Guidance for prescribing melatonin for sleep disorders in paediatrics (children and adolescents) in South East London

This guidance was developed on behalf of the South East London Integrated Medicines Optimisation Committee (SEL IMOC, formerly the Area Prescribing Committee) by Evelina London Children's hospital and SLaM Pharmacists with support from the Greenwich Medicines Optimisation Team.

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

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Introduction

The pathways on the following pages outline the processes that the specialist paediatric teams in local hospitals (acute and mental health Trusts) and community paediatric clinics will follow when starting a paediatric patient on melatonin for sleep disorders. Melatonin is an option after a trial (at least 3 months) of behavioral interventions fails to adequately manage the patient's sleep disorder.

Melatonin preparations and their place in in therapy. To avoid confusion in the selection of products, it is recommended that melatonin preparations are prescribed by brand, other than generic melatonin 2mg MR tablets

Preparation	Licensing status in paediatrics	Place in therapy	Other points to note
Melatonin 2mg modified release (MR) tablets Summary of Product Characteristics (SPC) available here and further information can be found in the paediatric formulary. Prescribe generic version, no brand recommendation.	Not licensed in paediatrics. Off-label use in paediatrics of a licensed product.	First line choice unless patient meets the licensing criteria for the other preparations noted. Second line choice, off label, in those children with a diagnosis of ADHD unable to tolerate Adaflex®.	• Patients who are currently stabilised on this formulation do not necessarily need to be switched, unless it is clinically indicated by the specialist team • For those children with a diagnosis of ADHD a switch may be considered and any change to formulation will be initiated by the child's specialist team. **For patients with swallowing difficulties:** • Tablets can be crushed to a fine powder and mixed with water or given with cold soft food such as a teaspoon of yoghurt or jam. Use a small amount of food to ensure the full dose is taken. The prescription should state that the medication is to be crushed prior to administration. N.B. Crushing the tablet will remove the modified release property of the tablet. • Tablets can also be halved (using a tablet cutter) **For administration via an enteral feeding tube:** • Tablet can be crushed to a fine powder and added to 5 - 10ml of water and mixed well.
Adaflex®1mg, 2mg, 3mg, 4m, 5mg tablets. Summary of Product Characteristics (SPC) available here and further information can be found in the paediatric formulary	**Licensed for the treatment of insomnia in children and adolescents aged 6-17 years with ADHD,** where sleep hygiene measures have been insufficient. Licensed maximum dose 5mg.	**First line choice in patients who meet the licensing criteria for treatment.** Second line choice, off label in those children where the other listed preparations are not clinically appropriate and/or tolerated.	**For patients with swallowing difficulties:** • Tablets can be crushed to a fine powder and mixed with water or given with cold soft food such as a teaspoon of yoghurt or jam. Use a small amount of food to ensure the full dose is taken. The prescription should state that the medication is to be crushed prior to administration. • Tablets can also be halved (using a tablet cutter) **For administration via an enteral feeding tube:** • Tablet can be crushed to a fine powder and added to 5 - 10ml of water and mixed well.
Slenyto® 1mg and 5mg prolonged release mini-tablets Summary of Product Characteristics (SPC) available here and further information can be found in the paediatric formulary.	**Licensed for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith- Magenis syndrome**, where sleep hygiene measures have been insufficient.	**First line choice in patients who meet the licensing criteria for treatment.**	• Adaflex® is the first line preparation in patients who have insomnia due to attention deficit hyperactivity disorder (ADHD) but do not have ASD. • Slenyto™ is not licensed for use in adults. **For patients with swallowing difficulties** • Tablets should not be broken, crushed or chewed • Tablets can be put in food such as yoghurt, orange juice or ice cream to facilitate swallowing and improve compliance. If the tablets are mixed with food or drink, they should be taken immediately and the mixture not stored.
Ceyesto® 1mg/ml oral solution Summary of Product Characteristics (SPC) available here and further information can be found in the paediatric formulary	**Licensed for insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD)**, where sleep hygiene measures have been insufficient. Approved in SEL as an alternative formulation of melatonin for any diagnosis listed above – see place in therapy.	**Reserved for use in patients with fine-bore enteral feeding tubes (gauge less than 9fr) where there is risk of tube occlusion, or if there are compliance issues with the crushed tablets.**	• The liquid should be prescribed by brand • In cases where the enteral feeding tube is no longer required, the need for liquid preparation should be reviewed.

Long term data and safety of melatonin

In the more recent largest placebo-controlled studies to date involving children with learning disability, autism and epilepsy (Coppola et al. 2004; Garstang and Wallis 2006; P. Gringras, Gamble, and Jones 2012; Buckley et al. 2020), there were no excess adverse effects in the treatment group over that recorded for placebo, and in particular seizures were not worsened. A Cochrane review found no worsening of seizure frequency in patients with epilepsy given melatonin. (Brigo, Igwe, and Del Felice 2016). There was no detectable impact on puberty in a paper by Malow et al. (Malow et al. 2006)

Choice of melatonin formulation and brand

Melatonin brands will preferably be prescribed within their licensed indications. However, there may be individual cases where a brand or formulation may be recommended and prescribed off-label**.** For certain children an immediate-release formulation may be more beneficial for its action in inducing sleep, whereas in other children a modified-release formulation may be more beneficial for its action in increasing sleep duration. The specialist will determine which type of melatonin agent is best suited to the patient.

Switching melatonin preparations

Switching of melatonin preparations can be undertaken by the primary care clinician. Any changes to a patient's medication should be discussed with the patient/parent/carer and they should be appropriately counselled with relevant information on the change.

Specialist advise can be sought if any additional support is required or if the primary care clinician is unsure about which is the most appropriate preparation for the child they are treating.

Patients currently prescribed Kidmel (unlicensed Special 1mg/1mg oral solution) or any other unlicensed Special formulation of melatonin should be reviewed and a switch to a licensed alternative considered. Please refer to the table on page 2 and the information on page 4 for advice on the suggested formulation.

Daily dose of melatonin

The different formulations have different licensed maximum doses, however the BNF for Children, states that the maximum daily dose of melatonin modified-release should not exceed 10mg daily, and immediate release Adaflex® should not exceed 5mg. The specialist will advise on the maintenance dose required, being the lowest effective dose.

Transition to adult services

As part of the process of transitioning to adult services, the continued need for melatonin and choice of preparation should be reviewed by the adult team that the patient transfers to. Where continued melatonin treatment is considered clinically appropriate in adulthood, the preparation should be reviewed to ensure it is appropriate.

Melatonin prescribing guidance

This pathway should be interpreted in the context of the 'Sleep Pathway' (page 5) which assumes that adequate parent led sleep behavioural advice takes place before prescribing and that there is documentation of the child's sleep pattern.

Baseline eligibility for Melatonin

1. **Sleep measurements:** Sleep Latency (SL) more than 60 minutes, and/or longest sleep period (LSP) less than 6 hours and/or total sleep time (TST) more than 2 hours less than recommended for child's age
2. **Daytime:** Consider fatigue, irritability, attention difficulties, externalising behaviours (reported by school and/or parents)
3. **Parent opinion** on overall benefits and adverse effects

Treatment Target Outcomes

1. Sleep latency reduced to less than 60 minutes, for at least 3 days of the week
2. Longest sleep period (LSP) increased by at least 45 minutes
3. Total sleep time increased by at least 45 minutes

If young person continues to have insomnia where healthy sleep practice interventions have been insufficient, consider melatonin

Age 6 – 17 with a diagnosis of ADHD

- Prescribe Adaflex® tablets
- Starting dose 1-2 mg 30-60 minutes before bedtime
- If an inadequate response has been observed, the dose should be increased by 1 mg every week until up to a maximum 5 mg per day, independent of age. The lowest effective dose should be used
- Tablets may be crushed and mixed with water directly prior to administration
- Review after first 3 months then every 6 months

Age 2 – 18 with a diagnosis of autism spectrum disorder or Smith-Magenis Syndrome

- Prescribe Slenyto® prolonged-release tablets available as 1mg and 5mg
- Starting dose 1mg once daily, increasing in increments of 1mg.
- If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg daily.
- Tablets should be taken once daily, 0.5-1 hour before bedtime and with or after food.
- Tablet should be swallowed whole, and not broken, crushed or chewed. They may be mixed into food such as yoghurt, orange juice or ice cream to aid swallowing.
- Review after first 3 months then every 6 months

Age 2 – 18 other neurodevelopmental diagnoses

- Prescribe melatonin 2mg MR tablets
- Starting dose 2mg 30-60 minutes before bedtime
- If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg daily.
- Tablets may be crushed and mixed with water directly prior to administration
- Review after first 3 months then every 6 months

It is accepted practice that the duration of therapy may exceed the licensed duration

- Continue to use healthy sleep practices – please refer to Appendix I for advice on what this means
- Reviews to include parent completed documentation of child's sleep pattern
- During ongoing treatment, if efficacy is uncertain, discontinuation attempts should be done regularly at least annually or earlier. Consider 5-7 day complete break. Carers to complete diary before break, during break and on restarting
- Stop melatonin if ineffective.

Sleep Problems in Children and Young People: Patient Pathway

*Use in conjunction with **Melatonin for paediatric sleep disorders - process for initiation, assessment and dose optimisation by specialists***

Primary Care Responsibilities

Specialist Team Responsibilities (either community services, secondary care of tertiary care)

1. *See BEARS sleep screener- available online, here*
2. Sleep and young children - NHS
3. Sleep Resources | Community Children's Health Partnership (cchp.nhs.uk)

START OF PATHWAY

GP review of young person with sleep problems

Consider use of Sleep Screener[1]

Type of sleep problem

Sleep Apnoea Symptoms

Refer – ENT general/respiratory paediatrics

Non-Sleep Apnoea

Give sleep behavioural advice leaflet[2] if behavioural insomnia

No improvement or non behavioural

Refer to general paediatric/community paediatrics or CAMHS/CAMHS LD service if associated with mental illness

Consider Sleep Disorder Screen[1]/Neurodevelopmental Assessment

Ensure adequate sleep behavioural input before any medication
Introduce idea of sleep documentation to monitor sleep[3]
Discuss treatment evaluation and sleep outcomes from melatonin initiation and dose optimisation pathway

Initiate appropriate medication as per table on pg 2 – consider underlying diagnosis and formulation

Reassess against agreed sleep outcomes

Improvement

Initiate transfer of care to the GP. Ensure awareness of monitoring and reviewing responsibilities – see pg 7

No improvement

Reconsider sleep diagnosis and medication choices

Still no improvement

Refer to specialist sleep/CAMHS/Neurodisability tertiary service

Melatonin for paediatric sleep disorders – process for initiation, assessment and dose optimisation by specialists

This pathway should be interpreted in the context of the 'Sleep Pathway' which assumes that adequate behavioural advice takes place before prescribing and the further information/advice provided in this document

Baseline Eligibility for Melatonin

- **Sleep measurements:**

Sleep Latency (SL) more than 60 minutes, and/or longest sleep period (LSP) less than 6 hours and /or total sleep time (TST) more than 2 hours less than recommended for child's age[1]

- **Day time:**

Consider fatigue, irritabililty, attention difficulties,externalising behaviours (reported by school and/or parents)

- **Parent opinion**

Discussion on overall benefits and adverse effects

Primary Care Responsibilities

Specialist Team Responsibilities (either community services, secondary care of tertiary care)

Initiate Melatonin 1-2mg daily.
Refer to box on pages 2-4 for appropriate preparation initiation
(30-60 minutes before age-appropriate bed time)

Continue for 1 week[3]

Improvement

Assess improvements according to agreed outcome targets[2]

Improvement

No Improvement

Maintain on optimal dose and evaluate with completed sleep documentation every 6 months

Increase dose by 1mg increments each week to initial target of 5mg-6mg

If no response carefully reassess before continuing to **maximum of 10mg**

No Improvement

Discontinue melatonin

Annually (or earlier at the discretion of the prescriber) consider 5-7 day complete break. Carers to complete sleep documentation before, during and on restarting – restart as before by titrating dose from starting dose to previous optimal dose

Maintain current optimal dose but with regular 5-7 day breaks e.g. every month

Evaluate response to break

Improvement – not slow metaboliser[4]

Melatonin still improves sleep but **no** evidence of increased effectiveness immediately following break

No improvement on melatonin

Discontinue melatonin

Improvement – probable slow metaboliser who may have a loss of response to melatonin when on prolonged therapy[4]

Melatonin still improves sleep but evidence of increased effectiveness immediately following break

Treatment Target Outcomes[2]

a) Sleep latency (SL) reduced to less than 60 minutes, for at least 3 days of the week
b) Longest Sleep Period (LSP) increased by at least 45 minutes
c) Total sleep time (TST) Increased by at least 45 minutes

1. Sleep Foundation | Better Sleep for a Better You
2. *Oxford Handbook of Sleep Medicine*
3. *Melatonin for Sleep in Children with Autism : A controlled trail examining dose, tolerability and outcomes. Malow, Adkins et al.* J Autism Dev Disord. 2012 Aug; 42(8): 1729–1737.
4. *Loss of response to melatonin treatment is associated with slow melatonin metabolism. Braam et al.* J Intellect Disabil Res 2010

Roles and Responsibilities

Consultant/Specialist Team

- Make the necessary diagnosis as part of a thorough assessment. This should include a thorough history and a sleep diary if there is any doubt about the extent of the problem.
- Establish and document any allergies and previous hypersensitivity.
- Discuss the treatment options with the patient/carer(s) to include explanation of the nature of the melatonin, ensuring and documenting that they have a clear understanding of benefits, side effects, frequency of administration and monitoring requirements and obtaining appropriate consent to treatment.
- Discuss the concept of treatment breaks with the patient/carer(s) including the rationale behind them, when these may happen and what to expect.
- Provide written information on melatonin to families
- Initiate treatment with melatonin if agreed.
- Prescribe melatonin as a second-line treatment option where non-pharmacological strategies such as healthy sleep practice/advice have failed, and underlying causes are managed and continue to prescribe during the dose titration/stabilisation phase until the patient's condition is stable or predictable.
- The stabilisation phase may take 1-3 months and during this time the specialist would continue to review the patient.
- Provide written documentation to the GP on the anticipated duration of therapy, and information relevant to the treatment of the individual patient.
- Be available as a point of contact should the GP have any queries, including if treatment outcomes have deviated from the specialist documentation provided.

GP

Initially

- Review young person with sleep problems
- If sleep apnoea symptoms refer to respiratory paediatrics
- If behavioural insomnia give sleep behavioural advice with leaflet. If after there is no improvement, refer to paediatrics or CAMHS/CAMHS LD service if associated with mental illness. The time to referral should be at the discretion of the GP and individual patient/parent circumstances.

After initiation of melatonin and handover from specialist

- Review patient at 3 months and then every 6 months after initiation of melatonin.
- The review is to include assessment of efficacy, continuing need and any adverse effects. A trial withdrawal should be considered at each medication review. This can take the form of a treatment holiday where the melatonin is withdrawn for a period of 5-7 days. Treatment holidays can be used to inform the clinician whether the child may be able to stop melatonin permanently.
- If appropriate sleep habits are established after a treatment break, melatonin should be stopped.
- If sleep deteriorates after a withdrawal break the melatonin can be reintroduced at the previous optimal dose.
- If melatonin still improves sleep but evidence of increased effectiveness immediately following break - maintain current optimum dose but consider more frequent regular 5-7 day breaks.
- **Refer to the relevant preparation's summary of product characteristics when prescribing any additional medication to check for possible adverse effects and drug interactions.**

Duration of Treatment and Criteria for Stopping Treatment

- The duration of treatment should be determined on an individual basis. The aim is to establish healthy sleeping habits with the lowest effective dose of melatonin.
- It is suggested that at least 6 months of an improved sleep pattern should elapse before withdrawal takes place. These can take the form of 5 -7 day complete treatment breaks, and a change in sleeping pattern observed. For some children withdrawal is not successful and treatment may be necessary for the longer term.
- Specialist advice should be sought if there are any concerns on stopping treatment.

Treatment should be stopped;

- if there is significant adverse reaction(s)
- if there is a lack of efficacy
- at the request of patient/family

Appendix I

Healthy Sleep Practices

General healthy sleep practices, that are recommended in all children, include:

- Having a healthy level of physical activities during the daytime, preferably in the outdoors, which is known to help improve sleep health.
- Having set bedtimes and wake-up times that remain roughly the same every day of the week, as this helps maintain a healthy body clock.
- Stopping screen-based activities at least 1 hour before bedtime (the blue light emitted from screens makes the brain think it is daytime, and stops the body's natural melatonin hormone from working).
- Reducing caffeine, vaping, smoking and stopping illicit drug use. These will be screened for by the specialist team and should be monitored by the GP in follow up appointments.
- Removing all screen-based devices from the bedroom; this prevents them being a distraction as the child is trying to settle, or during the night.
- Engaging in wind-down activities before bedtime that create a calm atmosphere, such as engaging in simple board-games, reading or looking at books together, listening to calming music or audiobooks.
- Having a set bedtime routine that happens in the same way every night; using a visual schedule to support the bedtime routine, for children with communication impairments
- The child falling asleep in the place where they are expected to sleep for the rest of the night.
- Having a transitional object (e.g. a comforting toy) to develop sleep confidence, and a healthy sleep association
- Children need to feel safe and secure in order to sleep well, therefore considering any other factors that may be causing them worry, and working to address these factors.

Age group	Age range	Recommended hours of sleep
Infant	4-12 months	12-16 hours (including naps)
Toddler	1-2 years	11-14 hours (including naps)
Preschool	3-5 years	10-13 hours (including naps)
School-age	6-12 years	9-12 hours
Teen	13-18 years	8-10 hours
Adult	18 years and older	7 hours or more

(table taken from How Much Sleep Do You Need? | Sleep Foundation)

Appendix II

Useful information/resources that may be provided to the patient/carer

- Helping Your Child Sleep – information for parents of disabled children – published by Contact a Family (2018). This is available either in Clinic or at Helping-your-child-sleep.pdf (contact.org.uk)
- Sleep Problems in Children and Young People; Yemula C.R. Dwarakanathanb, Yemula R (2014) Published by Health Insights 4 U Ltd. Sleep problems in children and young people – A simple guide for parents – Health Insights 4U
- Medicines for Children have also produced a PIL and is available via Melatonin for sleep disorders – Medicines For Children
- A sleep diary is available from https://patient.info/health/insomnia-poor-sleep/features/sleep-diary
- Sleeping Well. http://www.rcpsych.ac.uk/mentalhealthinfo/problems/sleepproblems/sleepingwell.aspx
- Specific advice relating to teens. How to sleep well for teenagers | Evelina London

Appendix III

Useful Contact Information

The child's specialist team's contact details should be provided on any communication including clinic letters and individual management plans. Below are some additional generic contact details that might be useful.

Bexley Community Paediatrics: oxl-tr.BexleySCS-SPA@nhs.net

Greenwich Community Paediatrics: oxl-tr.childrenstherapies@nhs.net

Medicines Information at Oxleas: oxl-tr.medicinesinfo@nhs.net

Evelina London Paediatric Sleep Team: gst-tr.PaediatricSleepSecretaries@nhs.net

Evelina London Medicines Helpline: LetsTalkMedicines@gstt.nhs.uk

Medicines Information at South London and Maudsley (SLAM): Pharmacy_Staff_Medicines_Advice@slam.nhs.uk

King's College Hospital NHS Foundation Trust Paediatric Pharmacy Team: kch-tr.WomenandChildrenPharmacyTeam@nhs.net

Lewisham and Greenwich NHS Trust Medicines Information Services: LG.QE-Medinfo@nhs.net

Southwark and Lambeth Community Paediatric Sleep Team: gst-tr.communitysleep@nhs.net