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 with support from the Greenwich Borough Medicines Management Team.

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Introduction

The pathways on the following two pages outline the process 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 behavioural interventions fails to adequately manage the patient's sleep disorder.

Guidance on managing paediatric patients in primary care can be found in the associated shared care guideline, which sets out the responsibilities of the specialist team, the GP and the patient/their carers.

Preparations and their place in in therapy (refer to the pathways on pages 3 and 4 for dosing information)

Preparation	Licensing status in paediatrics	Place in therapy	Other points to note
Melatonin 2mg modified release tablets (Circadin®) (Summary of Product Characteristics [SPC] available here.	Off-label use in paediatrics of a licensed product. Circadin® is licensed for use as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.	First line choice unless patient meets criteria for the other preparations noted below.	**For patients with swallowing difficulties:** · Circadin® 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. · Circadin® tablets can also be halved (using a tablet cutter) **For administration via an enteral feeding tube:** · Circadin® tablet can be crushed to a fine powder and added to 5 - 10ml of water and mixed well.
Melatonin 1mg and 5mg prolonged release mini- tablets (Slenyto®) SPC 1mg prolonged release tablet SPC 5mg prolonged release tablet	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.	Reserved for use in patients who meet the Slenyto® licensed cohort.	· Circadin™ remains 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. · Data are available for up to 2 years' treatment. · SPC notes monitoring of patient at regular intervals (at least every 6 months).
Melatonin 1mg per 1mL oral solution	Unlicensed preparation (special)	Reserved for use in patients with fine-bore enteral feeding tubes (gauge less than 9) where there is risk of tube occlusion or if there are compliance issues with the crushed tablets.	· The preferred oral solution is Kidmel® due to a more acceptable excipient profile. See template clinical need letter on page 5 to send to suppliers. · In cases where the enteral feeding tube is no longer required, the need for liquid preparation should be reviewed.

Ongoing review of patients on melatonin for sleep disorders

Patients will remain under the specialist paediatric team and the specialist paediatric team will retain responsibility for regular review of treatment (6 monthly recommended). Patients will be reviewed by the specialist team against the outcomes noted in the pathways. The process for implementing any treatment breaks (e.g. 5 days in every month or annual treatment breaks) will be communicated to the GP by the paediatric specialist.

Long term data and safety of melatonin

In the more recent largest placebo-controlled studies to date involving children with learning difficulty, 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)

Switching melatonin preparations

Switching of stable patients prescribed Circadin® to alternative melatonin preparations is not supported by this guidance. However switching from unlicensed oral solution to tablets (in a whole or crushing) following review could be more cost-effective.

Prescribing by brand

To avoid confusion in the selection of products, it is recommended that melatonin preparations are prescribed by brand.

Daily dose of melatonin

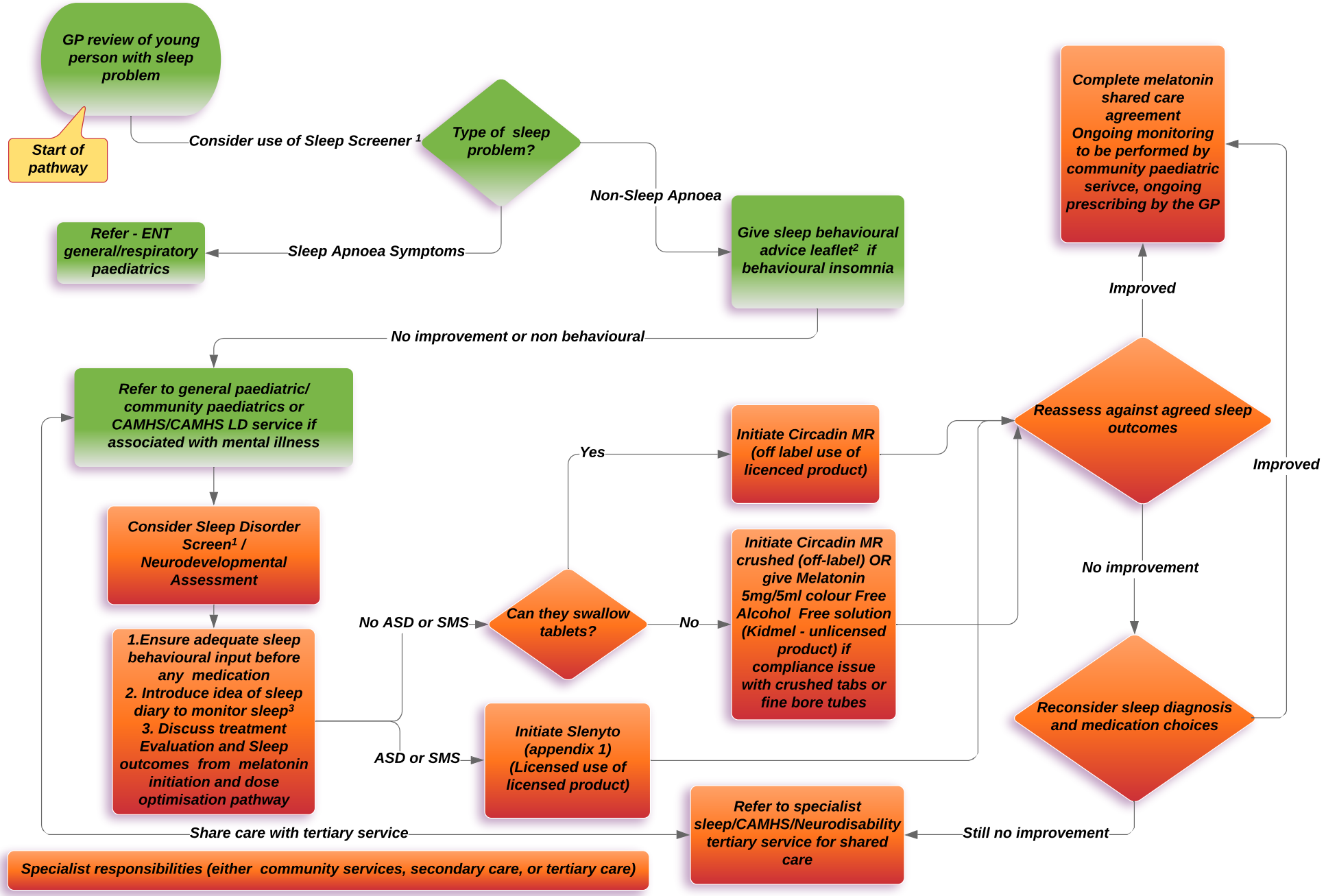
Based on local expert opinion, in most patients a total daily dose of melatonin up to 6mg daily is usually sufficient to manage the patient's sleep disorder. In line with the BNF for Children, the maximum daily dose of melatonin should not exceed 10mg daily.

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 (for example, Slenyto® is currently only licensed in ages 2 – 18 years or consider if patients receiving the oral solution can change over to the tablet formulation).

Sleep problems in children and young people; patient pathway, and melatonin product choice (specialist use)

Use in conjunction with 'Melatonin - process for initiation, assessment and dose optimisation by specialists" and the South East London Shared Care Agreement for melatonin in paediatric sleep disorders



1. See BEARS sleep screener
2.https://www.nhs.uk/conditions/pregnancy-and-baby/sleep-problems-in-children/
3. https://cchp.nhs.uk/sites/default/files/attachments/Detailed%20Sleep%20Diary.doc

ASD= Autistic Spectrum Disorder
SMS = Smith Magenis Syndrome

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 parent led sleep behavioural advice takes place before prescribing, and the melatonin in paediatrics shared care guidance which delineates the responsibilities for the prescribing and monitoring of treatment (specialist initiate treatment, with prescribing responsibilities transferred in stable patients on acceptance of the SCA)

Baseline Eligibility for Melatonin

1. Sleep measurements: Sleep Latency (SL) >30 minutes, and/or longest sleep period (LSP)<6 hours and /or total sleep time (TST) >2 hours less than recommended for child's age[1]

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

3. Parent opinion on overall benefits and adverse effects

Treatment Target Outcomes[2]

1.Sleep latency (SL) reduced by at least 30 minutes

2. Longest Sleep Period (LSP) increased by at least 45 minutes

3. Total sleep time (TST) Increased by at least 45 minutes

Initiate Melatonin 1-2mg daily

Refer to box on right hand side for appropriate preparation for initiation

(30 minutes before agreed age -appropriate bed-time)

Continue for 1 week[3]

Improvement

Assess improvements according to agreed outcome targets[2]

No improvement

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

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

Improvement

Maintain on optimal dose and evaluate with carer completed 1 week sleep diary every 6 months

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

Maintain current optimum dose but with regular 5 day breaks eg every month

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

Improvement -not slow metaboliser[4]

Evaluate response to break period

No improvement on melatonin

No improvement

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

Improvement - probable slow metaboliser[4]

Discontinue melatonin

Specialist responsibilities (either community services, secondary care, or tertiary care)

Primary care responsibilities

1. https://www.sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times
2. OUP Sleep Handbook
3. Malow, Atkins et al 2012
4. https://www.ncbi.nlm.nih.gov/pubmed/20576063

Melatonin preparations available in South East London:

(refer to sleep pathway for detailed considerations as to where each would be prescribed)

Circadin 2 mg MR tablets:

First line choice in non Autistic Spectrum Disorder patients

Use in paediatric sleep disorders is off-label

Can be halved or crushed if required, though loses the drug slow release mechanism

Slenyto 1 mg or 5 mg prolonged release tablets

Licensed for use in insomnia in children with Autism Spectrum Disorder and / or Smith-Magenis syndrome (first line preparation for these patients)

Formulated as a microtab to facilitate adherence

Melatonin 5 mg in 5 mL liquid (Kidmel brand)

Unlicensed product

Reserved for use in those unable to swallow and unable to adhere to crushed Circadin tablets, and in those with fine bore tubes.

Ethanol free, and most appropriate excipient profile for use in children

- **This flowchart is designed to apply to all melatonin preparations**. The available doses of each preparation will affect the starting dose and titration steps. Circadin for example will usually be started at one tablet or 2mg, whereas Slenyto or melatonin liquid can start with 1mg dose.
- Note that prescriber can start with 2mg Slenyto as per manufacturing recommendations but we favour a 'start low and go slow approach'
- 75% of children in Slenyto trials improved TST/SL or both sleep by>1 hour. Of these 'responders' 75% of children in trials responded to 5mg or less and 25% to 10mg.

Templete letter: Clinical need for melatonin 5 mg in 5 mL oral solution (KidMel®)

Purpose of letter

Suppliers require justification for the supply of an unlicensed melatonin oral solution (KidMel®) where an equivalent UK licensed preparation is available due to concern of containing the following excipients which may be potentially problematic when used in children:
Propylene glycol 150.37 mg per 1ml dose
Sorbitol 140 mg per 1ml dose

The template letter below can be used by prescribers when requesting KidMel® for suitable paediatric patients.

Please refer to individual Summary of Product Characteristics for a list of excipients and suitability for individual patient.

Template letter of clinical need for melatonin 5mg in 5ml oral solution (KidMel®)

To whom it may concern,

Request for use of melatonin 5mg in 5ml oral solution (KidMel®)

We are aware that there is a licensed pharmaceutical preparation of melatonin 5mg in 5mL oral solution; however we requesting supplies of Kidmel® melatonin 5mg in 5mL alcohol free oral solution to meet the special clinical needs of this patient as we are more satisfied with the excipient profile of this product in terms of appropriateness for use of children.

Doctor name:……

GMC number:……

Date:……