Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

Sleep disorders in children and young people with complex neurological / neurodevelopmental disorders (age 1-18years): MELATONIN

Shared Care Protocol

This protocol provides prescribing and monitoring guidance for melatonin therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc , the BNF and the Shared Care Protocol Responsibilities.

****FOR USE BY COMMUNITY PAEDIATRICS AND PAEDIATRIC NEUROLOGY ONLY****

All primary care prescribing of melatonin must be in line with this SCP. The OCCG Commissioning Policy Statement No. 274 requires prescribing to be in line with local Medicines Optimisation prescribing formulary or guidance, including the choice of melatonin preparation.

Shared Care Responsibilities

Shared care assumes communication between the specialist, GP and patient/parent/carer. The intention to share care should be explained to the patient/parent/carer and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy.

Specialist

- Advise the patient/parent/carer that there is no safety or efficacy evidence available to support long-term use.
- Complete pre-treatment assessment (detailed below)
- Initiate treatment and prescribe until the dose is stable and the GP formally agrees to shared care. Specialist will prescribe until benefit is evidenced and dose is stable, which may take up to 3 months. If no benefit is seen then prescribing will be stopped and no request made to the GP.
- Only request prescribing of Circadin® 2mg tablets by GP, unless patient has a small-bore enteral feeding tube or has severe oral sensitivity preventing the effective use of crushed tablets (see Administration section).
- Ensure the patient/parent/carer understands the nature and complications of drug therapy and their role in reporting adverse effects promptly
- Provide copy of patient information leaflet
- Send a letter to the GP immediately requesting shared care. Outline shared care protocol criteria
- Advise the patient/parent/carer and GP if an, at least, annual drug holiday will be implemented.
- If appropriate, undertake periodic, at least annual, treatment withdrawals. Advise the GP on continuing (including dose changes) or stopping melatonin following medical review of the patient and associated drug therapy (including drug holidays). Advise the GP when therapy should be discontinued for patients receiving medication long-term and provide necessary supervision and support during drug discontinuation phase.

- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments
- Agree a plan with patient/carer for transition to adult services or discharge
- Be available to give advice to GP and patient/parent/carer throughout treatment

GP

- Prescribe medication once the dose is stable and shared care is agreed
- Prescribe Circadin® 2mg tablets unless patient has small-bore enteral feeding tube or has such severe oral sensitivity that the tablets cannot be administered successfully
- Ensure all monitoring is completed in accordance to the specific shared care protocol (listed under on-going monitoring).
- Notify the specialist to any changes in patients condition, any adverse drug reactions or failure to attend tests
- Support implementation of annual drug holiday for patient, unless stated as inappropriate by specialist who will advise on the process.

Patient/parent/carer

- Agree to treatment and monitoring after making an informed decision
- Agree to being under the shared care of the GP and specialist
- Attend for blood tests and monitoring when required
- Agree to an annual drug holiday to review benefit unless considered inappropriate by specialist. This will involve maintenance of a sleep diary and stopping the drug for two weeks before reviewing benefit or stopping.
- Report any side effects to the GP or a member of the specialist team
- Understand that there is no safety or efficacy evidence available to support long-term use.
- Agree a plan with specialist for transition to adult services or discharge.

Background for Use

There is no safety or efficacy evidence available to support long-term use.

Sleep disorders may include delayed onset of sleep, frequent waking, early morning waking or day-night reversal of sleep pattern Melatonin is a pineal hormone which may affect circadian rhythms and sleep pattern[1]. Production is affected by light exposure detected by the retina; it is thought that this rhythm is disturbed in children with brain damage or visual disturbance. Sleep problems are common in neurodevelopmental disorders such as Autism[2] and Melatonin is effective in reducing sleep problems in children with Autism[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. Melatonin has been widely used for number of paediatric pathologies including sleep onset disorders[4]. Melatonin is the preferred agent over benzodiazepines and antihistamines in this group of patients to aid sleep as there are fewer interactions and less “hangover effect”. Contrary to other sedative therapies, there is no evidence of tolerance or addiction to melatonin.

Melatonin is indicated for children and young people with severe sleep disturbances when the sleep problem persists after a behavioral intervention, and then only: after consultation with a psychiatrist or a specialist paediatrician for a child or young person with expertise in its use in people with a learning disability together with non-pharmacological interventions and regular reviews[5].

There is no safety or efficacy evidence available to support long-term use.

Contraindications and Precautions

Contra-Indications	
Hypersensitivity	To the active substance or any of the excipients
Liver Disorders	Manufacturer of the UK licensed product advises to avoid
Autoimmune disease	Manufacturer of the UK licensed product advises to avoid
Precautions	
Epilepsy	Some reports suggest melatonin improves seizure control when used in patients with epilepsy; others indicate that it may worsen seizure control. When used in patients with epilepsy, it is important to closely monitor the effect of melatonin on seizure frequency[6].
Renal disorders	Manufacturer of the UK licensed product advises caution
Rare hereditary glucose tolerance disorders	Caution due to lactose content
Asthma	A recent review on the use of melatonin suggest that it should be used with caution in patients with asthma[7]

Dosage

Indication	**Dose**
Problems with sleep initiation, problems with sleep maintenance or early morning waking	Child 1 month–18 years: initially 2mg increased if necessary after 1–2 weeks in increments of 2mg to 4–6 mg; max. 10 mg. The dose should be given 30-60 minutes prior to bedtime. It is recommended that melatonin be given on an empty stomach, since the absorption may be delayed when taken with large meals.

Administration

- If the patient is able to swallow tablets Circadin® modified release tablets (unlicensed use) may be swallowed whole and given with or without food. Circadin® tablets can be halved (using a tablet cutter) or crushed if necessary.

- For children with difficulties swallowing, the tablet can be crushed to a fine powder and mixed with water or given with cold soft food such as a teaspoon of yoghurt or jam. Use a small amount of food to ensure the full dose is taken. The prescription should state that the medication is to be crushed prior to administration.

- For administration via an enteral feeding tube, the tablet can be crushed to a fine powder and added to 5 - 10ml of water and mixed well.

- Melatonin oral solution 5mg/5ml in 200ml (prescribed in this format/presentation) may be prescribed for patients with small-bore enteral feeding tubes (gauge less than 9) where there is risk of tube occlusion, or for patients with severe oral sensitivity in whom a trial of crushed tablets has been unsuccessful.

NOTE: crushing the MR tablet will mean that it is no longer modified release.

Melatonin is generally well tolerated. Sedation and fatigue, headaches, skin disorders, restlessness, increased pulse, itching and nausea have all been reported as side effects associated with melatonin use. Full list of side-effects is given in the Melatonin summary of product characteristics (SPC)[8]. [Melatonin is monitored intensively by the CHM and MHRA - Please report any adverse reaction to the CHM, using the yellow card system. https://yellowcard.mhra.gov.uk/]

Time to Response

If there is no response or insufficient response after a minimum of 7 to 14 days therapy the dose is increased in steps. The patient's consultant should normally take the decision to stop treatment where appropriate particularly if there has been no response to treatment after a trial period of usually 2-3 months, in discussion with parents, and communicate this decision to the patient's GP. NB no request to be made to GP unless benefit has been evidenced and dose is stable.

Pre-Treatment Assessment

The initiating consultant will discuss benefits and side effects of treatment with the patient/parent/carer and obtained informed consent. This is particularly important for unlicensed products. The consultant will initiate Melatonin in appropriate patients and **prescribe until benefit has been evidenced and dose is stable, which may take up to 3 months**. The consultant will also provide the patient/parent/carer with a written patient information leaflet Melatonin Medicines for Children Leaflet Information[9]: (http://www.medicinesforchildren.org.uk/search-for-a-leaflet/melatonin-for-sleep-disorders/) The GP will be asked to take over prescribing once it has been confirmed that the melatonin is effective and the dose has been stabilised.

Ongoing Monitoring

The GP should continue to prescribe for the patient as advised by the consultant. However, if the patient/parent/carer approaches the GP about stopping treatment and the GP feels the request is reasonable then treatment can be stopped and the consultant notified of this decision. They will seek the advice of the consultant if there are any concerns with the patient's therapy. The GP can also stop treatment immediately after a serious adverse drug reaction if deemed appropriate.
Some patients may benefit from reducing treatment from regular use to an as needed dose (for example when sleep routines are disrupted through travel or illness.)

It has been suggested that melatonin may affect the reproductive system[10] by inhibiting the hypothalamic-pituitary-gonadal axis. Growth and sexual development monitoring is advisable, especially with long term melatonin use. **This is primarily the responsibility of the Consultant clinician** but any concerns from the primary care clinician should be reported to the Consultant clinician. The GP should check for any reported adverse effects.

Review of benefit and drug free holidays
If treatment is beneficial, at least 6 months of improved sleep pattern should elapse before attempting to withdraw treatment.
In those who require long term treatment, a drug holiday should be introduced at least annually to assess the continued need for treatment, unless the specialist considers this inappropriate. This could take place two weeks before the annual review with the patient and/or the parent/carer keeping a sleep diary. A drug free holiday should also be taken in those who stop responding to melatonin.
The consultant will review the appropriateness of the melatonin at least every 12 months, possibly by initiating drug free holidays.

If and when melatonin is restarted, consideration should be given to starting at the lowest dose of melatonin (usually 2mg).
The outcome of any drug holiday must be recorded in the patient's notes.
The specialist will advise on management of drug free holidays

Actions to be taken

Side Effects	Action
Impaired growth or sexual development[10]	*refer to specialist*
Uncommon: Abdominal pain; abnormal dreams; anxiety; chest pain; dizziness; dry mouth; dry skin; dyspepsia; glycosuria; headache; hypertension; irritability; malaise; mouth ulceration; nausea; nervousness; proteinuria; pruritus; rash; restlessness; weight gain	*Stop medication or refer to specialist*
Rare: Aggression; arthritis; electrolyte disturbances; flatulence; gastritis; haematuria; halitosis; hot flushes; hypersalivation; hypertriglyceridaemia; impaired memory; increased libido; lacrimation; leucopenia; mood changes; muscle spasm; nail disorder; palpitation; paraesthesia; polyuria; priapism; prostatitis; restless legs syndrome; syncope; thirst;	*Stop medication or refer to specialist*

thrombocytopenia; visual disturbances; vomiting	
Unknown: Galactorrhoea; mouth oedema; tongue oedema	*Stop medication or refer to specialist*

Notable Drug Interactions (Refer to BNF and SPC)

Fluvoxamine and cimetidine has been shown to increase melatonin levels by inhibiting cytochrome P450 (CYP) isozymes CYP1A2 and CYP 2D respectively and these combinations should be avoided. There is a theoretical risk that any CYP1A2 inhibitors could cause an increase in melatonin levels (e.g. oestrogens, quinolones). CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin. Alcohol should be avoided as it reduces the effect of melatonin on sleep. Melatonin may enhance the effects of sedatives and hypnotics (e.g. benzodiazepines). On initiation of melatonin the specialist will be responsible for checking interactions and making necessary alterations in treatment. If a patient is started on any of these medications contact the specialist for advice. The above details are not a complete list and the BNF and the SPC remain authoritative.

Back-up Information and Advice

Contact Details	
Community Paediatrics	
City, South, Bicester and Kidlington	01865 231994
North	01295 229510
West	01993 776920
Locality consultant/secretary	Contact details at top of clinic letter
Paediatric Neurology	
Consultant	JR Switchboard: 01865 741166
Registrar (working hours only)	bleep 1079

References

1. ESUOM2 Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin. NICE - Evidence Summary: Unlicensed or off-label medicine - (January 2013) link https://www.nice.org.uk/guidance/esuom2/resources/sleep-disorders-in-children-and-young-people-with-attention-deficit-hyperactivity-disorder-melatonin-pdf-1503234972035269
2. NICE CG170, 2013: Autism spectrum disorder in under 19s: support and management https://www.nice.org.uk/guidance/cg170
3. SIGN, 2016: Assessment, diagnosis and interventions for autism spectrum disorders(ASD) http://www.sign.ac.uk/assets/sign145.pdf

4. Sanchez-Bacelo EJ et al (2011). Review Article - Clinical uses of melatonin in pediatrics, *Int J Pediatr*. : Article ID 892624 https://www.hindawi.com/journals/ijpedi/2011/892624/
5. NICE guideline NG 11 (29 May 2015): Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges https://www.nice.org.uk/guidance/ng11/chapter/1-recommendations
6. Jain S, Besaq FM. (2013). Does Melatonin affect epileptic seizures? *Drug Saf*., 207-15. https://www.ncbi.nlm.nih.gov/pubmed/23532506
7. Marseglia L et al. (2014). Melatonin and Atopy: Role in Atopic Dermatitis and Asthma. *Int. J. Mol. Sci.,* 13482-93. http://www.mdpi.com/1422-0067/15/8/13482
8. Summary of Product Characteristics of Melatonin Modified Release (Circadin® from Flynn) available at http://www.medicines.org.uk/emc/ingredient/2072/melatonin/
9. Melatonin Medicines for Children Leaflet Information: http://www.medicinesforchildren.org.uk/search-for-a-leaflet/melatonin-for-sleep-disorders/
10. McGuire N et al. (2011). Effects of Melatonin on Peripheral Reproductive Function: Regulation of Testicular GnIH and Testosterone. *Endocrinology*, 3461-3470. https://www.ncbi.nlm.nih.gov/pubmed/21771888

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