THE SHEFFIELD AREA PRESCRIBING GROUP

Shared care protocol

For

Melatonin in the treatment of sleep disorders in Children

(note - not recommended for primary care initiation)

Shared care protocol developed by:

Dr Caroline Bleakley, Associate Specialist, Neurodisability, SC(NHS)FT
Dr Neil Harrower, Consultant Paediatrician, Neurodisability, SC(NHS)FT
Dr Ovidiu Sandica, Consultant Child & Adolescent Psychiatrist CAMHS, SC(NHS)FT
Heidi Taylor, MOT, Sheffield CCG
Susan George, Pharmacy, SC(NHS)FT

Reviewed January 2020 by Dr Caroline Bleakley, Prof. Heather Elphick (consultant in paediatric sleep medicines), Seena Praveen (CAMHs consultant), Heidi Taylor (Clinical Effectiveness Lead Pharmacist) and Francesca Blakemore (pharmacist SCHFT).

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SCP adapted from the original version produced in February 2016

Shared care protocol for Melatonin in the treatment of sleep disorders in Children

Statement of Purpose

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients (2-18 years) initiated on **melatonin** by the Specialist Clinicians at Sheffield Children's NHS Foundation Trust. Some of the melatonin preparations included within this SCP are not licensed in children and prescribing in children should be in line with details within this SCP.

Responsibilities of specialist clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed verbal consent. This is particularly important if melatonin being prescribed is an unlicensed product / preparation being used off label. Its long-term effects are unknown.
- Prior to initiating melatonin sleep hygiene should be addressed (see Appendix 1).
- To initiate melatonin in patients unresponsive to sleep hygiene. Where available a licensed preparation should be considered first line if being used for their licensed indications. See table for the different preparations and their current licensed indications.
- To explain to the patient / carer that melatonin is intended as a short-term intervention and **must** be used in line with sleep hygiene techniques.
- To prescribe until response to treatment has been confirmed and optimal dose achieved. After at least 3 months of treatment, the specialist should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen.
- Once a response to treatment is seen, contact the patient's GP to request prescribing under shared care arrangements and send a link to or copy of this shared care protocol
- To ensure the patient is reviewed to monitor response to treatment, adherence to sleep hygiene advice and adverse effects (including possible impact on pubertal development). This should be done by the specialist ideally after 6 months of starting treatment, then usually every 6 months but at least annually. Consideration of stopping treatment should be explored at each review.
- If a patient is taking a formulation of melatonin that is not licensed or is being used 'off-label' when a licensed preparation is available (i.e. Slenyto® is licensed for 2-18 year olds with Autistic Spectrum Disorder (ASD) or Smith–Magenis Syndrome (SMS), then consider if continuation is clinically appropriate. An informed discussion with the patient / carer around licensed alternatives should be explored. If the child / carer prefer to maintain on Circadin® then this should be documented and the GP informed.
- After 2 years a trial of withdrawal from treatment should be discussed and documented. Safety data around the use of melatonin is not available beyond two years.
- If still on melatonin approaching the age of transition from children's services, reassess continued need. Most patients will no longer require continued treatment, but where the continued need is felt to be in the patients best interest, advise the primary care clinician of ongoing care plan, including ongoing prescribing, monitoring and review arrangements.
- To advise the GP regarding continuation of treatment, including the length of treatment and trials off medication.
- To discuss any concerns with the GP regarding the patient's therapy

The patient to remain under the consultant's care for the duration of prescribing.

Responsibilities of the primary care clinician

- Prior to referral to specialist for sleep problems / consideration of melatonin, parent-directed behavioural sleep interventions should be tried. (see Appendix 1).
- To agree to prescribe for patients in line with the shared care protocol as advised by the consultant
- To report any adverse reaction to the MHRA (yellow card) and the referring consultant
- To consider informing the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient's therapy
- To conduct an annual medication review. During the review the continued need for melatonin should be discussed and a trial stop in treatment explored, and sleep hygiene reinforced.
- Prior to the age of transition from children's services the continued need for melatonin should be assessed by the specialist. Most patients will no longer require continued treatment, but where the continued need is felt to be in the patients best interest responsibility ongoing prescribing, monitoring and review will be the responsibility of primary care. (Note use in patients age 19-55 years is off-label).
- In the event that the GP is not able to prescribe, or where shared care is agreed but the consultant is still prescribing certain items e.g. Hospital only product; the GP will provide the consultant with full details of existing therapy promptly on request.
- For hospital prescribed drugs GPs are advised to follow recommendations for Recording Specialist issued Drugs on Clinical Practice Systems
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Responsibilities of Patients or Carers

- To practice sleep hygiene alongside any melatonin prescribed
- To be fully involved in, and in agreement with, the decision to move to shared care
- To attend hospital and GP clinic appointments. Failure to attend will potentially result in the medication being stopped.
- Present to the GP or specialist should their clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or GP whilst taking melatonin
- To read the drug information given to them
- To take melatonin as prescribed
- Inform the specialist, GP or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Indication

Melatonin is indicated for the treatment of sleep disorders (e.g. sleep onset delay or recurrent night time wakening) in children and young people with developmental and psychiatric disorders. There is currently only one brand of melatonin licensed for the use in children - Slenyto®. It is however only licensed for children and adolescents 2-18 years with autistic spectrum disorder (ASD) or Smith-Magenis Syndrome (SMS). The table below lists the preparations covered by this shared care protocol.

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 (1-3). Randomised-controlled trials and clinical experience suggests that it may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment,

cerebral palsy, attention deficit hyperactivity disorder, epilepsy, autism, and learning difficulties (4-8).

Table 1

Product and cost	**Licensed indication**	**Local advice for new patients**	**Local advice for patients already being prescribed**
Slenyto® 1mg and 5 mg prolonged release tablets 1mg - £19.23/28 and 5mg - £96.13/28	Treatment of insomnia in 2-18 year olds with ASD and/or Smith-Magenis Syndrome	Slenyto® should be offered first line for 2-18 year olds with ASD or SMS. Use for other indications is off-label and informed consent should be sought and documented.	Review in line with monitoring below
Circadin® 2mg prolonged release tablets 2mg - £14.28/28	Short-term treatment of primary insomnia in pts over 55years.	Circadin® should be considered to treat insomnia in children / adolescents who do not have ASD or SMS. This use is off-label and informed consent should be sought and documented.	Review in line with monitoring below. Specialist - If the patient has ASD or SMS and continued need is established, then discuss licensed alternative, Slenyto® at next review. If the child/adolescent/ carer makes an informed decision to continue with Circadin®, document this in the patients notes and communicate to the patients GP.
Melatonin 1mg/ml oral solution (Colonis®) Contains 150.37mg/1ml of propylene glycol	Short-term treatment of jet-lag in adults.	Liquid preparations should only be used for administration via an enteral feeding tube or if a child has swallowing difficulties and all other ways of administering a solid dosage form has been tried, for details see below. This use is off-label and informed consent should be sought and documented. **If to be used in a child under 5 please contact Medicine Information at SC(NHS)FT to discuss** content of propylene glycol. Contact details below.	N/A

Swallowing difficulties.

Below are options that can be used if a child has swallowing difficulties;

For an immediate release dose: Half, quarter or crush *Circadin® prolonged release 2mg tablets or *Slenyto® prolonged release 1mg, or 5mg tablets

For a prolonged-release melatonin dose: Mix Slenyto® P/R 1mg or 5mg tablets with yoghurt, orange juice or ice-cream taken immediately to aid swallowing. Do not break, crush or chew them.

Melatonin oral solution should only be prescribed to those with swallowing difficulties if the above options have been tried and have not been successful. The continued need for melatonin and in its liquid form should be regularly assessed. If ongoing melatonin is indicored patients should be switched to a solid dosage form as soon as able.

Only melatonin preparations listed in table 1 are covered by this shared care protocol, all other preparations are black on the Sheffield traffic light drug list.

All patients on 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 preparation where available (i.e. Slenyto® if the child /adolescent has ASD or SMS).

Selection of patients

Melatonin maybe indicated for children with severe sleep disturbances to establish a regular nocturnal sleep pattern, when behavioral modification and sleep hygiene has been unsuccessful or is very difficult to achieve.

Behavioral modification and sleep hygiene are very effective. In the MENDS (MElatonin in children with Neurodevelopmental Disorders and impaired Sleep) study 117 of 263 (44%) patients who completed 4-6 weeks of behavior therapy responded and did not need melatonin treatment.[9] Sleep hygiene should be checked and re-emphasized at every review.

Dosage

By mouth

Child 2 - 18 years

Initially 2mg at night, with or after food. If there is no response or an insufficient response after a minimum of 14 days, reassess sleep hygiene and if complying increase to 4mg (Circadin®) / 5mg (Slenyto®).

The maximum daily dose is 10 mg [(4)] However doses above 4mg/5mg are rarely needed.

The specialist team will titrate any increase in dose needed and any change required will clearly be communicated to the primary care clinician.

Problems with sleep initiation

If the sleep problem is associated with initiation (falling asleep) then a standard release melatonin effect is indicated. This can be obtained by either;

- administering the slow release formulation earlier in the evening or
- crushing Circadin® or Slenyto® prolonged release tablets. The dose should be given 30 minutes before bedtime.

Problems with sleep maintenance or early morning waking

Controlled/Modified release melatonin is indicated in the first instance. Slenyto® (in patients with ASD or SMS) or Circadin® 2mg prolonged release tablets should be prescribed, to be swallowed whole 30-60 minutes prior to bedtime. A second dose should not be given during the night.

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

In children and adolescents who have problems with both sleep initiation and sleep maintenance/early morning awakening, a **Controlled/Modified** release preparation.

In some children a combination of crushed and whole modified release tablets may be required.

Contra-indications

Hypersensitivity to the active substance or to any of the excipients

Cautions

The manufacturer of the UK licensed product advises melatonin should not be used in patients with autoimmune diseases, liver disease and some rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption (due to it containing lactose).[10]

Side –effects

The details below are not a complete list and the BNF and the SPC remain authoritative. Full list of side-effects is given in the Slenyto® and Circadin® summary of product characteristics (SPC), available from **www.emc.medicines.org.uk** [10].

Somnolence, fatigue, mood swings, headache, irritability, aggression and hangover. Epilepsy, visual impairment, dyspnoea, epistaxis, constipation, decreased appetite, swelling face, skin lesion, feeling abnormal, abnormal behaviour and neutropenia.

Although not referenced in the SPC, there have been some concerns around impact on pubertal development.

Monitoring

Once a response to treatment has been established, ongoing response to treatment, adherence to sleep hygiene advice and adverse effects (including possible impact on pubertal development) should be monitored every six months. This should be done by the specialist ideally after 6 months of starting treatment. Thereafter the specialist and the GP should both review the patient annually, rotating so the child is seen every 6 months. (Note in some cases the specialist may see the patient more frequently, however an annual review with the GP is still recommended).

At the review assess;

- Adherence to sleep hygiene (see appendix 1)
- Continued response to treatment
- Signs of adverse effects.

Regular breaks in treatment should be encouraged to assess if continued need. However stopping treatment should be discussed and documented after 2 years. The effects of long term use beyond 2 years is not available.

Stopping Treatment.

- The general aim is to use melatonin as a short-term treatment; this will be made clear to the parents and carers at initiation.
- An attempt to withdraw/have a break in treatment should be made at least every 6 months*.
- Sleep hygiene should be reinforced throughout treatment and prior to any attempt to stop.
- Treatment may be stopped by the GP or the 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.
- 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 2mg daily (using a licensed preparation if available – see table), increasing as per above, (doses above 4mg / 5mg rarely needed. Total daily dose should not exceed 10mg daily or the maximum of previous dose agreed by specialist).

The GP should stop treatment immediately if a serious adverse drug reaction is experienced. This should be reported to the specialist and the MHRA using the yellow card . There is no risk from abrupt withdrawal of melatonin.

* A trial of withdrawal may be tried earlier than 6 months if the clinician and parents decide it is appropriate. Also a longer treatment period may be appropriate in some patients as advised by the specialist clinician.

Switching preparations

- A period of 14 days without melatonin can be trialled. Reiterate the importance of sleep hygiene. For best success, agree a suitable time to stop treatment (e.g. during school holidays); avoiding periods of stress (e.g. during exams).
- A re-bound worsening in sleep pattern may occur initially but this may improve over time
- If sleep deteriorates significantly after a period of 14 days, then switch to Slenyto® MR tablets (2-18 year olds with ASD or SMS) or Circadin® MR tablet. Review response after 2-4 weeks. Use the lowest effective dose and do not exceed previously prescribed dose.

Interactions
Interactions with other medicines

The details below are not a complete list and the BNF and the SPC remain authoritative. Full list of side-effects is given in the Slenyto® and Circadin® summary of product characteristics (SPC), available from www.emc.medicines.org.uk

Concomitant use of the following medicinal products is not recommended

- Fluvoxamine increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum Cmax) - the combination should be avoided.

- Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.
- Benzodiazepines/non-benzodiazepine hypnotics sedative properties are enhanced by melatonin
- Thioridazine and imipramine
- There is a theoretical risk that any CYP1A2 inhibitors could cause an increase in melatonin levels (e.g. oestrogens, quinolones), if a patient on melatonin is started on any medication that inhibits CYP1A2 then advise and monitor about the possibility increased drowsiness and consider if a reduction of the dose of melatonin should be considered.
- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.

Financial implications

<u>Controlled/Modified release melatonin</u>	
Slenyto 1mg and 5mg prolonged release tablet	£19.23/28 (1mg) and £96.13/28 (5mg)
Circadin® 2mg prolonged release tablet	£15.39* for 30 tablets
<u>Immediate release (for enteral tube administration)</u>	
Melatonin 1mg/ml oral solution (Colonis®)	£130.00 for 150ml

*** Drug Tariff January 2020 (Prices quoted are exclusive of VAT)**

Support, education and information

Child Development and Neurodisability **Telephone No:** 0114 2717609	**Sleep Clinic** Sheffield Children's NHS Foundation Trust **Telephone No:** 0114 2717400	**CAMHS Teams** Centenary: 0114 2262348 Beighton: 0114 2716540	**Pharmacy Department**, Sheffield Children's NHS Foundation Trust **Telephone No:**0114 2717259

Sheffield Children's NHS Foundation Trust - Melatonin Patient Information Leaflet (Available from SCHFT pharmacy department)

Or Medicines for Children – Melatonin patient information leaflet - https://www.medicinesforchildren.org.uk/melatonin-sleep-disorders

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12. Flynn Pharma. Slenyto 1mg and 5 mg prolonged-release tablets. Summary of Product Characteristics. https://www.medicines.org.uk/emc/search?q=slenyto
13. PrescQIPP melatonin bulletin. September 2019
14. Background review for the excipient propylene glycol - https://www.ema.europa.eu/en/documents/report/background-review-excipient-propylene-glycol-context-revision-guideline-excipients-label-package_en.pdf

Appendix 1. Sleep Tips

1. **Have a consistent bedtime and wake-up time, even at weekends.**
2. **Plan a relaxing routine an hour before bedtime with, say, jigsaws, colouring or play dough.**
3. **Stop using screens an hour before bedtime and keep devices out of the bedroom overnight.**
4. **Avoid energy drinks and caffeine-based products from noon onwards.**
5. **Make the bedroom calm and comfortable, not stimulating.**
6. **Keep the bedroom as dark and 'boring' as possible, if light is required ideally use a red light bulb to avoid inhibiting the production of melatonin.**

The following are useful resources / websites / apps to support parents and children / adolescence with good sleeping habits.

- NHS Healthy sleep tips for children - https://www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tips-for-children/
- NHS 10 tips to beat insomnia - https://www.nhs.uk/live-well/sleep-and-tiredness/10-tips-to-beat-insomnia/
- Every mind matters, understanding sleep problems - https://www.nhs.uk/oneyou/every-mind-matters/sleep/
- Sleep diary - https://www.nhs.uk/Livewell/insomnia/Documents/sleepdiary.pdf

NHS app library;

- Pzizz - https://www.nhs.uk/apps-library/pzizz/ (free to download, but some in-app purchases)
- Sleepio - https://www.nhs.uk/apps-library/sleepio/ (for those over 16 years of age)

Further useful patient information:

Taken from Encouraging Good Sleep Habits in Children with Learning Disabilities. Research Autism 2007. http://www.researchautism.net/publicfiles/pdf/good_sleep_habits.pdf (accessed September 2015)

NHS choices - https://www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tips-for-children/

The Sleep Council - https://sleepcouncil.org.uk/seven-steps-to-a-better-nights-sleep/ including information on;

- Teen sleep
- Sleep advice for children (Meet Daisy)

The children sleep charity leaflets - https://www.thechildrenssleepcharity.org.uk/leaflets.php including information on;

- Sleep and Diet
- Relaxation tips for bedtime
- How to create a calm bedroom
- Bedtime routine