2: Not really
- 1: Not really
- 0: Not really

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a) Is sleep difficulty experienced more than twice a week?
b) Has been present for longer than 3 months?
c) Difficulty coping – score > 5
d) Ready to make change – score > 5

If answers yes to questions (a) to (d) above, refer to sleep clinic. If no, re-discuss sleep hygiene.
Appendix 1

Section 2

Fife Children’s Sleep Clinic Referral Form

Please complete this form in block capitals and send it to:
ife-uhs.fifechildsleepclinic@nhs.net

Child’s name: ........................................................................................................................................

Date of birth: ...........................................  CHI NO (if known): .................................................................

Address: ..................................................................................................................................................

Postcode: ................................................................. Tel No: .............................................................................

School: ..................................................................................................................................................

Sex:  Male  □  Female  □

Parent’s name: ........................................................................................................................................

GP name and address: ..........................................................................................................................

Other relevant information

At risk factor  □  Developmental delay  □  Other  □

Behaviour difficulties  □  Family illness  □

Chronic illness  □  Social problems  □

Give details: .............................................................................................................................................

Is this appointment routine  □  or urgent □

Is this referral being made by  Parent/Patient  □  or  Clinician/Healthcare Professional  □

Referrer’s signature: ...........................................  Designation: .............................................

Print name: ..............................................................................................................................

Date of referral: ............................................................................................................................

Telephone Number/Email Address: .................................................................................................
Appendix 1

Section 2

Is the young person attending secondary school?  Yes ☐ no ☐

If yes, an appointment will be arranged through school to meet with the young person.

Are there any concerns regarding this?  Yes ☐ no ☐

If yes please give details:

______________________________

We offer parent workshops as an alternative to an individual appointment.
Attendance at this may reduce waiting time to our service.

Is parent/carer willing to attend a workshop?  Yes ☐ no ☐

I agree to referral to the sleep clinic to help me work to improve my/my child’s sleep pattern.

Signed: ........................................ Parent/Carer

Signed: .............................................................Young Person (if 12 years and over & has capacity)

Date:______________________________

Please tick box if you are happy that your family’s contact details may be used for future evaluation of the sleep clinic service ☐
Crushing Melatonin (Circadin®) MR Tablets

If you have been prescribed Melatonin MR (Circadin®) tablets or if your prescription has changed to Melatonin MR (Circadin®) tablets from an alternative product, you may have been asked to crush the tablets prior to taking the dose. Crushed tablets may be mixed with a little water, or soft food, e.g. yoghurt or jam to aid swallowing.

Crushing tablets is quite simple. You can do it using either a tablet cruser or two spoons. You can purchase a tablet cruser from your local community pharmacy. They cost just a few pounds and are re-usable - just rinse and dry after use.

You can also place the tablet between two dessert spoons to crush it.

- The spoons should be arranged so that one spoon sits in the spoon below.
- Make a small gap between the spoons and place one tablet in the gap between the spoons.
- Gently squeeze the spoons together so that the tablet breaks up, but does not shoot out.
- You only need to roughly crush the tablet - it is not necessary to crush it into a fine powder.
- Repeat if more than one tablet is required to provide the dose.

If you have any questions on crushing your tablets, you can talk to your Community Pharmacist.
# Appendix 3

## Comparison of licensed melatonin products – February 2020

<table>
<thead>
<tr>
<th>Product</th>
<th>Licensing</th>
<th>Warnings &amp; precautions</th>
<th>Release profile</th>
<th>Cost per pack</th>
<th>Cost per year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin m/r tablets 2mg</td>
<td>Short term treatment of primary insomnia in age 55 years and over, for up to 13 weeks.</td>
<td>Not recommended for use within Scotland by SMC. Contains lactose.</td>
<td>Prolonged release</td>
<td>£15.39 (30 tabs)</td>
<td>£562</td>
</tr>
<tr>
<td>Pharma Nord – Melatonin 3mg tablets</td>
<td>For short term treatment of Jetlag in adults for a max of 5 days. Max 16 courses per year.</td>
<td>Not recommended in children &amp; Adolescent 0-18 years.</td>
<td>Immediate release</td>
<td>£15.95 (30 tabs)</td>
<td>£388</td>
</tr>
<tr>
<td>Colonis – Melatonin 3mg tablets</td>
<td>For short term treatment of Jetlag in adults for a max of 5 days. Max 16 courses per year.</td>
<td>Not recommended in children &amp; Adolescent 0-18 years. Contains Lactose.</td>
<td>Immediate release</td>
<td>£65 (30 tabs)</td>
<td>£1582</td>
</tr>
<tr>
<td>Colonis - Melatonin oral solution 1mg/1ml</td>
<td>For short term treatment of Jetlag in adults for a max of 5 days. Max 16 courses per year.</td>
<td>Not recommended in children &amp; Adolescent 0-18 years. Contains sorbitol, ethanol &amp; propylene glycol.</td>
<td>Immediate release</td>
<td>£130 (150mis)</td>
<td>£1898</td>
</tr>
<tr>
<td>Slenyto tablets 1mg and 5mg MR</td>
<td>Treatment of insomnia in children &amp; adolescents aged 2 to 18yrs with autism spectrum disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.</td>
<td>Not recommended for use within Scotland by SMC. Contains small amounts of lactose.</td>
<td>Modified release</td>
<td>1mg £41.20 (60 tabs)</td>
<td>£1,606</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5mg £103 (30 tabs)</td>
<td></td>
</tr>
</tbody>
</table>

*Cost per year is based on a 6mg daily dose.  
Prices indicated are representative of BNF May 2019. NHS dm+d Jan 2020 & Scottish Drug Tariff (March 2020)

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**Colonis – Melatonin 1mg/ml solution safety limit (Max daily dose) in children.**

Colonis Melatonin 1mg/ml contains the following excipients.  
- Propylene glycol 150.37mg per 1ml dose  
- Ethanol 0.00045mg per 1ml dose  
- Sorbitol 140mg per 1ml dose.

The total daily dose of excipients should be calculated and checked to ensure within safety limits for age and weight.

<table>
<thead>
<tr>
<th>Safety Limits (Max daily dose)</th>
<th>1 month - 4 years</th>
<th>&lt; 6 years</th>
<th>5 years - 17 years</th>
<th>6 years - 12 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>50mg/kg</td>
<td>-</td>
<td>500mg/kg</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-</td>
<td>6mg/kg</td>
<td>-</td>
<td>75mg/kg</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>140mg/kg/day</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Information gathered from:  
PressGAPP bulletin - Newly licensed melatonin preparations, 12 July 2019