Guideline on the use of melatonin for the management of sleep disorders

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BACKGROUND

Melatonin is a naturally-occurring hormone produced in the brain by the pineal gland. It is normally produced in a circadian manner in response to falling light levels, with production starting in the evening and peaking around 2-4am. Its primary function is to induce the physiological changes which prepare the body for sleep, including a hypnotic effect and a fall in body temperature.[1,2,3,4]

Synthetic melatonin is used to promote sleep in a variety of conditions and is considered to have a favourable side-effect profile.[5]

SLEEP HYGIENE

Advice on sleep hygiene should be offered to those with insomnia.[6] For further information refer to: https://www.choiceandmedication.org/nhs24/generate/handyfactsheetsleephygiene.pdf.

MONITORING

A sleep diary (Appendix 1) is recommended before commencing a trial of melatonin in children and adults.[7] This should be completed for at least 2 weeks prior to starting melatonin to determine the baseline sleep pattern and assess if sleep hygiene measures are being adhered to. Sleep hygiene measures and a sleep diary should continue throughout treatment with melatonin.

Patient response to treatment and the ongoing effectiveness of melatonin should be monitored using sleep diaries and assessment of sleep hygiene measures. Melatonin should only be continued where there is clear evidence of ongoing effectiveness. Prescribing of melatonin should be reviewed regularly[7] and treatment breaks are recommended to assess ongoing need.

INDICATIONS AND PRESCRIBING RECOMMENDATIONS

(A) Adults with insomnia

Large-scale study evidence to support the use of melatonin in the treatment of insomnia is lacking and the long-term effects are unknown.[8] The British Association for Psychopharmacology (BAP) recommend that when a hypnotic is indicated for the treatment of insomnia in adults aged over 55 years, prolonged-release melatonin should be tried first.[9]

Prolonged-release melatonin may be considered in adults aged over 55 years as a short-term adjunctive treatment with behavioural therapy in insomnia of **less than 3 months' duration** (when sleep hygiene measures have failed, daytime impairment is severe and causing significant distress, and insomnia is unlikely to resolve quickly). The lowest effective dose should be prescribed for the shortest possible time. Further prescriptions should not be issued without reviewing the patient.[4]

Those aged over 55 years of age with persistent insomnia of **over 3 months' duration** may be considered for treatment with prolonged-release melatonin. The recommended initial duration of treatment is 3 weeks, continued for **up to** a further 10 weeks if a response is demonstrated. Patients should be reviewed every 2-4 weeks.[4] Further prescriptions should not be issued without reviewing the patient.

Melatonin is not recommended for primary insomnia in adults aged under 55 years.

The risk of falls and fractures associated with melatonin should be considered before commencing

treatment (use with caution in the elderly). [4]

Prescribing recommendation in NHS Lanarkshire	
Indication	Insomnia (short-term use)
Eligible patients	Adults aged 55 years and over
Formulation	Melatonin 2mg prolonged-release tablets Note: The Scottish Medicines Consortium have advised that the brand Circadin® is not recommended for use within NHSScotland.[10] Prescribing branded Circadin® for the licensed indication is subject to the Individual Patient Treatment Request (IPTR) process.
Licensing	Licensed
Dose	2mg once daily, 1-2 hours before bedtime
Treatment duration	Up to 13 weeks
Review periods and follow-up	Review patient every 2-4 weeks
Prescribing initiation	Primary care or specialist prescribers
Ongoing prescribing	Primary care or specialist prescribers
Refer to the British National Formulary (BNF) and/or Summary of Product Characteristics (SPC) for full prescribing information	

(B) Adults with circadian rhythm disorders

Jet-lag

Immediate-release melatonin preparations are licensed for the short-term treatment of jet-lag in adults.[11] In a meta-analysis of randomised controlled studies, it was concluded that melatonin did not have a significant effect on sleep onset latency associated with jet lag.[8]

NICE do not recommend the use of melatonin to promote sleep due to jet-lag.[12]

Prescribing recommendation in NHS Lanarkshire
Not recommended

Other circadian rhythm disorders

Melatonin may be useful in delayed sleep wake phase disorder and non-24-hour sleep rhythm disorder in non-sighted individuals. Patients with these disorders need to be treated in a specialist sleep clinic because of the requirement for caution in relation to timing of interventions.[9]

Prescribing recommendation in NHS Lanarkshire
Tertiary specialist sleep clinic recommendation only

(C) Adults with parasomnias

The evidence for treatment of parasomnias is sparse. To enable an adequate diagnosis to be made, referral to a specialist sleep clinic is usually necessary, especially for rapid eye movement behaviour disorder (RBD). Evidence for melatonin in RBD comes from a single, small, crossover randomised trial. BAP make no specific recommendations for the use of melatonin in these conditions.[9]

Prescribing recommendation in NHS Lanarkshire
Tertiary specialist sleep clinic recommendation only

(D) Children and adults with autism spectrum disorders (ASD)

SIGN Guideline 145 on ASD advises that behavioural interventions should be considered before the use of pharmacological intervention in children and adults. Where behavioural interventions have been unsuccessful at improving sleep onset in children with ASD, a trial of melatonin (in conjunction with behavioural interventions) should be considered following the advice of a paediatrician or psychiatrist with expertise in the management of sleep medicine in children and/or ASD.[7]

Consensus guidelines from BAP also conclude that melatonin is effective at improving sleep and is well-tolerated in children with ASD, however behavioural intervention should be tried first-line.[5,9] Both immediate- and prolonged-release melatonin preparations have been shown to be effective in reducing sleep onset latency and increasing sleep duration in children with ASD. However, no changes in night-time awakenings have been reported.[5,7]

SIGN and BAP conclude that no evidence was identified on the use of melatonin for sleep difficulties in adults with ASD.[5,7] However, where behavioural interventions have been unsuccessful, a trial of melatonin (in conjunction with behavioural interventions) may be considered following the advice of a psychiatrist with expertise in the management of sleep medicine and/or ASD.[7]

Prescribing recommendation in NHS Lanarkshire
See under section (G) below

(E) Children and adults with learning disabilities

Behavioural interventions should be considered for sleep problems in children, young people and adults with a learning disability and behaviour that challenges.[9,13] Medication should only be offered to aid sleep if the problem persists following behavioural intervention and only on the advice of a psychiatrist or paediatric specialist.[13]

If medication is required, melatonin should be considered in conjunction with ongoing behavioural interventions and regular review.[13] BAP consider melatonin to be effective at improving sleep disturbance in adults with intellectual disability. A review by Sajith et al. concluded that melatonin appears to be effective at reducing sleep onset latency in children and adolescents with intellectual disability and probably had a similar effect in adults. They considered melatonin to be relatively safe for short-term use, however its safety in long-term use has not been established.[14]

Prescribing recommendation in NHS Lanarkshire
See under section (G) below

(F) Children with cerebral palsy

Sleep disorders in children and young people with cerebral palsy are common. Sleep hygiene should be optimised and the use of sleep questionnaires or diaries should be considered. A trial of melatonin may be considered in the management of sleep disturbances (particularly for problems with falling asleep) if no treatable cause of the sleep disturbance is identified.[15]

Prescribing recommendation in NHS Lanarkshire
See under section (G) below

(G) Children with attention deficit hyperactivity disorder (ADHD)

There is some evidence of melatonin abnormalities in individuals with ADHD.[16]

A NICE Evidence Summary discusses the evidence for the efficacy of melatonin in sleep disorders in children and young people with attention deficit hyperactivity disorder. The review concludes that limited evidence from two small trials suggested that melatonin may reduce sleep onset latency and increase sleep duration in children aged 6 to 14 years with ADHD and sleep onset insomnia (prescribed immediate-release melatonin 3–6 mg daily for between 10 days and 4 weeks – the longer term efficacy is unclear). Good sleep hygiene and behavioural therapy are also noted as first-line treatments for children with sleep problems and ADHD.[1]

BAP recommend behavioural intervention first-line in children. Melatonin can be used to reduce sleep onset in children with ADHD who are not taking stimulant medication.[9]

Prescribing recommendation in NHS Lanarkshire	
Indication	Sleep onset latency
Eligible patients	• Children and adults with ASD • Children and adults with learning disabilities • Children with cerebral palsy • Children with ADHD
Formulation	**1st line:** Melatonin 3mg immediate-release tablets (listed in Scottish Drug Tariff Part 7) **2nd line:** Melatonin 2mg prolonged-release tablets (for use when a prolonged-release preparation is required either alone or in combination with the immediate-release preparation) Note: The Scottish Medicines Consortium have advised that the brand Slenyto® is not recommended for use within NHSScotland. Prescribing branded Slenyto® for the licensed indication is subject to the Peer Approved Clinical System Tier 2 (PACS2) process.[17] Note: The Scottish Medicines Consortium have advised that the brand Circadin® is not recommended for use within NHSScotland.[10] Prescribing branded Circadin® for the licensed indication is subject to the Individual Patient Treatment Request (IPTR) process.
Swallowing difficulties	Immediate-release tablets can be crushed (off-label use) and mixed with a small amount of cold or room temperature soft food such as yogurt, jam or mashed potato – the mixture should be swallowed straight away, without chewing.[18] Crushing of prolonged-release tablets to aid swallowing difficulties is not recommended as this changes the release profile; an immediate-release preparation may be considered as an alternative. Melatonin 1mg/mL oral solution may be required where the intended dose is below 3mg or when crushing tablets is unsuitable. Excipients in the licensed oral solution include sorbitol and propylene glycol[19] which may be unsuitable for children under 5 years old – Paediatrics may recommend Kidmel® (melatonin) 1mg/mL **unlicensed*** oral solution (Veriton Pharma Ltd) in this age group. *MHRA guidance requires that anyone supplying an unlicensed medicinal product where an equivalent licensed medicinal product is available, must be satisfied as to the

	existence of a special need for the unlicensed medicinal product. Community pharmacies and/or wholesalers may therefore require confirmation of the need for the unlicensed product from the GP.[20] An example of how the GP may communicate this is to add the following information to the prescription within the 'notes to prescriber' section: "Due to excipients in the licensed oral solution which are unsuitable in children under 5 years old, the unlicensed oral solution is required."
Enteral feeding tubes	Administration of melatonin preparations via enteral feeding tubes is an off-label use and the decision is at the discretion of the prescriber. Limited evidence specific to melatonin is available therefore general information only on formulations is provided below as a guide. Immediate-release tablets should be crushed well enough to prevent clogging of the tube. Immediate-release tablets may be film-coated. If film-coated tablets are crushed for administration via enteral feeding tubes it is important to ensure that the coating is broken up well, and that the feeding tube is flushed well following administration.[21] Crushing of prolonged-release tablets for administration via enteral feeding tubes is not recommended as this changes the release profile; an immediate-release preparation may be considered as an alternative. Liquids/solutions may be preferred for administration via enteral feeding tubes however preparations containing sorbitol may cause diarrhoea. Sorbitol-containing liquids should be diluted before administration and the feeding tube should be flushed with 10mL of water after administration.[21]
Licensing	Off-label use for the indications stated above.
Dose	3mg immediate-release tablets once daily before bedtime for 1–2 weeks, increasing as required to max. 9mg daily (max. 10mg daily if used in combination with prolonged-release 2mg tablets). The above dose may differ from product literature; this is the preferred regime agreed in NHS Lanarkshire.
Treatment duration	Duration of treatment will be based on the individual patient and should be determined by the specialist. Long-term treatment is **not recommended** as the long-term effects are unknown. Melatonin should only be continued where there is clear evidence of ongoing effectiveness (e.g. from sleep diaries), and treatment breaks are recommended to assess ongoing need.
Review periods and follow-up	Review patient at least every 6 months[22] (monthly during initial trial). There is limited information about the long-term effects of melatonin.[9,14,22]
Prescribing initiation	Specialist prescribers or on the advice of a specialist.
Ongoing prescribing	Treatment should be initiated and supervised by a specialist however ongoing shared care with a GP/primary care prescriber may be appropriate.[22]
Refer to the BNF/BNF for Children and/or SPC for full prescribing information	

RESPONSIBILITIES WHEN SHARED CARE IS AGREED

Shared care within NHS Lanarkshire may be appropriate for the management of sleep disorders in:

- Children and adults with ASD
- Children and adults with learning disabilities
- Children with cerebral palsy
- Children with ADHD

A template letter for shared care is provided in Appendix 2.

Shared care with tertiary specialist sleep clinics may be appropriate for adults with delayed sleep wake phase disorder, non-24-hour sleep rhythm disorder in non-sighted individuals or RBD. Guidance from the tertiary specialist sleep clinic on shared care and prescribing should be followed.

Responsibilities of the specialist

- Assess suitability of the patient for treatment with melatonin
- Undertake baseline investigations and ongoing monitoring as required (e.g. assess sleep hygiene measures and sleep diary)
- Provide the relevant counselling, including the off-label/unlicensed status of melatonin to patient or welfare guardian to enable informed/legal consent to treatment as required†
  For further information, refer to:
  - https://www.choiceandmedication.org/nhs24/generate/handyfactsheetunlicensedmedicinesuk.pdf
  - https://www.medicinesforchildren.org.uk/melatonin-sleep-disorders
- Discuss and set expectations for treatment at the outset (including proposed duration and withdrawal of treatment) with the patient or welfare guardian
- Initiate and/or recommend prescribing of the appropriate dose, form and strength of melatonin to the GP/primary care prescriber and review these regularly
- Assess and monitor patient's response to treatment, using sleep diaries as a guide
- Review patient monthly during initial trial and then at least 6-monthly throughout treatment
- Remind patient/welfare guardian to complete a sleep diary (preferably throughout treatment or for at least 2 weeks prior to review appointment as a minimum)
- Discontinue treatment if ineffective, or advise on treatment breaks to assess on-going need
- Communicate regularly with the GP/primary care prescriber (particularly after each medication review) and advise on any dose adjustments
- Report any suspected adverse events to the CSM via the yellow card scheme
- Complete Form C PC when recommending off-label/unlicensed use of melatonin in adults†
- Accept responsibility for prescribing and/or recommending melatonin out-with its licensed indications
- Assess if the patient should continue to be prescribed melatonin when discharged from the specialist service and request that ongoing prescribing and assessment of sleep hygiene measures/sleep diary is continued by the GP/primary care prescriber where relevant

† NB: The Royal College of Paediatrics and Child Health consider that in general it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain the consent of parents, carers and child patients to prescribe or administer unlicensed medicines or licensed medicines to children for unlicensed applications.[23]

Responsibilities of the GP/primary care prescriber

- Prescribe melatonin in line with specialist advice
- Contact the specialist for advice or to report any concerns
- Accept responsibility for prescribing melatonin out-with its licensed indications
- Consider ongoing melatonin prescribing and assessment of sleep hygiene measures/sleep diary when patient is discharged from the specialist service and ongoing treatment is considered to be clinically necessary
- Prescribers are under no obligation to prescribe melatonin at the request of a private clinic or patient where they consider treatment to be clinically unnecessary or where they have insufficient expertise to accept clinical responsibility for prescribing

Responsibilities of the patient/welfare guardian

- Attend specialist clinic and GP/primary care appointments – failure to do so will delay the treatment plan/issuing of prescriptions
- Engage in discussions about the expectations for treatment, including proposed duration and withdrawal of melatonin
- Order prescriptions in a timely manner
- Report any concerns during treatment to the specialist or GP/primary care prescriber
- Maintain sleep diaries and sleep hygiene measures as directed by the specialist or GP/primary care prescriber – failure to do so will delay the treatment plan/issuing of prescriptions

APPENDIX 1

Sleep Diary

Sleep is important for health and wellbeing. This sleep diary will help keep track of your sleeping routine.

It takes just a few minutes to complete each day – some questions need answering at the end of the day, some need answering first thing in the morning.

Please complete every day for 2 weeks. Don't worry too much about giving exact answers, an estimate is ok.

Your completed diary will help us to review your sleep habits and find out how your sleep can be improved.

Name:

Date beginning:

Please write day of the week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Questions to answer at the end of the day, before bedtime							
Did you have a nap during the day/evening and for how long?							
How would you rate your mood during the day? (1 - very poor, 5 - very good)							
How tired did you feel during the day from 1-5? (1 – not very tired, 5 – very tired)							
What drinks did you have after 5pm?							
How much exercise/activity have you done today?							
Questions to answer in the morning about:							
Bedtime							
What time did you go to bed last night?							
What did you do in the hour before bedtime?							
What did you do in bed? E.g. read, watch TV							
What time did you turn the lights off?							
How long did it take you to fall asleep?							
During the night							
After falling asleep, how many times did you wake up in the night?							
How long were you awake during the night in total?							
What disturbed your sleep? E.g. worry, noise, lights							
Morning							

What time did you wake up this morning?							
What time did you get out of bed?							
How would you rate the quality of your sleep last night? (1 - very poor, 5 - very good)							
How do you feel this morning? 1. Refreshed 2. OK 3. Still tired							

What strategies have you tried to help you sleep? Mark each strategy out of 5 (1 – not helpful, 5 - very helpful)

Any other comments?

APPENDIX 2

<Prescribing Clinician Details>

<Patient Details>
<Date>

Dear Dr ……..

Your patient, …… attended clinic today.

(Delete as appropriate) I have prescribed them / I recommend that they are prescribed melatonin as per the NHS Lanarkshire guideline on the use of melatonin for the management of sleep disorders.

If you agree, the ongoing prescribing of melatonin will form part of a shared care agreement with you in line with the NHS Lanarkshire guideline.

Indication:	

Please prescribe the following *(tick preparation and specify dose):*

	Melatonin 3mg immediate-release tablets (1st line)	Dose:
	Melatonin 2mg prolonged-release tablets (2nd line)	Dose:
	Melatonin 1mg/mL oral solution (3rd line)	Dose:
	Kidmel® (melatonin) 1mg/mL unlicensed* oral solution (Veriton Pharma Ltd). Restricted to use in children under 5 years old following recommendation by Paediatrics and where the above preparations are deemed unsuitable. *MHRA guidance requires that anyone supplying an unlicensed medicinal product where an equivalent licensed medicinal product is available, must be satisfied as to the existence of a special need for the unlicensed medicinal product. Community pharmacies and/or wholesalers may therefore require confirmation of the need for the unlicensed product from the GP.[20] An example of how the GP may communicate this is to add the following information to the prescription within the 'notes to prescriber' section: "Due to excipients in the licensed oral solution which are unsuitable in children under 5 years old, the unlicensed oral solution is required."	Dose:

I will keep you updated on the treatment plan and communicate any dose changes.

Yours sincerely

……..

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