NHS
Kent and Medway
Clinical Commissioning Group

Kent and Medway Policy Recommendation and Guidance Committee
Policy Recommendation

Policy:	**PR 2021-10: Melatonin for sleep disorders in children with neurodevelopmental disorders**
Issue date:	**May 2021**
This policy recommendation replaces PR2013-03	

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) considered NICE and other guidance, the evidence base, baseline position, other CCG policies, the views of stakeholders and the potential impact of changing policy. All decisions were made with reference to the Ethical Framework. Taking these into account the PRGC recommends:

Overarching principles

- Melatonin should only be considered:
  - For persistent sleep disorders in children with neurodevelopmental disorders;
  - Where an adequate trial of non-pharmacological strategies has failed;
  - According to the commissioned pathway; it should not be initiated by acute paediatricians
- Treatment duration is intended to be short; it is important that this is emphasized to children and their carers at the outset
- The aim of melatonin treatment is to establish healthy sleeping habits. Non-pharmacological strategies need to be promoted and persevered with alongside melatonin treatment, so that progress is maintained after melatonin treatment ends. This should include use of sleep questionnaires to explore the nature of sleep problems and sleep diaries to assess the benefits of interventions. Prescribing melatonin may provide the opportunity for better rested children and carers to more effectively employ sleep hygiene measures and reduce the need for long-term melatonin use. This should include empowering children to determine what works best for them. Also, children may well outgrow their sleep onset latency as they get older. Prescribing melatonin should be viewed in this context.
- Children (and their carers) should be made aware that:
  - Little is known about the long-term effects (>2 years treatment) of melatonin in children. There is uncertainty on what effects exogenous melatonin has on other circadian rhythms including endocrine or reproductive hormone secretion. There are some concerns that long-term use of melatonin might delay children's sexual maturation.
  - Melatonin does not work for everyone – this has been established in clinical trials; it is appropriate that treatment is stopped if a clinically relevant treatment effect is not seen.
  - The continued need for melatonin will be reviewed regularly (including planned gradual trial withdrawals). This will include the use of sleep diaries.
  - Melatonin is not commissioned for adults with sleep disorders
  - There is a concerted drive across the NHS to reduce polypharmacy in general and more specifically (supported by NHS England and the Royal College of Paediatricians and Child Health) to stop the over medication of children with a learning disability, autism or both, with psychotropic medicines (including hypnotics such as melatonin).

Continued overleaf

  - Evidence on the use of melatonin for sleep disorders in ADHD is limited, particularly in children with ADHD taking stimulant medication

- Management of sleep problems in children with ADHD using stimulants should include:
  - A review of possible causes of sleep problems (it is important to refer back to the baseline sleep evaluation undertaken prior to initiation of ADHD medication to ensure reported sleep problems are related to medication rather than to a longer term problem)
  - Consideration of stopping ADHD medication
  - Implementation of non-pharmacological strategies
  - Re-evaluation of ADHD medication. This may involve either changing the medication dose, the dosing regimen or the treatment formulation, or switching to alternative ADHD medications (such as atomoxetine).
  - Where sleep problems persist after non-pharmacological strategies and review/ adjustment of primary ADHD medications, the use of adjuvant melatonin may be considered.

Initiating prescribing

- Melatonin (max daily dose 10mg as per BNFc) may be considered for children aged <18 years with neurodevelopmental disorders and significant sleep latency problems provided the following criteria are met:
  - Individual has been assessed by a specialist clinician and identified to have a neurodevelopmental disorder
  - Individual has a documented severe sleep disorder persisting for >3–6 months that is having a significant adverse impact on the quality of life (and/or school performance) of the child and their family/ carers
  - Other causes of sleep disorder have been assessed and managed
  - An adequate trial of non-pharmacological strategies (sleep hygiene advice and behavioural strategies where available, based on an initial assessment of sleep problems) has failed to satisfactorily address the sleep disorder (and its impact)
  - Parents/ carers have completed a sleep diary for 2 weeks which demonstrates significant ongoing problems with sleep latency
  - A specialist clinician[1] initiates treatment with melatonin. The specialist should confirm the effectiveness of treatment using a sleep diary[2], and stabilise the dose before ongoing prescribing in primary care under formal shared care arrangements is considered. Treatment should be stopped if ineffective[3].
  - Behavioural interventions should be continued after melatonin is prescribed
- Melatonin is not funded solely for the treatment of night time waking in children with neurodevelopmental disorders.

Continued overleaf

Ongoing prescribing

Individuals should be reviewed by the specialist 3–6 months after initiation of melatonin and 6–12 months thereafter

- At each review by the specialist[1]:
  - the benefits of continued treatment should be confirmed (documented using a sleep diary over the 2 weeks prior to the appointment). Treatment should be stopped if ineffective[2,3].
  - a gradual, planned trial withdrawal of melatonin (whilst monitoring change in sleeping pattern using a sleep diary) should be considered
  - children prescribed unlicensed melatonin preparations not recommended locally should be reviewed for a switch to a preferred formulation
- As use should be short-term and reviewed regularly, it is recommended that melatonin should only be added to the repeat prescription list to coincide with the next specialist review (i.e. for either 3–6 months following melatonin initiation or every 6–12 months thereafter). Each repeat prescription should be for a maximum duration of 4 weeks.
- Melatonin use should be discontinued by late adolescence (by 18 years) on the recommendation of the specialist.

Resources

- Healthy sleep tips for children on nhs.uk
- The Teen Sleep Hub website and downloadable eBook aimed at teenagers developed by The Sleep Charity
- Leaflet with advice on swallowing pills is available here; short training video on swallowing pills hosted on youtube.com is available here[4]
- Advice on crushing Circadin (Table 1)

[1]*Specialist community paediatrician (not acute paediatrician), child psychiatrist or child psychologist with expertise in the management of neurodevelopmental disorders in children.*

[2]*The MENDS study defined clinical significance as an increase of 1 hour for total sleep time and a reduction in sleep onset latency of 30 minutes compared to baseline.*

[3]*The EMA assessment of Slenyto noted that many of the participants in the pivotal clinical trial may have been non-responders to any dose of melatonin, which emphasizes the need for a stopping rule related to insufficient efficacy. According to the SPC for Slenyto, after at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment.*

[4]*Dersch-Mills D and Kaplan BJ 2020; see also: Kaplan BJ 2010.*

This policy recommendation will be reviewed when new information becomes available that is likely to have a material effect on the current recommendation.

Kent and Medway Clinical Commissioning Group (CCG) will always consider appropriate individual funding requests (IFRs) through its IFR process.

Supporting documents

NEL Health Policy Support Unit (HPSU) (2021) *Melatonin for sleep disorders in children with neurodevelopmental disorders – Scoping report*

Equality Analysis Screening Tool – Melatonin for sleep disorders in children with neurodevelopmental disorders (2021)

Table 1 – Advice on crushing Circadin

Information leaflet for parents and carers

If your child has recently been prescribed Circadin 2mg prolonged release tablets then the following information may be useful. Please note that this information only applies to this particular brand of melatonin tablets.

- Circadin tablets should normally be swallowed whole with a glass of water once a day, between half an hour and one hour before your child's agreed bedtime. Give the medicine at about the same time each day so that this becomes part of your child's daily routine, which will help you to remember. Swallowing the tablet whole means that the melatonin is released gradually over a period of time and the effect is maintained.
- If your child has problems swallowing tablets or the specialist wants a quicker effect, you may be advised to crush the tablets and give with a spoonful of milk or yoghurt. If the tablets are crushed, they should be given just before bedtime.
- Crushing a Circadin tablet will not damage the active ingredient (melatonin) and there are no safety concerns. However, crushing will affect the prolonged release properties of the product, so we advise swallowing the tablet whole if possible to maximise the effect for as long as possible. Most of the prolonged-release properties will be maintained if the tablet is halved but not if the tablet is divided into 4 quarters or crushed.
- Crushing tablets is usually quite simple, but some techniques are easier than others.
    - You can purchase a tablet crushing device from your local community pharmacy. These are often made of plastic and are relatively inexpensive. They are reusable, can be rinsed and dried after use, and can be used to crush other suitable tablets too.
    - Alternatively, you can use two similarly sized dessert spoons to crush the tablet. Put the spoons together so that one spoon sits on top of the other. Make a small gap between the spoons, place one tablet in the gap and gently squeeze the spoons together. The tablet should break up without escaping. Further crushing will make a finer powder. Please note that it is not necessary to crush to a very fine powder. Repeat if more than one tablet is required to provide the dose prescribed by your doctor.

If you have any queries, please speak to your GP or pharmacist.

Reference: Surrey & North West Sussex Area Prescribing Committee Circadin® (melatonin) 2mg Prolonged-Release Tablets. Originally developed by Surrey Heath CCG Medicines Management Team Dec 15 and updated by Lis Stanford NWS CCG Medicines Optimisation team and Alison Marshall SABP August 2019.

Key points

What are neurodevelopmental disorders?

Neurodevelopmental disorders are neurologically based conditions that appear early in childhood and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning. A wide range of conditions fall under this definition, including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), cerebral palsy, genetic disorders, and non-specific diagnoses such as 'learning disability (LD)'. Neurodevelopmental disorders frequently co-occur.

What are sleep disorders?

Sleep has been described as an active 'restorative process' and is essential for optimal physical and mental functioning and well-being. Sleep disorders (such as difficulty getting to sleep or staying asleep) in children are common. For children with neurodevelopmental disorders, sleep problems are more common and usually more difficult to treat compared with typically developing children. Sleep disorders can affect children's and parents' mental, physical and emotional well-being.

Ensuring adequate sleep hygiene and, when appropriate, the use of specific behaviour therapy to improve sleep are first-line treatments for many sleep disorders in children with neurodevelopmental disorders. However, behavioural approaches can be difficult to apply. Melatonin may be considered where such interventions prove ineffective, alongside ongoing non-pharmacological interventions.

What is melatonin?

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep.

A licensed melatonin preparation (Circadin 2mg melatonin prolonged-release tablets [Flynn Pharma Ltd]) for use in adults aged ≥55 for the short-term treatment of primary insomnia has been available since 2008. Melatonin has a naturally short half-life which is why a prolonged-release (P/R) formulation was developed to achieve sustained melatonin levels during sleep.

The following additional melatonin preparations have been licensed more recently:

- Slenyto 1mg and 5mg melatonin P/R tablets (Flynn Pharma Ltd) licensed for the treatment of insomnia in children aged 2-18 with ASD and/ or Smith-Magenis syndrome (SMS)[1], where sleep hygiene measures have been insufficient. Slenyto is the first and only melatonin preparation licensed for use in children.
- Melatonin 3mg tablets and melatonin 1mg/ml oral solution (both Colonis Pharma Ltd) licensed for the short-term treatment of jet-lag in adults.

Patients that have difficulty taking tablets (or that require doses not available in a licensed tablet form) may also be prescribed an unlicensed melatonin preparation to meet their special clinical need. Unlicensed melatonin liquid formulations, tablets and capsules have immediate release profiles. Unlicensed melatonin preparations are obtained from special manufacturers or are imported products. Some of these imported products are classified as supplements, not pharmaceuticals in their country of origin.

The MHRA advises that an unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient.

What is the cost of melatonin?

The annual cost of melatonin prolonged-release Slenyto and Circadin 2mg to 10mg daily is £502–£2,508 and £187–£937 respectively. The costs of unlicensed melatonin preparations vary considerably (and fluctuate) and may be substantial.

What does NICE guidance say?

There is no NICE technology appraisal guidance on the use of melatonin, but a number of NICE clinical guidelines include recommendations on pharmacological interventions for sleep problems in people with a range of different neurodevelopmental disorders:

- NICE clinical guideline (CG) 170 (2013) on ASD in under 19s and NICE guideline (NG) 11 (2015) on challenging behaviour and learning disabilities recommend that pharmacological

[1] SMS is a rare developmental disorder. Patients manifest a severe phase shift of their circadian melatonin rhythm with the diurnal secretion of this hormone. In addition to problems sleeping at night, daytime sleepiness is common.

interventions to aid sleep should only be used where sleep problems persist despite non-pharmacological interventions, after consultation with a specialist and with regular reviews. Both guidelines recommend that pharmacological interventions should only be used in conjunction with non-pharmacological interventions.

- NICE CG53 (2007) on chronic fatigue syndrome/ myalgic encephalomyelitis (or encephalopathy) and NG62 (2017) on cerebral palsy in under 25s recommend that melatonin should be considered for sleep difficulties in children with these conditions following specialist advice.
- NICE NG87 (2018) on ADHD does not make specific recommendations on the use of medication to aid sleep in children with ADHD, but does recommend that changes in sleep pattern should be monitored and medication adjusted accordingly.

What does other national guidance say?

- The All Wales Medicines Strategy Group (AWMSG) recommends use of Slenyto for its licensed indication within NHS Wales (2021). This recommendation was based on a resubmission by the company that included a patient access scheme (i.e. confidential discount on list price).
- The Scottish Medicines Consortium (SMC) does not recommend use of Slenyto for its licensed indication within NHS Scotland because the company did not present a sufficiently robust economic analysis (2021). The SMC appraisal was based on a resubmission by the company that included a patient access scheme (i.e. confidential discount on list price).
- The SMC does not recommend use of Circadin within NHS Scotland for its licensed indication because the company has not made a submission (2008)
- The AWMSG does not endorse the use of melatonin 1mg/ml oral solution or 3mg tablets (both Colonis Pharma Ltd) within NHS Wales for the short-term treatment of jet lag in adults because the company has not made a submission (2019)
- SIGN guideline 145 (2016) recommends that a trial of melatonin to improve sleep onset should be considered in children with ASD who have sleep difficulties not resolved by behavioural interventions
- The STOMP initiative – launched in 2016 by NHS England jointly with several of the Royal Colleges – is a national project to stop the over medication of adults with a learning disability, autism or both, with psychotropic medicines (including hypnotics such as melatonin). The STOMP-STAMP initiative – launched in December 2018 – extends this to children and young people.

What does professional society guidance say?

- According to a British Association for Psychopharmacology consensus statement (2019), melatonin improves sleep in children with ASD and can be used to advance sleep onset to normal values in children with ADHD who are not on stimulant medication
- According to European best practice guidance (2013), the management of sleep problems during treatment with ADHD medications should include: ruling out differential diagnosis, implementation of non-pharmacological strategies, reviewing/ adjusting ADHD medications and consideration of adjuvant melatonin

What is the evidence base for melatonin for sleep disorders in children with neurodevelopmental disorders?

A systematic literature search identified:

- 1 placebo-controlled RCT (and long-term follow-up studies) assessing P/R melatonin (Slenyto) in 125 children with ASD (97%) or SMS (3%) and sleep problems that behavioural intervention alone failed to improve. Slenyto (versus placebo) increased total sleep time by about 32 minutes on average and reduced sleep onset latency by about 25 minutes in children with ASD, which was considered clinically relevant by the European Medicines Agency (EMA). However, Slenyto did not improve the number of awakenings or duration of wake time. The effects of treatment (up to 52 weeks) on total sleep time and sleep onset latency were maintained.
- 1 systematic review and meta-analysis of 13 RCTs evaluating a variety of melatonin preparations (but not Circadin or Slenyto) for sleep problems in children with neurodevelopmental disorders. Included RCTs assessed a number of melatonin formulations in children with a range of neurodevelopmental disorders; some RCTs only included children with a single neurodevelopmental disorder, others included mixed populations. The review concluded that there is some evidence of benefit for melatonin compared with placebo on the management of sleep disturbances in children with neurodevelopmental disorders, but the

degree and duration of benefit, which children might benefit most, and the significance of the benefit to the well-being of the child/ family remain uncertain because of the diverse populations in the studies and the predominantly poor-quality evidence. The adverse event profile suggested that melatonin was well-tolerated. Subgroup analysis suggested that benefit may be greatest for populations with ASD; however, this should be interpreted with caution and further research is required before definitive recommendations can be made.

- No studies were identified comparing the efficacy of Slenyto with that of off-label Circadin or unlicensed immediate-release melatonin products in children with neurodevelopmental disorders
- No studies assessing the cost-effectiveness of melatonin were identified. Low-quality evidence from the economic model developed for NICE NG11 suggests that combined therapy of melatonin (i.e. Circadin) and psychological intervention is the most cost-effective treatment option for the management of sleep problems in children and young people with a learning disability (compared to melatonin and psychological intervention alone or waitlist).

What is the baseline position?

- Services for children with neurodevelopmental disorders across Kent and Medway (K&M) are provided by Children and Young People's Mental Health Services (CYPMHS) delivered by North East London NHS Foundation Trust (NELFT) and (community) paediatricians, depending on age and condition
- Provision of services to deliver non-pharmacological interventions for sleep problems in children with neurodevelopmental disorders differ significantly across K&M, with pathways in some areas enabling greater emphasis on non-pharmacological interventions before melatonin is considered and greater support of ongoing non-pharmacological interventions alongside melatonin should it be prescribed.
- Prescribing of melatonin for sleep disorders in children with neurodevelopmental disorders differs across K&M:
    - The East Kent formulary does not recommend routine prescribing of melatonin in primary care; prescribing by CYPMHS (i.e. NELFT) and East Kent Hospitals University NHS Foundation Trust (EKHUFT) remain the responsibility of these teams
    - The remaining areas recommend primary care prescribing of melatonin (Circadin is the formulation of choice) under formal shared care guidance (following specialist initiation) where non-pharmacological strategies have failed. Shared care guidance differs somewhat across these areas.
- Estimated expenditure on prescribing of melatonin across K&M is as follows:
    - According to ePACT prescribing data, the former K&M CCGs spent £789k on melatonin (all presentations) for children (<18 years) in 2019/20, up from £680k in 2018/19. This includes prescribing by primary care and CYPMHS (i.e. NELFT) but not EKHUFT (see below). The most commonly prescribed preparation was Circadin 2mg P/R tablets (91% of total items and 74% of total cost). The average cost per item varied significantly.
    - Total expenditure on all melatonin presentations at EKHUFT for the 12 months June 2019 to May 2020 was £325k. Expenditure was greatest on Circadin 2mg MR tablets (57% of total cost) and melatonin 5mg/5ml oral solution (34% of total cost).
    - Total expenditure on all melatonin presentations per 100,000 <18 population in 2019/20, by integrated care partnership was £220k in West Kent, £282k in Medway and Swale, £294k in East Kent and £318k in Dartford, Gravesham and Swanley.

Change sheet

Reason for review:
Current provision of melatonin for sleep disorders in children with neurodevelopmental disorders differs across Kent and Medway.

Kent and Medway CCG requested development of an overarching policy and guiding principles on the use of melatonin for sleep disorders in children with neurodevelopmental disorders. Product selection, shared care guidelines and commissioning of sleep pathways to better support non-pharmacological interventions will be developed separately.

Change from baseline:
The intention of PR2021-10 is to support a standardised approach to managing sleep disorders in children with neurodevelopmental disorders across Kent and Medway; reserving melatonin for short-term use (where possible), with regular reviews by specialists at the end of a pathway of care that emphasizes and promotes non-pharmacological interventions before melatonin is considered and alongside melatonin should it be prescribed.

Agreement of PR2021-10 will constitute the first step in developing a standardised approach to managing sleep disorders in children with neurodevelopmental disorders across Kent and Medway; additional actions will be required to support implementation of the policy, such as the commissioning of sleep pathways across Kent and Medway that better support non-pharmacological interventions.

Implementation of PR2021-10 is unlikely by itself to lead to a large change from baseline prescribing of melatonin; it is largely consistent with current local shared care guidance, does not make recommendations on product selection and does not require increased provision of non-pharmacological interventions (although it supports such a change). Whilst PR2021-10 supports ongoing prescribing in primary care under shared care guidance following specialist initiation, this is not mandated, so this would not require a change from baseline in East Kent (where shared care arrangements are not currently in place).

Rationale for PR2021-10:
PR2021-10 is consistent with NICE guidance on the management of sleep disorders in children with neurodevelopmental disorders (i.e. NICE CG170, NG11, CG53, NG62). It also takes account of current local shared care guidance, the views of local specialists, the STOMP-STAMP initiative and European best practice guidance on the management of sleep problems during treatment with ADHD medications.

Estimated cost impact of implementing PR2021-10:

- Implementation of PR2021-10 is unlikely by itself to lead to a significant cost-impact, because PR2021-10 is largely consistent with current local shared care guidance, does not make recommendations on product selection and does not require increased provision of non-pharmacological interventions.
- The following changes (not recommended in PR2021-10 but may be undertaken as part of additional work to support a standardised approach to managing sleep disorders in children with neurodevelopmental disorders across Kent and Medway), may lead to a cost impact in the future:
    - commissioning of more comprehensive sleep pathways that better support non-pharmacological interventions
    - recommendations on product selection
    - introducing primary care prescribing of melatonin in east Kent, considering that unlicensed melatonin formulations dispensed at EKHUFT appear to be cheaper than unlicensed melatonin formulations dispensed at community pharmacies across Kent and Medway.