Kettering General Hospital NHS Trust
Northamptonshire Clinical Commissioning Group
Northampton General Hospital NHS Trust
Northamptonshire Healthcare Foundation Trust

SHARED CARE

GUIDELINES

Melatonin

For the Treatment of chronic Sleep Disorders in Children and Adolescents

with neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance

including ADHD and ASD, Smith-Magenis syndrome, Down Syndrome, chronic fatigue syndrome

but not for the treatment of acute conditions or sleep disorders in depression

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MELATONIN IS CATEGORISED AS "DOUBLE RED" BY NPAG; PRIOR APPROVAL MUST BE AGREED BEFORE PRESCRIBING IS INITIATED*

**this includes prescription via FP10 or hospital prescription.*

Accessing sleep hygiene interventions before considering treatment with melatonin Melatonin should not be considered unless confirmation can be obtained from Sleep Right (Scope) [formerly Sleep Solutions] ***that parents have attended the recommended treatment programme and this has been unsuccessful.*** *Specialists – that is Consultant Paediatrician, Paediatrician or Child Psychiatrist and non-medical independent prescribers working in the ADHD/ASD service (Psychologists and Specialist Nurses) - or GPs may refer the child to Sleep Right. Sleep Right has made their patient leaflets available for GPs and other health professionals. These are available on the Primary Care Portal and can be printed off when advising parents and/or children about sleep problems. If the GP refers a child to Sleep Right and the child is under specialist care, the GP should notify the Community Paediatric Service or CAMHS responsible clinician. If prescribing is initiated by a Specialist, care may be shared if appropriate as described below. Sleep Right will liaise directly with a GP who has referred a child to them without a need for secondary care referral, to gauge whether they are in agreement with prescribing before requesting prior approval.*

Prior Approval
A Prior approval application by the Specialist is still be required in the rare exceptional situations when melatonin may need to be started in advance of the Sleep Right programme e.g. in situations where the family is in crisis or there is an exceptional waiting time to access the sleep programme.
Where a sleep programme has been completed and Sleep Right and the secondary care specialist agree that a trial of melatonin is appropriate, Sleep Right will submit the Double Red Prior Approval request to the CCG.
If a patient has been referred to Sleep Right by a GP without a need for secondary care referral, Sleep Right will liaise with the GP to gauge whether they are in agreement with prescribing before requesting prior approval.
(See under 'Indications' for further information)
Retrospective Prior Approval is NOT required for existing patients

Acute prescribing for inpatients
These guidelines do not cover short-term prescribing for 5-10 days for in-patients. The Specialist should complete an NHFT application form for the use of melatonin for in-patients and submit to the appropriate Senior Mental Health Pharmacist for approval. If the Specialist wishes to continue prescribing beyond the acute phase they will then need to submit a Prior Approval application.

Treatment of depression
These guidelines do not cover the treatment of depression in adolescents. However, a Prior Approval application to the CCG is still required before melatonin can be prescribed. Sleep interventions may still be beneficial. NHFT has made their patient leaflets available for GPs and other health professionals. These are available on the Primary Care Portal and can be printed off when advising parents and/or children about sleep problems. Patients should continue to be reviewed regularly to assess continuing need.

See sleep disorder guidelines at

http://gp.neneccg.nhs.uk/clinical-topics/sleep/99425

SHARED CARE RESPONSIBILITIES

Aspects of care for which the Specialist is responsible:

- Assessing suitability of patients for treatment with melatonin – N.B. use is restricted to the group of children for whom it is indicated i.e. neurodevelopmental disorders (ADHD/ASD), epilepsy, Smith-Magenis syndrome, visual impairment, physical disability and complex developmental disorders (see full details under 'Indications').
- Ensuring any ADHD medication is optimised e.g. well timed immediate release methylphenidate after school to enhance calm pre-bedtime routine for children on treatment for ADHD
- Ensuring that the child and family have worked with Sleep Right as above, Submitting prior approval application to the CCG unless this has been organised by Sleep Right on behalf of the prescriber on completion of the sleep programme.
- If Prior Approval application is granted, advise the family that melatonin will only be prescribed for 3 months in most cases and that they should continue to work with Sleep Right during this time to achieve good sleep hygiene (Sleep Right to report on progress to Specialist in writing after 3 months);
- Share a copy of the shared care agreement treatment plan with the patient/parent/carer to include regular trials of withdrawal (treatment holidays) will be undertaken.
- Initiation and supply of melatonin (prescribed as Circadin® M/R 2mg) for a trial period of 3 months
- Reviewing the patient at 3 to 6 months after treatment initiation and annually thereafter if treatment with melatonin continues beyond the 3 month trial.

Role of Sleep Right during melatonin treatment trial period after completion of sleep intervention programme

- During the 3 month trial period the child and family will continue to work with Sleep Right to maintain good sleep hygiene with the intention that melatonin can be tapered and stopped during month 3 for the majority of cases;
- Sleep Right to report on progress to Specialist in writing after 3 months. Sleep Right to advise the Specialist and GP whether melatonin successfully stopped or not;
- If Sleep Right cannot wean the child off melatonin they will advise the Specialist that prescribing should be continued, with regular review; prescribing can be passed to the GP if to be continued beyond 3 months and will include regular trials of withdrawal (treatment holidays) will be undertaken.

Shared care arrangements

- Liaison with GP to agree to share the patient's care using a standard shared care request letter and notification of the treatment plan to the GP
- Assess and monitor patient's response to treatment
- Cease medication when not effective
- Cease medication where an appropriate sleep pattern has been established and maintained during a treatment break
- Ensure patient's parents/carers are aware that regular trials of withdrawal will be undertaken
- Report any suspected adverse events to the MHRA.

- Minimum annual review of on-going need for treatment (by clinic review, telephone contact or other appropriate route) and notification to the GP. NB If a child on melatonin fails to attend their annual review appointment then a decision may be made to withdraw treatment.
- Treatment holidays
  The risks of long term melatonin have not been well characterised. Generally it should be made clear at the outset that regular trials of withdrawal should be undertaken. Some clinical experience suggests that the efficacy of melatonin may be lost if it is taken for longer than two years; withdrawal prior to this may re-establish sensitivity to allow melatonin to be successfully reintroduced. To maintain sensitivity, regular melatonin holidays are recommended and should take place at least once every 6 months. Melatonin holidays should ideally take place over weekends or school holidays and can be as long as a weekend or 7 days (1 week).
  Some children may only require melatonin during the school week and can omit on weekends
- Discontinuation – advising the GP when a trial withdrawal of melatonin should be undertaken.
- Re-refer to the sleep clinic if treatment has continued for two years or more

Aspects of care for which the GP is responsible while shared care arrangements are in place:

- Confirmation of agreement to prescribe
- Prescribing melatonin if this is to continue beyond 3 months
- Liaison with the Specialist regarding any complications of treatment.

Additional GP responsibilities where the child's care has been discharged to the GP:

- Where care has been discharged to the GP because the child's condition does not require ongoing specilaist review,the GP may refer the child / family back to Sleep Right; this is recommended if a child has been taking melatonin for more than two years

Traffic Light Status of Melatonin -DOUBLE RED

Where Sleep Right and the secondary care specialist agree that a trial of melatonin is appropriate, Sleep Right will submit the Double Red Prior Approval request to the CCG.
If a patient has been referred to Sleep Right by a GP without a need for secondary care referral, Sleep Right will liaise with the GP to gauge whether they are in agreement with prescribing before requesting prior approval.

In the rare exceptional situations when melatonin may need to be started in advance of Sleep Right programme the initiating Specialist is responsible for the prior approval application. *Patients falling in this category should still be referred to Sleep Right but see under Indications for further information.*

The usual duration of prescribing is for 3 months for most children. In cases where prescribing is to continue for more than 3 months prescribing may be transferred to GPs under shared care arrangements.

Shared Care: As outlined in the NHS Circular 1992 (Gen 11) a Specialist may seek the GP's involvement in prescribing for a patient where there is a Shared Care agreement.

For full Traffic Light System/Shared Care information see: -

http://gp.neneccg.nhs.uk/medicinesoptimisation/traffic-light-drugs.htm

Background to Sleep Disorders

Sleep disorders are common in children with neurological disorders, autism, mood disorders and visual impairment. These children often have disturbed sleep patterns, with delayed onset, fragmentation and frequent nocturnal awakening. Sleep disorders can be a major source of stress for the whole family.

Melatonin

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep. It is commonly used for the treatment of sleep disorders in children with Attention Deficit Hyperactivity Disorder (ADHD) but the evidence for this is poor.

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[1-5]. The MENDS study by Paul Gringras found that melatonin did not improve total sleep by a significant amount of time. A more recent study, Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin[9] for Insomnia in Children with Autism Spectrum Disorder has found it to be efficacious when compared to a placebo, but this study was undertaken for up to 52 weeks. . Sleep disturbances in children with neurological or behavioural disorders are very common. There are multiple factors for this that are frequently interrelated and which include delayed brain maturation, malfunction of sensory organs (particularly vision) and abnormalities or malformation of the sleep centres.

The types of sleep disruption experienced include delayed onset, frequent waking, early morning wakening and reversal of the day-night sleep pattern. Such children have a variable response to behavioural therapies, although studies show that a good proportion benefit from sleep hygiene measures[6].

The use of traditional hypnotic or sedative drugs can cause adverse reactions, lead to tolerance and dependence and may affect learning due to daytime drowsiness. For these reasons, they are not recommended in children and other treatments are preferable. Melatonin has become the mainstay of pharmacological treatment for sleep disturbance in children, particularly sleep onset difficulties[7].

In its evidence summary of melatonin[8] (N.B. not formal NICE guidance), NICE noted that "Limited evidence for unlicensed melatonin products was identified from 2 small (n=105 and 19) short-term RCTs and 1 small, long-term follow-up study (n=94). The evidence suggests that unlicensed melatonin products, taken for 10 days to 4 weeks, may reduce sleep onset latency (the time taken for a child to go to sleep) in children with sleep onset insomnia and ADHD by approximately 20 minutes. In addition melatonin may improve average sleep duration by 15 to 20 minutes. However, there are limitations to these small studies, and longer term efficacy is unclear"

https://www.nice.org.uk/advice/esuom2/resources/sleep-disorders-in-children-and-young-people-with-attention-deficit-hyperactivity-disorder-melatonin-1503234972035269

GP prescribing costs for melatonin were approximately £220K in 2018-19, with additional prescribing costs incurred by prescribers in Northamptonshire Healthcare Foundation Trust and Northampton General Hospital.

Three forms of melatonin (Circadin®, Slenyto® and Colonis®,) are currently licensed in the UK.

- Circadin® is licensed for the short-term treatment of primary insomnia, in adults who are aged 55 years or over.
- Slenyto® 1mg and 5mg MR tablets are licensed for the 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.
- Colonis® liquid 1mg/ml and Colonis® 3mg tablets are licensed for jet lag.
- All other melatonin products are unlicensed "specials". Thus for most patients there is no licensed product available with a marketing authorisation for use in children and young people without the neurodevelopmental or development disorders listed for Slenyto®.

NPAG have considered the place of the three licensed forms of melatonin in treatment of sleep disorders:

- Circadin® should continue to be used off label in treating children with sleep problems where behavioural interventions are not sufficient, including in those cohorts where Slenyto® is licensed. (Medicines derogation application, NPAG 24th June 2020).

- Melatonin Liquid 1mg/1ml (Colonis®) contains propylene glycol and alcohol and an alcohol free preparation is preferred. Clinicians should continue to use Circadin® off label for most patients who could not or would not swallow tablets and where tablets need to be crushed.

Therefore, all melatonin prescribing will be for Circadin® 2mg M/R tablets.

Any prescribing of melatonin should be Circadin® brand

Melatonin is unlikely to be a cost-effective intervention for most children and it should not be routinely used as a first-line intervention for children with sleep disorders. Extra capacity has been resourced for behavioural interventions via Sleep Right through the provision of Workshops in addition to the treatment programme. Melatonin should be the next line treatment if Sleep Right sleep hygiene support materials available from Primary Care Portal are not successful in improving sleep patterns

Melatonin should not be considered unless confirmation can be obtained from Sleep Right that parents have attended the recommended treatment programme and this has been unsuccessful.

Indications

For the purposes of this guideline, the indications agreed by NPAG are as follows:

Off-label indication in children and young adolescents:
For use in children with neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance: specifically the child or young person has at least one of the following conditions:

- Neurological or behavioural disorders including Attention Deficit Hyperactivity Disorder

- Neurodevelopment disabilities / disorders e.g. delayed brain maturation i.e. Smith - Magenis syndrome, Autistic Spectrum Disorders, sensory dysfunction - especially visual dysfunction, cerebral palsy, Rett syndrome; in addition Down Syndrome (see below)
- Chronic fatigue syndrome / myalgic encephalomyelitis with associated sleep difficulties (as recommended in NICE clinical guideline 53).
- 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

and melatonin may then only be prescribed if:

- there is chronic (6 months or more) sleep disturbance resulting in severe stress for the patient and/or family, and impacting on the functioning of the child and family
- Attendance at the recommended Sleep Right program has been unsuccessful. Melatonin should only be used in children and young people for whom sleep hygiene and behavioural modification strategies after consistent input from Sleep Right and dedicated engagement from parents has not produced the desired improvement confirmed by the Sleep Right team
- *There may be rare exceptional situations when melatonin may need to be started in advance of the Sleep Right programme e.g. where there is exceptional waiting time for an appointment with Sleep Right and / or there is urgent intervention to prevent family breakdown (family in crisis). These situations require a Prior Approval application to be made by the Specialist describing the exceptional circumstances and a referral to Sleep Right should be made (but see below)*.

In all cases:

- Prior approval must be agreed by the CCG before prescribing melatonin
- However, there are some indications where it is appropriate to prescribe melatonin long term e.g. multisensory impairment, epilepsy, visual impairment and although these indications require prior approval this would not be conditional on attendance at a Sleep Right programme. Nevertheless some of these patients can benefit from behavioural interventions and referral to Sleep Right may still be appropriate.
- Where an application has been made to start melatonin in advance of the Sleep Right programme, if patients do not report to Sleep Right for review then the responsible clinician (Specialist) must be notified by the Sleep Right team; the Specialist must ensure the melatonin prescription is discontinued. However, there may be instances where the family situation preclude engagement with Sleep Right and in these cases it may be appropriate to continue melatonin prescribing.

Down Syndrome

Behavioural sleep problems are common in children with Down syndrome. They include difficulty in settling the child to sleep, repeated night time waking with demands for parents' attention, early morning waking and insisting on sleeping with parents.

Studies have consistently shown that children with Down syndrome are also more prone to obstructive sleep apnoea than children in the general population. This is due to various physical characteristics associated with the condition including floppy muscles in the throat, enlarged tonsils and adenoids and a smaller upper airway.

Some children may have both a physical and a behavioural sleep problem and it is possible that one may perpetuate the other. Careful assessments need to be carried out to establish the nature of the problems present and treatment tailored accordingly. A multidisciplinary approach is almost

certainly needed in such cases. Whenever possible, the physical problem should possibly be treated first and the behavioural problem tackled afterwards.

Although altered endogenous melatonin profiles have been reported in patients with Down Syndrome, Prader-Willi syndrome, and Sanfilippo syndrome, but there is very little information concerning the efficacy or safety of melatonin treatment in children with these conditions. The recommendation, as in all cases is to use behaviour management strategies i.e. referral to Sleep Right after physical causes have been excluded. Some children with Down Syndrome may respond to behavioural strategies, removing the need for melatonin. Sleep solutions will submit a prior approval form for the prescription of melatonin if their interventions are not successful.

Dosage and Administration

Dosage Range:
Circadin® 2mg M/R tablets once daily increased if necessary after 1-2 weeks to 4-6 mg: maximum dose 10mg. Treatment should usually be for a maximum of 3 months, as above.

Circadin® 2mg M/R tablets can be crushed; the immediate release characteristics are then similar to an immediate release dose form[10].

Circadin® 2mg M/R costs £15.39 for 30 tablets and is available from all major wholesalers.

Treatment optimisation:
In addition to ensuring good sleep hygiene and behavioural therapy, sleep disturbances in some patients may respond to optimised treatment with ADHD medication. Sleep disturbances may be related to pre-existing ADHD symptoms and could respond to dose adjustment or switching to a stimulant agent associated with fewer sleep difficulties.[8]

Adverse Effects

Melatonin is generally well tolerated and no significant adverse effects have been reported with pharmacologically regulated melatonin. Both increased and reduced seizure frequency has been reported in children with epilepsy.

The most common adverse reactions with Circadin® were headache, nasopharyngitis, back pain, and arthralgia, which were common by MedDRA definition, in both the Circadin® and placebo treated groups.

Tachycardia, confusion, drowsiness / sleepiness, dizziness / disorientation, dysphoria, increased seizure activity, psychosis, gynaecomastia, decreased luteinizing hormone levels, decreased temperature, autoimmune hepatitis, elevated liver enzymes, pruritis, flushing, rashes and withdrawal effects have all been reported rarely. and vomiting have been reported locally.

It is advised that the Specialist provides written information about the mechanisms of action of melatonin and possible side effects be given to children and family

Precautions and Contra-indications

It is contra-indicated in pregnancy due to unknown effects. Contra-indicated in people with Intolerance to galactose, LAPP lactase deficiency, glucose-galactose malabsorption; hypersensitivity

to active substance or any of excipients. No clinical data exist concerning the use of Circadin® in individuals with autoimmune diseases. Therefore, Circadin® is not recommended for use in patients with autoimmune diseases, Not recommended in patients with hepatic impairment. Should be used with caution in children with epilepsy (seizure frequency should be monitored), liver disease, kidney disease, history of cerebrovascular disease, history of other neurological disorders, depression, concurrent use of beta blocking agents. Smoking may make Circadin® less effective

Drug Interactions

- Levels of melatonin are increased by fluvoxamine - AVOID
- Increased blood pressure with calcium channel blockers e.g. nifedipine.
- concurrent use of melatonin and warfarin may result in INR and PT changes and affect coagulation activity – increase INR monitoring
- Co-administration with other CNS depressants, tachycardia may enhance sedative effects and affect the ability to perform skilled tasks

Patients >19 years

There is currently no provision of Sleep-Right-style behavioural support for patients aged 19+. Self-help resources are available on the Primary Care portal which may be beneficial for a proportion of these patients:

http://gp.neneccg.nhs.uk/clinical-topics/sleep/99425

Transfer to Adult Services

If the young person is not successfully weaned off medication, then the young person should be referred back to GP who will need to take on the responsibility of monitoring the young person's treatment. This will require them to conduct annual reviews including melatonin treatment holidays, which are recommended across all ages.

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