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 and the BNFc.

BACKGROUND FOR USE

Melatonin is a pineal hormone which affects sleep. It is indicated for sleep disorders in children and young people between 1 - 18 years of age with neurodevelopmental disorders, e.g. attention deficit hyperactivity disorder (ADHD), ASD, visual impairment, learning difficulties, developmental delay or any other neurodevelopmental condition where symptoms have been present for at least 6 months or sleep disturbance is so severe that the family is heading for crisis. Sleep disturbance can involve problems with the onset of sleep (sleep onset latency), frequent night awakenings, and early morning waking. Sleep disturbances can be chronic, leading to worsening learning or behavioural difficulties during waking hours, as well as causing significant disruption to family life.

Melatonin can only be initiated by specialist paediatricians or specialists for Learning Disabilities/psychiatrists and continued by GPs in accordance with this shared care protocol.

Melatonin should be used only when behavioural sleep interventions alone have failed. All patients who are currently taking the melatonin immediate release 3 mg tablets should be switched to melatonin m/r 2 mg tablets.

SUPPORTING INFORMATION

NICE clinical guideline 170 sets out the expectations of management for sleep disturbance in children with ASD. It recommends attempting a sleep plan first and introducing pharmacological intervention (melatonin) if the problem persists. This guideline clearly identifies the lack of robust randomised controlled trial (RCT) data for meta-analyses. SIGN clinical guideline 145 on the assessment, diagnosis and interventions for ASD also recommends melatonin as a trial to improve sleep onset if sleep difficulties have not resolved following behavioural interventions.

NICE clinical guideline CG11 recommends the use of melatonin in children with ADHD and cerebral palsy. There is also a NICE evidence summary (ESUOM2) for these indications.

Licensed melatonin 2 mg modified-release (MR) should be used as the first line product, although its use in children is off-label.

RESPONSIBILITIES

Specialist

- Diagnosis of a sleep disorder in children with neurological or neurodevelopmental disorders should be made by a specialist paediatrician, a psychiatrist or a specialist in Learning Disabilities (LD).
- Prior to initiating melatonin, sleep hygiene should be discussed. Discuss benefits and side effects of treatment with the patient/carer and obtain informed consent. This is particularly important for unlicensed/off-label products.
- Initiate melatonin in patients unresponsive to sleep hygiene.
- Explain to the patient/carer that melatonin must be used in line with sleep hygiene techniques.
- Ensure the patient is regularly reviewed by a member of the specialist team to monitor response and adverse effects to treatment (usually once a year). Explore the idea of stopping treatment at each review.
- Prescribing should be retained by the specialist until response to treatment has been confirmed, optimal dose achieved and a decision has been made by the specialist that annual review by the specialist is acceptable.
- Provide patient/carer with a written patient information leaflet and advise on sleep hygiene.
• Contact patient’s GP to request prescribing under shared care with the specialist and patient’s signature on the shared care form and send a link to or copy of the prescribing guideline. Include a letter to advise on patient’s current dose.

• Advise the GP about continuation of treatment, including length of treatment and trials off medication. A drug holiday should be introduced at least annually to assess the continued need for treatment. This could take place a month before the specialist review with the patient, with the patient/carer keeping a sleep diary. The outcome of any drug holiday must be recorded in the patient’s notes.

• Discuss any concerns with the GP regarding patient’s therapy.

• Notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.

• Monitor the general health of the patient, including efficacy, adverse effects and ongoing need for treatment.

GP

• Within one week of receipt of the Shared Care Protocol return the completed [Shared Care Agreement Form](#) to indicate willingness to undertake shared care.

• Prescribe melatonin as part of the agreement once the patient has been stabilised.

• Report any suspected adverse drug reactions to the specialist and the Medicines and Healthcare products Regulatory Agency (MHRA) using the yellow card scheme.

• If the GP considers that the patient should be reviewed, they should contact the initiating prescriber but will continue to prescribe until the reassessment has taken place, unless an adverse effect has occurred.

• Communicate any problems to the specialist looking after the patient or inform the specialist if the patient discontinues treatment for any reason.

Pharmacy Duration of Supply

The hospital pharmacy will supply the first 8 weeks of treatment.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to melatonin or any excipients (refer to manufacturer’s information). Avoid use in patients with:

• Autoimmune disease (no clinical data exists concerning use)
• Hepatic impairment (clearance reduced)
• Pregnancy or breastfeeding (no information available in pregnancy but present in milk)
• Renal impairment (use with caution, no information)
• Rare heredity problems of galactose intolerance, LAPP lactase deficiency, or glucose-galactose malabsorption

DOSAGE

The aim is to establish healthy sleep habits with the lowest effective dose.

Initial dose is 2 mg given 30 - 60 minutes before bedtime.

If there is no improvement after 1 - 2 weeks, the dose is increased by 2 mg incrementally according to response, up to a maximum dose of 10 mg/day, although there is evidence that there is little additional benefit at doses over 6 mg.

MR tablets can be halved using a tablet cutter, retaining its MR properties or can be crushed for immediate-release and mixed into a small amount of food or liquid. A leaflet for parents and carers is available on the Medicines for Children website. If applicable, the prescription should state that the medication is to be crushed prior to administration.

Crushed melatonin MR tablets are not suitable for administration via enteral feeding tubes, and in these patients melatonin oral solution should be prescribed by the specialist and dispensing retained within the hospital (melatonin oral solution is RED on formulary).
TIME TO RESPONSE

If there has been no beneficial response within 7 - 14 days, the dose can be increased in 2 mg steps every 7 - 14 days, to the lowest effective dose.

A beneficial response must be demonstrated in the sleep diary and is defined as:

- An increase in sleep duration by 60 minutes or more
- A significant reduction in the number of night time waking episodes
- A consistent shift in sleep pattern towards earlier settling to sleep
- The ability to wake in the morning in order to get to school on time (if applicable)

Where patients fail to respond to treatment at the maximum doses stated above, treatment should be discontinued by the specialist (this can be done abruptly).

At least 3 - 6 months of an improved sleep pattern should elapse before withdrawal takes place. The specialist will attempt to withdraw treatment after 6 months and change in sleeping pattern observed. Rebound worsening in sleep pattern may occur initially but this may improve over time. If sleep patterns are maintained after this reduction then dose can continue to be weaned by the specialist every 4 - 6 weeks with an aim of stopping treatment. If difficulties recur, the melatonin dose can be reinstated by the specialist with a further attempt for withdrawal 6 - 12 months later.

For some children withdrawal may not be successful and treatment may be necessary long term. These patients can be referred to the GP as long as annual review by the specialist is acceptable. The specialist will keep the GP informed of any dose changes.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

Consider adjusting the dose of any stimulant medication if child is struggling to settle in the evening, e.g. reducing total dose, changing the regimen or formulation so that less medication is administered later in the day, adding a third dose of stimulant in the evening if sleep onset delay is due to a rebound effect or switching to an agent associated with fewer sleep difficulties (e.g. atomoxetine).

A trial of behavioural intervention or sleep hygiene measures for a minimum of 2 months. If trial successful, measures should be continued without prescribing of melatonin. If trial fails, melatonin should be considered for prescribing along with behavioural interventions/sleep hygiene measures.

Simple non-pharmacological measures include:

- Ensuring that there is an established bedtime routine and that a realistic sleep-wake schedule has been agreed.
- Ensuring that room conditions (temperature, light and noise) are at an optimum level to promote sleep, e.g. minimise background noise, use of blackout blinds.
- Ensuring no late afternoon/evening caffeine consumption.
- Removing television and electronic devices from the child’s room, since it is known that the blue-green light emitted by these screens can disturb sleep. Children should avoid looking at bright screens 2 - 3 hours before bed.

Engagement from the family is vital and there may be instances when it is difficult or impossible to establish behavioural interventions or sleep hygiene measures because the patient or carers are struggling to cope with the current situation. In these instances, melatonin may be initiated at the same time as behavioural interventions or sleep hygiene measures and consideration of withdrawal once the other interventions are established.

No baseline monitoring is required.

ONGOING MONITORING SCHEDULE

An annual review of melatonin therapy should be completed by the specialist with the patient.

The specialist should consider and give a written plan for a melatonin-free trial (“drug holiday”) at least annually to assess the continued need for treatment. The outcome of any treatment break must be recorded in the patient’s notes.
Treatment should be stopped when there is a lack of effect based on information from the drug holiday and patient/carer perception.

Monitoring, particularly with regard to growth and pubertal/sexual development is advised in children receiving melatonin for periods of a year or more as melatonin has been suggested to inhibit the hypothalamic-pituitary-gonadal axis. This monitoring can be completed as part of the annual specialist review, including height and weight. Monitoring should continue after melatonin is stopped whilst the child remains under the care of the paediatric/CAMHS teams.

It is unusual for a child to continue melatonin into adulthood. It is the responsibility of the referring specialist to decide if it is appropriate to continue for a specific individual. The specialist will then advise the GP on future management.

The GP should be informed of any changes to melatonin therapy.

SIDE EFFECTS AND ACTIONS TO BE TAKEN

Melatonin is generally well tolerated and adverse reactions reported are at similar levels to those reported with placebo. The long term side effects have not been evaluated.

Sedation and fatigue, headaches, dizziness, pharyngitis, abdominal pain, constipation, dry mouth, weight gain, skin disorders, restlessness and irritability, increased pulse, nervousness, sweating, hypertension, itching and nausea have all been reported as side effects associated with melatonin use.

There are conflicting reports on the effect of melatonin on seizure activity. Therefore, children with concomitant epilepsy should be monitored appropriately.

NOTABLE DRUG INTERACTIONS (REFER TO BNFc AND SPC)

Case reports, clinical experience and theoretical principles suggest the following:

- Caution with concomitant use of oestrogens, quinolones – may increase melatonin levels
- Caution with carbamazepine and rifampicin – may reduce melatonin levels
- May enhance sedative properties of hypnotics
- Cigarette smoking may decrease melatonin levels
- Interactions may also occur with anticoagulant/antiplatelet drugs, anti-diabetic agents, cetirizine, contraceptives, flumazenil, fluvoxamine, immunosuppressants, nifedipine and verapamil – see up to date BNFc for more detailed information

BACK-UP INFORMATION/ADVICE

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Appendix 1

**Buckinghamshire Shared Care Agreement Form**

**for use when prescribing one or more amber protocol drug**

This form is used to agree shared care between the specialist, patient and GP as follows:

1. Specialist to estimate date of GP prescribing continuation.
2. Specialist to provide pre-treatment counselling and discuss patient responsibilities.
3. Specialist and patient to complete and sign the shared care agreement form.
4. Copy to be filed in patient’s hospital notes.
5. Agreement form, drug specific protocol and responsibilities to be faxed to the GP and copies given to patient.
6. GP to complete and sign agreement form. If unwilling to ‘share care’, provide reason.
7. Scan copy of shared care agreement form, protocol and responsibilities into patient’s notes.
8. Fax signed copy back to specialist.

**For completion by specialist**

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