

Shared Care Guideline for Melatonin in Children and Adolescents for sleep disorders

This shared care guideline (SCG) has been written to enable the continuation of care by primary care clinicians of patients initiated on melatonin by the SWYPFT Barnsley Child and Adolescent Mental health service (CAMHS) and BHNFT Community Paediatrics, where this is appropriate and, in the patients', best interests. Primary care will only be requested to take over prescribing of melatonin within its licensed indication unless specifically detailed otherwise below.

Introduction

Melatonin is a pineal hormone which may affect sleep pattern. Production is affected by light exposure detected by the retina; it is thought that this rhythm is disturbed in children with neurodevelopmental disorders or visual disturbance (European Medicines Agency, 2018).

The prevalence of sleep disturbance in children and adolescents with autistic spectrum disorder (ASD) ranges from 30%–53% and up to 70% in those with attention deficit hyperactivity disorder (ADHD). If untreated, such sleep disturbances can negatively impact children, adolescents, and their families with respect to physical and mental health, social, academic, and cognitive functioning (Sivertsen, 2012). Sleep disturbance may include delayed onset of sleep, frequent waking, and early morning waking or day-night reversal of sleep pattern (Jan, 1994).

NICE summarised that the evidence to support the use of melatonin in children and young people with ADHD is very limited (National Institute for Health and Care Excellence, 2013)). However, clinical experience suggests that when appropriate behavioural sleep interventions fail, 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, autism, and learning difficulties (Paediatric Formulary Committee, 2022).

Use of Melatonin preparations for conditions outside of the licensed indication in the table below (page 3) is off-label use and requires consent from patient/parent/guardian and documented in the patient notes.

A trial of melatonin will only be offered if sleep hygiene measures have not been successful. It is recommended that a minimum of 3 months of behavioural interventions are required before melatonin is offered.

Sleep hygiene measures should continue alongside the administration of melatonin. Written guidance on sleep hygiene measures should be provided to the carers by the initiating specialist. A useful leaflet can be found on the Research Autism website (http://www.researchautism.net/publicfiles/pdf/good_sleep_habits.pdf). If families cannot implement sleep hygiene measures, then melatonin will not be offered.

When melatonin is prescribed off-license there should be additional information provided to the patient and/or carer by the initiating prescriber, this should be documented within the clinical records. The choice and medication website provides excellent resources:

<https://www.choiceandmedication.org/swyp/medication/melatonin/>

<https://www.choiceandmedication.org/swyp/generate/pillmelatoninsleepadhdcarer.pdf>

<https://www.choiceandmedication.org/swyp/generate/handyfactsheetunlicensedusesuk.pdf>

There were no detectable impact on puberty in a paper by Marlow et al. (Malow, 2021)

Indication

Melatonin is a naturally occurring hormone secreted by the pineal gland in the brain in a circadian manner. It is involved in co-ordinating the body's sleep-wake cycle helping to regulate sleep through its regulation of the activity of the suprachiasmatic nucleus and sleep related brain networks. Melatonin production is suppressed by light and stimulated by darkness, a rise in serum levels precede the onset of sleep by about 90 minutes.

Melatonin is indicated for use in: Sleep onset insomnia, delayed sleep phase syndrome, insomnia in patients with learning disabilities, insomnia in children and adolescents aged 6-17 years with ADHD where sleep hygiene measures have been insufficient, insomnia with Autism Spectrum Disorder (ASD) (Slenyto® only), insomnia with Smith-Magenis syndrome (Slenyto® only)

Barnsley Formulary Preparations	Melatonin Presentation	Licensed Indication	Formulary Position	Additional Information
	Adaflex® Tablets (AGB-Pharma) 1mg (£10.89) 2mg (£10.89) 3mg (£10.89) 4mg (£10.89) 5mg (£10.89) Pack size - 30 tablets	Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient	First Line Melatonin preparation for children / adolescents WITH ADHD or other indications where an immediate release formulation is suitable (off label use)	Can be crushed between two metal spoons and mixed with water directly before administration. Children and adolescents with both ADHD and ASD diagnoses should be prescribed the formulation/s which is /are most cost effective to the needs of the individual. <u>Maximum licensed dose 5mg at night</u> <u>Doses 6-10mg at night off label use</u>
	Melatonin 2mg prolonged release Tablets 2mg - £3.96 for 30 tablets (Drug Tariff May 24)	Short term treatment of primary insomnia in patients aged 55 years and over.	First line melatonin preparation for children/ adolescents WITH ADHD but without ASD and/or Smith-Magenis syndrome and a prolonged release formulation is required (off label use)	For an immediate release dose First line - Prescribe Adaflex® brand (off label use) or: Alternatively halve, quarter or crush melatonin PR tablets between two metal spoons (off label use). <u>Swallowing difficulties</u> For an immediate release dose (crush) – see above. If a prolonged release dose is indicated, consider Slenyto® prolonged release tablets (smaller in size than melatonin®) (off label use). Slenyto® tablets can be put into soft food such as yoghurt, orange juice or ice cream to facilitate swallowing. The tablet should <u>not be broken, crushed or chewed</u> because it will lose the PR properties.
	Slenyto® prolonged release (PR) Tablets (size 3mm diameter) (Flynn Pharma Ltd.) 1mg - £41.20 for 60 tablets. 5mg - £103 for 30 tablets (Drug Tariff May 2024)	Insomnia in aged 2 -18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis Syndrome where sleep hygiene measures have been insufficient.	Restricted to children /adolescents with ASD and/or Smith Magen is syndrome (or in other patients with swallowing difficulties as detailed in the additional information section)	For an immediate release dose First line - Prescribe Adaflex® brand (off label use) or: Halve, quarter or crush Slenyto® PR tablets between two metal spoons (off label use). <u>Swallowing difficulties</u> For an immediate release dose (crush) – see above. For a prolonged release dose, tablets can be put into soft food such as yoghurt, orange juice or ice cream to facilitate swallowing. The tablet should <u>not be broken, crushed or chewed</u> because it will lose the PR properties. Children and adolescents with both ADHD and ASD diagnoses should be prescribed the formulation/s which is / are most cost effective to the needs of the individual.

	<p>Ceyesto® 1 mg/ml oral solution (AlturixLtd)*</p> <p>100ml - £17.10 (dm+d NHSBSA browser)</p>	<p>Short term treatment of jet lag in adults.</p> <p>Delayed sleep wake phase disorder in children and adolescents aged 6-17 years where sleep hygiene measures have been insufficient</p> <p>Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene methods have been insufficient.</p>	<p>Restricted to children/ adolescents who require medication to be administered via a feeding tube (off label use) or in exceptional circumstances in other patients where Adaflex®, melatonin PR and Slenyto® have been trialled without success as detailed in the section below**</p> <p>Ceyesto® 1mg/ml oral solution is restricted to use in children 6yrs and over.</p>	<p>Excipients: Propylene glycol 52mg/ml (E1520), benzyl alcohol 6mg/ml, sucralose (E955), sodium ascorbate (1mg/ml), strawberry flavour and purified water.</p> <p>Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious effects in neonates.</p> <p>Excipients with known effect Benzyl alcohol may cause allergic reactions and has been linked with the risk of severe side effects including breathing problems (called “gaspings syndrome”) in young children. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing products should not be used in pre-term or full-term neonates (up to 4 weeks) unless strictly necessary.</p> <p>Large amounts of benzyl alcohol can build-up in the body and may cause side effects (metabolic acidosis). Large volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or those that are pregnant or breast-feeding. Caution is also advised in young children (under 6 years) due to the risk of accumulation. See dosage and administration section for further information.</p> <p>Shelf life after first opening: 1 month.</p>
	<p>Consilient Health melatonin 1 mg/ml oral solution* (Consilient health)</p> <p>100ml - £86.67 (Drug Tariff May 2024)</p> <p>PLEASE ENSURE THE CORRECT PRODUCT IS SELECTED FROM THE PRIMARY CARE PICKING LIST WITH SELECTION OF CONSILLIENT BRAND.</p>	<p>Short term treatment of jet lag in adults.</p> <p>Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient</p>	<p>Restricted to children/ adolescents who require medication to be administered via a feeding tube (off label use) or in exceptional circumstances in other patients where Adaflex®, melatonin PR and Slenyto® have been trialled without success as detailed in the section below**</p> <p><u>Restricted for use in children aged 3 to <6yrs. Use in children over 3 years of age, use will be off license but considered by APC to be suitable for use.</u></p>	<p>Excipients: Glycerol (E422), sorbic acid, methyl parahydroxybenzoate (1mg/ml) (E218), sodium hydroxide (for pH adjustments) and purified water.</p> <p>Excipients with known effect 1 ml oral solution contains 1 mg of methyl parahydroxybenzoate.</p> <p>Shelf life after first opening: 6 months.</p>

Barnsley Formulary Preparations (continued)	<p>At the request of the paediatric consultants the unlicensed option of Melatonin 3mg MR capsules (which can be opened and sprinkled on food) has been approved by the APC for restricted use where the licensed/off label alternatives detailed above have been trialled without success and documented. The rationale for the unlicensed Melatonin 3mg MR capsules should be detailed in the shared care request form (appendix A) and patients should have ongoing reviews by paediatrics as to the suitability of the formulation.</p> <p>- **At the request of the initiating prescriber the use of Ceyesto® 1mg/ml oral solution (age 6yrs and over) and Consilient Health Melatonin 1mg/ml oral solution (over 3yrs to < 6yrs) has been approved by the APC for restricted use in patients without enteral feeding tubes where the other licensed/off label preparations detailed above have been trialled without success and documented. The rationale for the use of Ceyesto® or Consilient Health Melatonin 1mg/1ml oral solution should be detailed in the shared care request form (appendix A) and patients should have ongoing reviews by the specialist as to the suitability of the formulation. Melatonin 2mg MR tablets should be prescribed generically.</p> <p>Melatonin oral solution 1mg/ml should be prescribed as the agreed brand Ceyesto® 1mg/ml oral solution for children age 6yrs and over and as the generic manufacturer Consilient health melatonin 1mg/ml oral solution for children age 3 to <6years.</p> <p>Other melatonin preparations not included in the above table are non-formulary. Patients currently prescribed preparations not listed in the table above should be reviewed and if there is a continued need for melatonin, switched to a preparation within the table, using a licensed/off label preparation where available</p>
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Dosage and Administration - Most patients respond at doses of 6mg or less (Horman, 2019)

Adaflex® tablets (standard release)

Problems with sleep initiation

The recommended starting dose is 1-2 mg 30-60minutes before bedtime; the dose can be increased by 1 mg every week until effect up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought.

Doses between 6-10mg are off label use.

It is recommended that food is not consumed 2 h before and 2 h after intake.

Problems with sleep maintenance or early morning waking

If Adaflex® is ineffective then modified release melatonin is indicated. Generic Melatonin 2mg prolonged release tablets should be prescribed, to be swallowed whole 60-90 minutes prior to bedtime.

Problems with both sleep initiation and sleep maintenance/fragmental sleep/early morning awakening

If Adaflex® is ineffective then modified release melatonin is indicated. Generic melatonin 2mg prolonged release tablets should be prescribed, to be swallowed whole 60-90 minutes prior to bedtime

In some children a combination of immediate release (i.e. Adaflex® or generic melatonin PR quartered, halved or crushed tablets) and whole tablets of generic melatonin PR may be required, up to a maximum total dose of 10mg.

Another strategy to consider is giving a whole generic melatonin PR tablet earlier in the evening and another dose at bedtime for help with sleep initiation and maintenance.

Melatonin 2mg modified release tablets (size 8mm diameter)

Problems with sleep initiation

A standard release melatonin is indicated, see Adaflex® above.

Alternatively, this can be obtained by quartering, halving or crushing generic melatonin 2mg prolonged release tablets between two metal spoons.

The starting dose is usually 2mg given 30 minutes before bedtime. If there is no response or an insufficient response after a minimum of 14 days therapy the dose is increased by 2mg. If further increases in dose are needed these should be made after a minimum of 14 days on each dose, in 2mg increments. In certain circumstances the dose can be increased up to a maximum dose of 10mg.

Problems with sleep maintenance or early morning waking

Modified release melatonin is indicated in the first instance. Generic melatonin 2mg prolonged release tablets should be prescribed, to be swallowed whole 60-90 minutes prior to bedtime.

Problems with both sleep initiation and sleep maintenance/fragmental sleep/early morning awakening

A generic melatonin prolonged release preparation is indicated. In some children a combination of immediate release (Adaflex® or quartered, halved or crushed melatonin PR tablets) and whole tablets of melatonin PR may be required, up to a maximum total dose of 10mg.

Another strategy to consider is giving a whole melatonin PR tablet earlier in the evening and another dose at bedtime for help with sleep initiation and maintenance.

Slenyto® 1mg and 5mg modified release tablets (size 3mm diameter)

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

The recommended starting dose is 2 mg daily. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg.

Slenyto® should be taken once daily, 0.5-1 hour before bedtime and with or after food.

Up to 2 years treatment is included in the product license and there is limited safety data with melatonin beyond this.

Problems with both sleep initiation and sleep maintenance/fragmental sleep/early morning awakening

A prolonged release preparation (Slenyto®) is indicated where generic melatonin MR tablets are unsuitable. In some children a combination of immediate release (i.e. Adaflex® or quartered, halved or crushed melatonin PR tablets) and whole tablets of Slenyto® may be required, up to a maximum total dose of 10mg.

Another strategy to consider is giving a whole Slenyto® tablet earlier in the evening and another dose at bedtime can help with sleep initiation and maintenance.

Ceyesto® oral solution 1mg/ml.

Only recommended when patients require medication administered by an enteral feeding tube or in the exceptional circumstances detailed in the previous 'Barnsley Formulary Preparations' section of the document. Please consider tablet forms above as detailed before considering oral solution.

Delayed sleep wake phase disorder in children and adolescents aged 6-17 years, where sleep hygiene measures have been insufficient.

Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

The recommended starting dose is 1 to 2 mg once a day, 1-2 hours before the fixed desired bedtime, given as 1-2 ml of the oral solution. The dose of melatonin should be adjusted individually until effective up to a maximum of 5 mg per day, independent of age. The lowest effective dose should be sought and taken for the shortest period.

Limited data are available for up to 3 years of treatment.

Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

The recommended starting dose is 1-2 mg, 30-60 minutes before bedtime.

The dose of melatonin should be adjusted individually until effective up to a maximum of 5 mg per day, independent of age. The lowest effective dose should be sought and taken for the shortest period.

The dose that adequately alleviates symptoms should be taken for the shortest period. There is insufficient safety data to support long term use of melatonin in children approaching puberty. 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.

The patient should be monitored at regular intervals (at least every 6 months) to check that melatonin is still the most appropriate treatment.

During ongoing treatment discontinuation attempts should be attempted regularly, e.g. once per year and treatment discontinued if it is not effective.

If the sleep disorder has started during treatment with other medicinal products, dose adjustment or switching to another product should be considered. If significant problems are seen in sleep maintenance or early morning waking, an alternative formulation of melatonin should be considered.

Limited data are available for up to 3 years of treatment.

Excipients

Ceyesto® contains:

52mg of propylene glycol per 1ml dose. The NPPG recommends a maximum dose of 500mg/kg in children over 5yrs of age. The average 6yr old weighs 18kg-20kg which would be a maximum dose of 9000mg - 10000mg. Maximum dose of 10mg melatonin would equate to 520mg propylene glycol so this dose is well within the recommended guidance¹³.

Benzyl alcohol 6mg per 1ml dose. The NPPG advises a maximum dose of 5mg/kg benzyl alcohol per day in children over 4 weeks. Average weight of a 6yr old is 18-20kg which equates to 90-100 mg per day. Maximum dose of 10mg melatonin would equate to 60mg benzyl alcohol so this dose is well within the recommended guidance¹³.

Consilient Health Melatonin 1mg/1ml oral solution

(Ensure prescribed as consilient brand on clinical system)

Only recommended when patients require medication administered by an enteral feeding tube or in the exceptional circumstances detailed in the previous 'Barnsley Formulary Preparations' section of the document. Please consider tablet forms above as detailed before considering oral solution.

Insomnia in children and adolescents (6-17 years of age, off-licence use for 3 to <6years) with attention deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been insufficient.

Recommended starting dose is 1-2 ml (equivalent to 1 to 2 mg) 1-2hrs before the desired bedtime. Maximum recommended daily dose: 5 ml (equivalent to 5 mg). The dose will be adjusted individually to a maximum of 5 ml (equivalent to 5 mg) daily, regardless of age. The lowest dose possible will be given.

Limited data are available for up to 3 years of treatment.

Sleep disorders for indications other than ADHD

As above (off label)

Doses between 6-10mg (off label use)

Excipients.

Consilient health melatonin oral solution contains methyl parahydroxybenzoate 1mg per 1ml.

As per the NPPG and RCPCH guidance the maximum acceptable dose in children is 10mg/kg/day. The average 3yr old weighs between 12-14kg. Hence the maximum dose for a 3yr old would be between 120mg and 140mg per day. With the max off label dose being suggested as 10ml of melatonin oral solution, this would not be a great concern¹³

Responsibilities of the specialist clinician initiating treatment

Summary

- To assess the suitability of the patient for treatment and initiate melatonin in appropriate patients. (including confirming the patient has no contra-indications to treatment and considering the relevance of any cautions, including interactions).
- To discuss with the patient:
 - the benefits and side effects of treatment.
 - the need for long-term monitoring (If applicable).
 - that the patient/care gives informed consent in line with national guidance. This is particularly important for an unlicensed product.
 - that they understand their responsibilities as a patient (see relevant section) and provide any patient information required.
- To perform baseline tests and if appropriate routine tests until the patient is stable (see details of baseline and routine tests which should be carried out by the specialist in the monitoring section below).
- To prescribe for the first 12 weeks of treatment and ensure the patient has sufficient medication to enable transfer to primary care. (include if the specialist will review the patient after initiation before prescribing is picked up in primary care).
- To ask the GP whether they are willing to participate in shared care.
- To review the patient in clinic regularly until the optimum dose is established and the shared care is accepted by the GP.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care (see shared care request form in Appendix A which includes a link to the shared care guideline).
- To advise the GP of any dosage adjustments required, monitoring required, when to refer back, and when and how to stop treatment (if appropriate).
- To advise the GP when the patient will next be reviewed by the specialist but if ongoing specialist co-ordination of the patient's care is not required, an individual care plan should be agreed on a case-by-case basis. This may include the access to advice and intervention of that specialist in a timelier manner than via a new referral and may fall outside shared care arrangements.
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow Card scheme).
- To provide the GP with contact details in case of queries.
- To provide patient / carer with contact details for support and help if required; both in and out of hours.
- To review children, as they move towards the age at which they will be discharged from the Paediatric pathway to determine on-going need:
 - To facilitate the cessation of drug therapy at this stage if clinically possible
 - To discuss with parent/carer the limitations of the duration of shared care agreement and ensure they understand that treatment will not be provided by the GP under this shared care agreement once the child has been discharged from the Paediatric pathway
 - To discuss with the GP regarding continuation of treatment should it be beneficial to the patient, including length of treatment and trials off medication.
 - To provide guidance to the parent/carer on lifestyle and sleep management should treatment be ceased (if applicable)

Responsibilities of the primary care clinician

Acceptance of Responsibility by the Primary Care Clinician

It is optional for the primary care clinician to participate in taking on responsibility for shared care for the patient. Primary care clinicians will take on shared care only if they are willing and able.

Summary

- To reply to the request for shared care as soon as possible (but within 14 days where possible) to either accept or decline the request.
- To prescribe and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To continue monitoring as agreed with secondary care in the monitoring section below.
- To inform the specialist if the patient discontinues treatment for any reason.
- To seek the advice of the specialist if any concerns with the patient's therapy. For example:
 - Patient or general practitioner is **not** comfortable to continue with the existing regime due to either change in condition or drug side effects.
 - Advice in respect of concordance.
 - Special situations, (e.g. Pregnancy).
- Discontinue the drug as directed by the specialist if required.
- To conduct an annual medication review or more frequently if required.
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA ([Yellow Card scheme](#)).

Responsibilities of Patients or Carers

Summary

- To be fully involved in, and in agreement with, the decision to move to shared care.
- To attend hospital and primary care clinic appointments and to bring monitoring information e.g. booklet (if required). Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the primary care prescriber or specialist should the clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or primary care prescriber whilst taking melatonin.
- To read the product information given to them.
- To take melatonin as prescribed.
- Inform the specialist, primary care prescriber or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Clinical Particulars

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF (<https://bnf.nice.org.uk/>) and the SPC (<https://www.medicines.org.uk/emc/>) remain authoritative.

BNF therapeutic class	Non-benzodiazepine hypnotics and sedative drugs
Cautions and Contraindications	<ul style="list-style-type: none"> • Hypersensitivity to melatonin or to any of the excipients listed within the preparation. • Autoimmune disease-Not recommended for use in patients with autoimmune diseases. • Galactose intolerance-Some preparations contain lactose, patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. • Hepatic impairment-There is no experience of the use of Melatonin in patients with liver impairment. Therefore, Melatonin is not recommended for use in patients with hepatic impairment. • Renal impairment-The effect of any stage of renal impairment on Melatonin pharmacokinetics has not been studied. Caution should be used when Melatonin is administered to patients with renal impairment. • Epilepsy- monitor effect on seizures. <p>Little is known about the long-term implications of melatonin use in children especially in relation to the impact it may have on other circadian rhythms including endocrine or reproductive hormone secretion (paediatric formulary committee 2019)</p>
Pregnancy and breast feeding	No information available – avoid. Present in milk – avoid.
Adverse Drug Reactions	<p>Melatonin is generally well tolerated. Adverse effects of melatonin include:</p> <p>Common or very common: Arthralgia, headaches, increased risk of infection, pain.</p> <p>Uncommon: Anxiety; asthenia; chest pain; dizziness; drowsiness; dry mouth; gastrointestinal discomfort; hyperbilirubinemia; hypertension; menopausal symptoms; mood altered; movement disorders; nausea; night sweats; oral disorders; skin reactions; sleep disorders; weight gain. Frequency not known: Angioedema; galactorrhoea.</p> <p>Full details can be found in the manufacture’s summary of product characteristics and the patient information leaflets. Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme: www.mhra.gov.uk/yellowcard</p>
Monitoring	<p>Treatment duration is intended to be as short as possible. It is important that patients continued need for treatment is reviewed at appropriate intervals (Horman, 2019). While the initiating specialist will retain for overall responsibility for the monitoring, GP’s who have an interest or feel competent to do so can use the guideline below to manage their shared care patients in primary care *.</p> <p>Treatment Targets (Espie, 2012)</p> <ol style="list-style-type: none"> 1. Sleep Latency reduced by at least 30minutes. 2. Longest Sleep Period increased by at least 45minutes. 3. Total sleep time increased by at least 45 minutes. <p>After 3 months treatment (specialist)</p> <ul style="list-style-type: none"> • If response is achieved and decision to continue, consider transfer of prescribing to GP under shared care arrangement. <p>After 6 months treatment (specialist or GP)</p> <ul style="list-style-type: none"> • Attempt withdrawal over a period of 3-4 weeks, with observation of changes to sleep pattern.

	<p>6-monthly thereafter (specialist or GP)</p> <ul style="list-style-type: none"> • Monitor for a possible impact of melatonin on their pubertal development and other adverse effects. • Monitor growth in children: annual height and weight. • Review the continued need for and effectiveness of melatonin. • Consider a trial withdrawal or dose reduction of treatment (over 3-4 weeks) • Continue to support behavioural methods of good sleep hygiene. <p>After 2 -3 years (specialist)</p> <ul style="list-style-type: none"> • Efficacy and safety data are not available beyond two years treatment. Do not continue melatonin beyond 2-3 years unless the specialist has authorised. <p>Melatonin Formulation Review (Specialist or Primary Care)</p> <ul style="list-style-type: none"> • For those prescribed an unlicensed formulation (e.g. melatonin 5mg/5ml oral solution) or a Melatonin preparation that is not in line with the Barnsley formulary, if continued need for melatonin identified, determine whether a switch to a licensed product (or licensed product used off-label) can meet patient needs (e.g. Adaflex ®/Melatonin 2mg PR / Slenyto®, Ceyesto® 1mg/ml oral solution) in line with the agreed formulary. <p>*If the GP makes changes then please liaise with the specialist to avoid duplication</p> <p>STOPPING TREATMENT</p> <ul style="list-style-type: none"> • It should be made clear to parents and carer at initiation that the treatment is intended for short term use. • An attempt to withdraw/have a break in treatment should be considered at least annually. • Those on lower doses (2-4mg) may be withdrawn without downwards titration, higher doses (6-10mg) may require a period of dose reductions. Attempted withdrawal is usually over a period of 3-4 weeks, with observation of changes to sleep pattern. • Sleep hygiene should be reinforced throughout treatment and prior to any attempt to stop. • Carer to complete sleep diary before, during and upon re-starting from treatment break. Mobile apps such as SnappD may be helpful. • Treatment may be stopped by GP or specialist. • For best success, mutually agree with the patient a suitable time to stop treatment, for example during school holidays, avoiding periods of stress e.g. during exams. <p>A rebound worsening in sleep pattern may occur initially but this may improve over time. If after 7-14 days sleep has deteriorated significantly melatonin can be restarted for another 6 months alongside sleep hygiene measures. Start at 1-2mg daily using a licensed preparation where possible, increasing by 1-2mg each week if required. Doses above 4-6mg are rarely required. Total daily dose should not exceed 10mg daily or the maximum of previous dose agreed by specialist.</p>
<p>Interactions</p>	<p>Interaction studies have only been performed in adults. In the absence of specific studies in children, the drug interactions with melatonin are those known in adults. Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible.</p> <p><u>Concomitant use not recommended</u></p> <p>Concomitant use of the following medicinal products is not recommended:</p> <p><u>Fluvoxamine</u></p> <p>Fluvoxamine increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.</p> <p><u>Alcohol</u></p> <p>Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.</p>

	<p><u>Benzodiazepines/non-benzodiazepine hypnotics</u> Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone. Combination with benzodiazepines and non-benzodiazepine hypnotics should be avoided.</p> <p><u>Thioridazine and imipramine</u> Melatonin has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, melatonin co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of “muzzy-headedness” compared to thioridazine alone. Combination with thioridazine and imipramine should be avoided.</p> <p><u>Concomitant use to be considered with caution</u> Concomitant use of the following medicinal products should be considered with caution:</p> <p><u>5- or 8-methoxypsoralen</u> Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 or 8-MOP), which increases melatonin levels by inhibiting its metabolism.</p> <p><u>Cimetidine</u> Caution should be exercised in patients on cimetidine which is a potent inhibitor of certain cytochrome P450 (CYP450) enzymes, mainly CYP1A2 and thereby increases plasma melatonin levels, by inhibiting its metabolism.</p> <p><u>Oestrogens</u> Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.</p> <p><u>CYP1A2 inhibitors</u> CYP1A2 inhibitors such as quinolones (ciprofloxacin and norfloxacin) may give rise to increased melatonin exposure.</p> <p><u>CYP1A2 inducers</u> CYP1A2 inducers such as carbamazepine and rifampicin may reduce plasma concentrations of melatonin. Therefore, when CYP1A2 inducers and melatonin are both given, dose adjustment may be required.</p> <p><u>Smoking</u> Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with melatonin, dose adjustment may be required.</p> <p><u>NSAIDs</u> Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, given in the evening may suppress endogenous melatonin levels in the early part of the night by up to 75%. If possible, administration of NSAIDs should be avoided in the evening.</p> <p><u>Beta-blockers</u> Beta-blockers may suppress the night-time release of endogenous melatonin and thus should be administered in the morning.</p> <p><u>Warfarin</u> Melatonin may affect the anticoagulation effect of warfarin.</p>
<p>Additional information</p>	<ul style="list-style-type: none"> • Other useful online sleep resources (behavioural strategies and sleep diaries): • Home - The Sleep Charity • Sleep Advice Service - Cerebra • https://www.autism.org.uk/advice-and-guidance/topics/physical-health/sleep/parents • Let's Sleep (letsleep.org)

Re-Referral guidelines	<ul style="list-style-type: none"> Please contact CAMHS 01226 644829 or Community Paediatrics 01226 644876
Ordering information	<ul style="list-style-type: none"> Not applicable

Communication and contact details

Specialist to primary care clinician

The specialist will inform the primary care clinician when they have initiated melatonin. When the patient is near completing the satisfactory initiation period, the specialist will write to the primary care clinician to request they take over prescribing and where possible give an indication as to the expected length of treatment. The specialist will also send a shared care request form to support the primary care clinician in undertaking shared care. (Appendix A)

Primary Care Clinician to specialist

If the primary care clinician has concerns over the prescribing of melatonin, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
Child and Adolescent Mental Health Service		
Dr Niloufar Mirhaghani, Consultant Psychiatrist	01226 644829	Niloufar.Mirhaghani@swyt.nhs.uk
Dr Lourence Lewis-Hanna, Consultant Psychiatrist	01226 644829	Lourence.Lewis-Hanna@swyt.nhs.uk
Dr. Ovidiu Sandica , Consultant Psychiatrist	01226 644829	Ovidiu.Sandica@swyt.nhs.uk
Dr Hillary Reed, Specialty Doctor	01226 644829	Hilary.Reed@swyt.nhs.uk
Dr Marco Haring, Specialty Doctor	01226 644829	Marco.Haring@swyt.nhs.uk
Dr Aly Middleton, Specialty Doctor	01226 644829	Aly.middleton@swyt.nhs.uk
Jo Newing, ADHD Advanced Nurse NMP	01226 644829	Jo.Newing@swyt.nhs.uk
Rebecca Pycko, ADHD Advanced Nurse NMP	01226 644829	Rebecca.Pycko@swyt.nhs.uk
Community Paediatrics		
Dr Jaya Dixit	01226 644876	Jaya.dixit1@nhs.net
Dr Andrea Nussbaumer	01226 644876	andrea.nussbaumer@nhs.net
Dr Angela Oliver	01226 644876	angela.oliver2@nhs.net
Dr Shobha Sivaramakrishnan	01226 644886	Shobha.sivaramakrishnan@nhs.net
Dr Mahmud Tumi	01226 644876	mtumi@nhs.net
Dr Fiona Blyth	01226 644866	fionablyth@nhs.net
Dr Limyaa Mohamed	01226 644876	limyaa.mohamed1@nhs.net
Terrie Mcniffe, Specialist Neurodisability Nurse	01226 644876	terrie.mcniffe@nhs.net
Andrea Robinson, Specialist Neurodisability Nurse	01226 644876	Andrea.robinson7@nhs.net

Equality and diversity

- Not applicable

References

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2. NHS England responsibilities for prescribing between primary and secondary care. Available at: <https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf>
3. European Medicines Agency. (2018). Committee for medicinal products for human use (CMHP) Slenyto overview. Available at: <https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto>
4. SPC Slenyto 1mg Prolonged release Tablets. Available at: <https://www.medicines.org.uk/emc/product/10023/smpc>
5. SPC Slenyto 5mg Prolonged release Tablets. Available at: <https://www.medicines.org.uk/emc/product/10024/smpc#about-medicine>
6. PresQuipp bulletin. Melatonin. Available at: <https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f4586%2f245-melatonin-21.pdf>
7. PresQipp Melatonin bulletin 318 January 2023. Available at: <https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f6403%2f318i-melatonin-briefing-20.pdf>
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10. Paediatric Formulary Committee. (2022). BNF for children. Available at: <https://bnfc.nice.org.uk>
11. SPC Adaflex 1mg Tablets. Available at: <https://www.medicines.org.uk/emc/product/13628>
12. Sivertsen, B. (2012). Sleep problems in children with autism spectrum problems: a longitudinal population-based study. Autism, 16(2), 139–150. Sleep problems in children with autism spectrum problems: a longitudinal population-based study). Available at: <https://pubmed.ncbi.nlm.nih.gov/21478225/>
13. RDTC formulary assesment tool Ceyesto® 1mg/ml oral soultion (Updated to include Colonis melatonin 1mg/ml oral solutionand Consilient health melatonin 1mg/ml oral solution). Available at: <https://rdtc.nhs.uk/prescribing-support-document/formulary-assessment-melatonin-ceyesto-1mg-ml-oral-solution/> (Account registration required).
14. NEWT. Please speak to a member of the medicines optimisation team to view a particular drug monograph.

Development Process

This guidance has been produced following an AMBER classification status of melatonin by the Barnsley Area Prescribing Committee. This guideline was ratified by the Area Prescribing Committee on 12th October 2022 Routine update ratified by APC 9th October 2024.

Appendix A – Shared Care request form (Amber) for [insert drug name or clinical area]

- Specialist to complete when requesting primary care clinician to enter a shared care arrangement.
- Primary care clinician to return signed copy of form. [Insert details of how to return the form e.g. to a safe haven e-mail address, postal address if the form should be returned by post]
- Both parties should retain a signed copy of the form in the patient’s record.

From (Specialist): _____ **To (Primary care clinician):** _____

As per the agreed Barnsley shared care guideline for melatonin, this patient is now suitable for prescribing to move to primary care.

The patient fulfils the criteria for shared care and I am therefore requesting your agreement to participate in shared care. I have carried out baseline tests and initial monitoring as detailed in the shared care guideline.

Patient details

Name: _____	NHS Number: _____
Address: _____	DOB: _____
Diagnosed condition: _____	

Amber Drug details

Drug name (please indicate): Adaflex / Melatonin PR tablets / Slenyto®/ <u>Consilient Health</u> Melatonin 1mg/1ml oral solution* / Unlicensed Melatonin MR 3mg capsules* (paediatrics only) <small>*rationale to be indicated</small>	
Dose and frequency: _____	Length of treatment: _____
Date of initiation: _____	
The patient has been provided with sufficient medication to last until: _____	
The patient will be reviewed by the consultant / prescriber on: _____	
The patient should be reviewed by the primary care clinician by: _____	

Monitoring

The following monitoring should be undertaken by the primary care clinician. Refer to the monitoring section of the shared care guideline.

Parameter	Date next test due	Frequency

Shared Care Guideline –remains open to review in light of any new evidence

Amber = To be initiated and titrated to a stable dose by a specialist with follow up prescribing and monitoring by primary care under a shared care agreement.

Communication

Consultant	
Telephone number: _____	Fax number: _____
Email address: _____	
Specialist Nurse/Prescriber	
Telephone number: _____	Fax number: _____
Email address: _____	

Confirmation of acceptance of shared care

Specialist (Doctor/Nurse) name: _____	
Specialist (Doctor/Nurse) signature: _____	Date: _____
I _____ [insert name of primary care clinician] can confirm I :	
<input type="checkbox"/> accept the request to participate in shared care for the patient named above and will complete the monitoring as set out in the shared care guideline for this medicine/condition.	
<input type="checkbox"/> reject the request to participate in shared care for the patient named above. The reason for this being	
Signature of primary care clinician: _____	Date: _____

To save resources you have been sent appendix A of the shared care document. The full document (*Melatonin SCG, date approved October 2022*) and updated October 2024 can be accessed on the Barnsley BEST website at the following link:

<http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/>

Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk