Shropshire Community Health NHS Trust

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

Document Details	
Title	Guidance for use of MELATONIN for children with severe sleep disorders
Trust Ref No	1855
Local Ref (optional)	
Main points the document covers	Guidance for use of MELATONIN for children with severe sleep disorders
Who is the document aimed at?	Clinicians working within Children, Young People and Families Service
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Approval process	
Approved by (Committee/Director)	Clinical Policy Group
Approval Date	09/09/2024
Initial Equality Impact Screening	Yes
Full Equality Impact Assessment	No
Lead Director	Director of Nursing, Clinical Delivery and Workforce
Category	Clinical
Sub Category	
Review date	09/09/2027
Distribution	
Who the policy will be distributed to	Clinicians with Children's', Young People and Families Service
Method	Via website
Document Links	
Required by CQC	Yes
Required by NHLSA	
Keywords	Melatonin, sleep disorder

Amendments History		
No	Date	Amendment
1	29/07/2013	Version 1
2	22/10/2015	Version 2
3	01/07/2020	Version 3: Change in layout Product availability and local formulary updated
4	14/02/2024	Version 4: RICaD added, formulation of product updated
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1. Introduction

1.1 Background

Melatonin is a pineal hormone which affects sleep. It is normally secreted at night and its main function is the regulation of circadian rhythm and sleep. It plays an important role, in setting the correct timing of sleep - wake cycles.

The administration of exogenous melatonin has a rapid, transient, mild sleep inducing effect and it lowers alertness, body temperature and performance for about 3 to 4 hours after the administration of low doses of immediate release formulations.

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, autism spectrum disorder, and learning difficulties. In practice, the use of melatonin for the treatment of paediatric sleep-wake cycle disorders is widespread.

Sleep disorders in children with neurodevelopmental difficulties such as ASD and ADHD are more common then the typically developed population. In ASD sleep problems, particularly insomnia can occur in 40-80% of children and adolescents (Cortesi et al, 2010). With regards to ADHD, within the clinic setting, 25-50% of individuals are reported to have sleep problems (Corkum et al, 1998; Gau et al 2007; Fisher et al, 2014).

Children with and or without co-morbid ADHD treated with melatonin have been shown to fall asleep earlier and sleep for longer when compared to controls. The current systematic reviews and meta-analyses of placebo-controlled, and randomised controlled trials in children with neurodevelopmental disorders, have demonstrated that melatonin significantly improves sleep onset latency and sleep duration compared to controls (Gringras et al., 2012). Melatonin may be most effective in those children whose sleep patterns indicate that their circadian rhythm is disrupted, and in whom sleep hygiene methods have been ineffective. Although it is important to note, in children/ adolescents with neurodevelopmental difficulties response to Melatonin can be variable.

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

BNFC	British National Formulary for Children
CAMHS	Child and Adolescent Mental Health Services

CHM	Commission on Human Medicines
CYP	Cytochrome P450
ICB	Integrated Care Board
MHRA	Medicine and Healthcare Products Regulatory Agency
Off-license	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-license. (www.gov.uk)
RICaD	Rationale for Initiation, continuation and Discontinuation
SCHT	Shropshire Community Health Trust
SPC	Summary of Product Characteristics

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 staff 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 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, attention deficit hyperactivity disorder, epilepsy, autism, and learning difficulties. Therefore, melatonin will only be considered if non-pharmacological methods have proven ineffective and other potential medical causes for sleep issues, such as sleep apnea, have been eliminated. It is important to first give patients suggestions for proper sleep hygiene.

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 strategies are essential in managing most disorders. Before turning to medication, clinicians should prioritize the following interventions.

Utilize a sleep diary is crucial for establishing sleep routines and identifying patterns of difficulty.

Directing individuals to reputable sleep management websites for essential information and providing parents with advice sheets and resources from pediatric sleep charities are vital steps in the management of sleep difficulties. These measures can lay a strong foundation for addressing sleep issues before considering medicinal treatment.

Resources recommended to families include:

- The Sleep Charity: https://thesleepcharity.org.uk
- Cerebra centre for neurodevelopmental disorders: https://cerebra.org.uk/uncategorized/sleep-tips-and-techniques/
- Children's Sleep Charity: www.childrensleepcharity.org.uk
- Scope Sleep Right: https://www.scope.org.uk/family-services/sleep-right
- NHS – Healthy Sleep Tips for Children https://www.nhs.uk/conditions/baby/health/sleep-and-young-children/#:~:text=Do%20not%20let%20your%20child,long%20naps%20in%20the%20afternoon.

Involving Health visitors trained in Millpond strategies for addressing sleep issues can also provide valuable assistance.

5.4 Pharmacological Treatment with Melatonin

5.4.1. Melatonin – brands of choice:

Circadin® MR 2mg tablets have been available since June 2008. These is a sustained release formulation of Melatonin which is licensed in the UK as monotherapy for the treatment of primary insomnia in adults aged 55 years and over. Until 2019 there was no licensed form of melatonin for use in children. However the use of Circadin® off label is preferable to the use of an unlicensed special because the MHRA recommends that a licensed product should be used, even if it is used off label, before considering the use of an unlicensed preparation. Circadin® , or the generic melatonin MR 2mg tablet, still remains the for formulary choice of melatonin https://www.shropshireandtelfordformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=4&SubSectionRef=04.01.01&SubSectionID=A100&drugmatch=3180#3180) however families should also be given the choice of any licensed products available so that a shared treatment decision is made.

Slenyto® is licenced for use in children and adolescence aged 2-18 years with an Autism Spectrum Disorder and Smith- Magenis Syndrome, where sleep hygiene measures have been insufficient. It is a prolonged release formulation with a tiny 3mm tablet which is easy to swallow for the paediatric population.

Adaflex® is licensed for insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

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 means it should not be prescribed off-license in children and young people.
An **unlicensed 10mg/5ml oral suspension** should be prescribed instead. However, it is only to be used if the patient cannot tolerate crushed tablets. A legal disclaimer will need to accompany the prescription to allow the community pharmacy to place an order with the wholesaler in accordance with MHRA guidelines (Melatonin RICaD .docx (live.com)).

5.4.2. Initiation and dosing

Consider initiating treatment with Melatonin when non-pharmacological measures have failed. Behavioral therapies will be continued alongside medication for at least four weeks, but preferably ongoing, as the combination has been found to be more effective than medication alone.
The dose will be advised by the specialist, please also refer to BNF (Melatonin | Drugs | BNF | NICE) and individual SPC for licensed doses. The aim is to establish healthy sleep patterns with the lowest effective dose.
Melatonin needs to be taken 30-60 minutes before bedtime.

Circadin® MR Modified release tablets: Child up to 18 years : Initially 2mg daily for 2 weeks, then increased by 2mg increments every 1-2 weeks up to a 4-6 mg; maximum of 10mg daily.(Note: If a dose of 6 mg is not effective higher doses are unlikely to be effective). This should be administered with or after food.

Adaflex® dose: 1-2 mg daily, can be increased by 1mg every week up to a maximum of 5 mg per day. It is recommended that food is not consumed 2 h before and 2 h after intake of Adaflex tablets.

Slenyto® dose: 2mg daily, increased if necessary to 5mg and then 10mg daily. This should be administered with or after food.

Unlicensed liquid: Dose as for Modified Release tablets, however release mechanism will be different.

The paediatrician initiating treatment will be responsible for the rationale behind the prescribing, along with product choice.

5.4.3. Assessing response to treatment

Significant improvement should be considered based on the following criteria:

- When melatonin results in young person having a reduction in sleep latency of at least 40 minutes and /or
- Increase in total sleep duration of at least 40 minutes or more and/or
- Qualitative improvement in sleep quality where young person wakes up feeling rested and refreshed and/or
- Qualitative positive impact on the quality of life of the young person and positive impact on family life as described by carers.

If melatonin is no longer effective after months or years of effective treatment, or a lower treatment effect is seen after titration to a higher dose of melatonin, consider titration to a lower dose or a 2-3 week period off melatonin followed by restarting at the lowest dose again. If this has not been effective, then consider complete discontinuation of treatment.

There are some individuals who are slow metabolisers of the exogenous Melatonin. A slow accumulation over time can lead to a lower treatment effect and a break will be needed before recommencing at a lower dose. If this has not been effective, consider complete discontinuation of treatment. If this is the case, however, it is more likely to occur within the initial period of use.

Melatonin can be stopped abruptly. No discontinuation effects are documented. Melatonin is not associated to produce tolerance, rebound insomnia or dependence.

5.5. Swallowing difficulties or feeding tubes administration

Circadin® is a modified release tablet and is not licensed to be given via 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, 2024).

Adaflex® may be crushed and mixed with water immediately before administration.

Slenyto® may be mixed whole into food (e.g. yoghurt, orange juice, or ice-cream) immediately before administration.

Unlicensed liquid should only be prescribed when the young person cannot tolerate crushed tablets.

5.6. Contra-indications

Hypersensitivity to the active substance or excipients in each preparation

5.7. Cautions

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

There is limited information available in prescribing with pre-existing autoimmune conditions; exacerbations have been reported occasionally.

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).

5.8. 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. This is not a complete list of side effects; refer to current BNFc or SPC for each product.

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).

5.9. Interactions

Fluvoxamine and cimetidine has been shown to increase melatonin levels by inhibiting cytochrome P450 (CYP), isozymes 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 drug interactions using BNFc or SPC and making necessary alterations in treatment.

5.10. 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.

5.11. 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

5.12. Monitoring

To monitor the effectiveness of treatment, it's important to keep an ongoing sleep diary documenting sleep patterns.

For individuals with epilepsy, it is advised to monitor the frequency of seizures.

After four weeks, patients should be reviewed to ensure that continued treatment with Melatonin is appropriate and effective.

A ‘treatment holiday’ should be considered for all suitable patients three months post initiation and six-monthly thereafter, to assess their need for ongoing treatment. Patients may be advised to take on school nights only and take a break at weekends, stop during school holidays or for every 3 months have one month off. This helps to avoid any physical

and psychological dependence or tolerance. If the break from melatonin has resulted in no deterioration in sleep cycle, the patient can remain off melatonin. If withdrawal of medication has impacted the patient's sleep cycle, it can be restarted at the same dose that the patient was stable on.

A drug holiday may also be recommended if melatonin stops working. In such cases, melatonin can be restarted at a lower dosage after a washout period.

Regularly reviewing patients undergoing long-term treatment is crucial in order to gradually reduce the dosage and, ultimately, aim for complete withdrawal of the treatment. After three months on a stable dosage, primary care providers can start prescribing by submitting RiCaD.

5.13. Transfer of prescribing responsibilities

After starting melatonin, a specialized clinician should oversee the treatment for at least 3 months, only continuing if there is substantial improvement and the patient is stabilized on a proper dose. Once this is achieved, the responsibility of the treatment can then be transferred to primary care. This new approach supersedes the shared care agreement currently in place and allows primary care to take over prescribing duties, provided they have been informed of the changes.

Should a primary care clinician refuse to continue the prescribing from the specialist team then a refusal to prescribe form will be completed by primary care 20220726 NHS STW Decline to prescribe.docx (live.com).
Refusal forms should then be discussed with ICB clinical lead for children, young people and family services as to the barriers to primary care prescribing given that a RiCaD document is in place to support the 'off label' prescribing.

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.
Prescribing data and costs are monitored within each department for as part of their budgeting responsibilities.

7. Consultation

Consultation with Community Paediatric team: Dr Preetha Raveendran, Dr S Buch, Dr G Minnaar, Dr S Ogilvie, Dr S Postings, Dr D Short, Dr H Unsworth, Mrs N Kular Nurse consultant, and Dr A Tarhini Specialist Registrar Doctors.
Expert opinion from:
Diane Kitching, Lead Pharmacist for Children's Community Services and Governance Medicines Management Team, Shropshire Community Health NHS Trust
Elizabeth Walker Head of Medicines Quality and Optimisation
Susan Watkins (Chief Pharmacist)
Andrew Riley Senior Pharmaceutical Adviser, Provider Collaboration and Performance
Priya George ICB Clinical Lead

8. Dissemination and Implementation

Dissemination to all Community Paediatric Clinicians who prescribe Melatonin within SCHT

9. Other useful patient resources

- National Autistic society - good sleep habits booklet [online] [Accessed 22.05.2024] [available at National Autistic Society (autism.org.uk)]
- Great Ormond Street Hospital – Sleep hygiene in children [online] Accessed 22.05.2024] [Available at GOSH_Sleep_Hygiene_in_children.pdf]
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children with neurodevelopmental disorders: An observational study', Developmental Medicine & Child Neurology, 44(5), pp. 339–344.
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