SHARED CARE GUIDELINE

Pennine Care NHS
NHS Foundation Trust

Title: Melatonin for the treatment of sleep disorders in children and adolescents with neurodevelopmental disorders

Scope:	**Version:**
Pennine Care NHS Foundation Trust NHS Bury NHS Oldham NHS Heywood, Middleton and Rochdale NHS Stockport NHS Tameside & Glossop	Version 3

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To be read in conjunction with the following documents:	Shared Care Guideline: Methylphenidate And Dexamfetamine For Childhood And Adolescent Attention Deficit Hyperactivity Disorder (ADHD) Shared Care Guideline: Atomoxetine for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents Pennine Care CL 16 The Prescribing, Supply and use of Unlicensed Medicines Pennine Care CL17 The use of Licensed Medicines outside the conditions of their Product Licence
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1. Scope

Pennine Care NHS Foundation Trust and associated Primary Care Trusts (PCTs). Acute Trust Service Level Agreement (SLA) partners.

2. Introduction

Insomnia

Insomnia and other non-respiratory sleep disorders, such as difficulty in falling asleep and/or staying asleep are a widespread problem in children and adolescents with neurodevelopmental or psychiatric disorders such as autistic spectrum disorder & attention deficit hyperactivity disorder (ADHD).

Although non-pharmacological treatments, such as behavioural therapy can be very effective in some forms of paediatric insomnia, children and adolescents with neuropsychiatric disorders tend to have a lower response rate to them.

The following medicines are currently licensed for sleep disorders in those under 18 years of age. [1]

- Chloral Elixir, Paediatric, BP 2000 (Chloral Hydrate 200mg/5ml)
- Triclofos Oral Solution BP (Triclofos sodium 500mg/5ml)
- Promethazine (Phenergan®) tablets 10mg, 25mg and elixir 5mg/5ml

These preparations are not recommended for long-term use, due to adverse effects and their tendency to cause persistent drowsiness.

3. Melatonin

3.1 Melatonin – Use for the Treatment of Insomnia

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day and night, and may be involved in the regulation of natural circadian rhythm.

A 2mg modified release preparation of melatonin (Circadin®) is licensed for the short-term management of primary insomnia in patients aged 55 or over, for up to 13 weeks.

Although melatonin is unlicensed in the UK for use in children, the British National Formulary for Children (cBNF) [1] states that clinical experience suggests that when behavioural sleep interventions fail, it may be of value for treating sleep onset insomnia or delayed sleep phase syndrome in children with various neuro-developmental conditions.

NICE Clinical Guideline CG 53 Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) [2] states that melatonin may be considered for sleep disorders in children; however this endorsement is based upon expert consensus opinion, rather than being derived from clinical trial evidence.

There is at least one systematic review, two meta-analyses and one subsequently published randomised controlled trial which assesses the safety and efficacy of melatonin in children and adolescents. Although somewhat limited by trial size, heterogeneity and specificity, typically these pieces of research support the use of melatonin in that they show it has some beneficial effect in measures of sleep efficiency. Although the evidence base for melatonin is limited, it is actually more substantial that that available to support the use of any alternative hypnotic in this population. [3]

In 2000, the Royal College of Paediatrics and Child Health issued a policy statement on the use of unlicensed medicines or the use of licensed medicines for unlicensed applications, in children and young people. This states clearly that such use is necessary in paediatric practice and that doctors are legally allowed to prescribe unlicensed medicines where there are no suitable alternatives and where the use is justified by a responsible body of professional opinion. [4]

3.2 Physiology and Pharmacology

Melatonin is a naturally occurring neurohormone produced by the pineal gland. There is evidence that it may have a role in the regulation of circadian rhythms, sleep, mood, reproduction, tumour growth and ageing.

In humans, melatonin secretion increases soon after the onset of darkness, peaks in the middle of the night, and gradually falls during the second half of the night.

Serum melatonin concentrations vary considerably with age. Infants younger than three months secrete very little. Melatonin secretion increases and becomes circadian in older infants; peak nocturnal concentrations are highest at the ages of 1 to 3 years, after which they decline gradually. Falling diurnal serum concentrations in adolescence are thought to be linked to the onset of puberty. [5]

3.3 Mechanism of Action

Melatonin receptors have been demonstrated in various regions of the brain, gut, ovaries, and blood vessels. Those in the suprachiasmatic nucleus of the hypothalamus are thought to be involved in the regulation of circadian rhythms.

Pharmacologic doses of melatonin, however, produce serum concentrations of up to one hundred times the usual endogenous night time peak levels, and have been shown to induce sleep in trial subjects independently of time of day. It may be therefore that the hypnotic effect of melatonin is not related to its synchronising effect on circadian rhythm. Two possible modes of action have been proposed; a lowering of core body temperature or some modification of central monoamine neurotransmitters. [5]

4. Prescribing, products available and monitoring

4.1 Prescribing

The indications for prescribing melatonin are:

- Documented neurological or neurodevelopmental disorder.
- Documented severe, disrupted sleep disturbance.
- Failure to respond to behavioural treatments.

4.2 Products available

Circadin®

Circadin® is a prolonged release formulation of melatonin 2mg tablets. It is licensed for the treatment of primary insomnia in adults over 55 years of age for up to 13 weeks. [6]
The use of Circadin® has not been evaluated in children or adolescents and hence it's in this age group is 'off-label'. [3]

Dose and directions

- One 2mg tablet at night.
- The dose should be taken 1-2 hours before bedtime and after food.
- The tablets should be swallowed whole. [6]
- The dose can be increased after 1-2 weeks to 4-6mg (if response or partial response). Maximum of 10mg/day.
- The 2mg prolonged release Circadin® tablet can be halved using a tablet cutter, and it will retain its slow release characteristics.
- For children with difficulties swallowing, the tablet can be crushed to a fine powder and mixed with water or jam. Use a small amount of food to ensure the full dose is taken.
- Once crushed, the tablet will **not** retain its slow release characteristics. Therefore the prescription should state that the medication is to be crushed prior to administration. [7]

Melatonin (unlicensed)

Melatonin is available in immediate-release tablet/capsule forms from a number of manufacturers. None of these are licensed as a medicinal product for the treatment of insomnia in the UK. One product available is Bio-Melatonin® 3mg immediate release tablet (licensed in the EU).

Most commercial melatonin is synthesised in the laboratory. However, in some cases it is derived from animal pineal gland. Melatonin from animal sources should be avoided due to the possibility of contamination. [3] Preparations made in laboratory may vary considerably in their bioavailability; prescriptions should therefore stipulate the name of manufacturer. [8]

Dose and directions

- Initially 1-3mg at night, increasing after 1-2 weeks to 4-6mg (if response or partial response). Maximum of 10mg/day.
- As the bioavailability of orally administered melatonin varies widely between individuals; dosing should begin at a low level and be gradually increased according to clinical response. [8]
- The dose should be taken an hour before bedtime.
- If the child wakes during the night, the same dose can be repeated during the night.
- Melatonin immediate release tablets can be crushed and mixed with cold soft food such as yoghurt. [7]

Melatonin liquid – by exception only

Liquid formulations of melatonin have to be manufactured specially for individual patients and are obtained from 'specials' manufacturers. They may take up to 2 weeks to order, obtain and supply and this may result in treatment delays and omissions whilst the patient/carer waits for the medication to be supplied.

For children and adolescents with swallowing difficulties both Circadin® and unlicensed melatonin tablets (for example Bio-Melatonin®) may be crushed and mixed with a small amount of food prior to administration. [7]

Liquid melatonin products are expensive to both the Trust and PCT therefore they should not be prescribed or advised unless specifically requested by the CAMHS consultant.

4.3 Monitoring

As there are currently no data on the effects of long-term treatment with melatonin, its use should be monitored by a CAMHS Consultant/ Specialist team every six months.

Continued monitoring of children during long term administration, particularly in the areas of growth and pubertal/sexual development is advised and is critical in those receiving melatonin for periods of a year or more. [5]

5. Medicines and Healthcare Regulatory Agency (MHRA) advice

Circadin® is a fully licensed formulation of melatonin and the MHRA state that it should be prescribed in preference to any unlicensed products, even when the use is off-label.

The MHRA have advised that the prescriber must complete a “special clinical need” letter stating why the licensed product (Circadin®) is not appropriate whenever an unlicensed form of melatonin is prescribed. [9]

If an unlicensed product is required, the EU licensed product Bio-Melatonin® 3mg tablet is preferred to other unlicensed imported products, as it is licensed in its country of origin.

6. Cost of treatment with melatonin

A community pharmacist may supply any brand or formulation at any price against a generic prescription for melatonin. There is also no guarantee that the patient will receive the same brand or formulation of melatonin each time a prescription is dispensed if the generic melatonin is prescribed. Therefore prescribers are advised to specify a brand and formulation (tablets) on all prescriptions.

The unlicensed melatonin products can vary in price from £21.50 to £101.00 per 28 days of treatment (at time of writing).

Currently a 28 day treatment course with Circadin® (melatonin prolonged release tablets) costs £14.36 and with Bio-Melatonin®) £10.50 [1]

Liquid preparations of melatonin are considerably more expensive than either licensed or unlicensed formulations of tablets. Prices may be as high as £200 for 300ml of melatonin liquid 5mg/5ml (at time of writing) and should not be prescribed without the prior approval of the Medical Manager (CAMHS) or the Chief Pharmacist.

Summary of Trust recommendations

Trust recommendations for the prescribing of melatonin for the treatment of insomnia in children and adolescents are:

Circadin® 2mg prolonged release tablet **OR**

Bio-Melatonin® 3mg immediate release tablet.

7. Regimen Management

a) Aspects of care for which the Specialist is responsible. The term Specialist includes Child and Adolescent Psychiatrist, Paediatrician, or nominated Advanced Practitioner/ Non Medical Prescriber (in agreement with their medical supervisor)

- Direct assessment or supervision of specialist team assessment, evaluation of prior treatment, and rationalisation of treatment with melatonin.

- Informing patient/ carer of diagnosis, care plan, treatment including side effects and 'off-label' use of melatonin, or use or unlicensed product. Use of Patient Information Leaflets (PILs), user-friendly information leaflets for children/ adolescents.
- Treatment decisions should be shared between patient, carer and the Specialist.
- Ascertaining patient/ family's commitment to safe storage and handling of medication.
- Initiation and titration of melatonin to a suitable dose or supplying instructions/directions to the GP for initiation and titration of melatonin to a suitable dose.
- Promoting access to any appropriate supporting therapies, carer education, and appropriate school liaison.
- Minimum 6 monthly Specialist review appointments.
- Asking General Practitioners (GP) if they are willing to participate in shared care.
- Written correspondence to GP from Specialist Team, summarising progress and recommendations for continued treatment.
- Ensure clear arrangements for GP back up, advice and support.
- Reporting suspected adverse drug reactions to the MHRA.
- Discontinuation of treatment, (or transfer if appropriate).

b) Conditions of assuming responsibility by the GP

- Communication of satisfactory baseline physical checks.
- Satisfactory directions/instructions for initiation, or titration to optimum dosage and response to treatment.

	Consultant	**Usual GP**
6 monthly follow up of progress and response to medication	Yes	N/A
If changes noted	Amend dose accordingly	Refer to Consultant

c) Aspects of care for which the GP is responsible:

- Replying to requests for shared care as soon as possible.
- Initiation and titration of melatonin / Continued prescribing of melatonin in the community under guidance of Consultant/ Specialist Team.
- Refer to the Consultant/Specialist Team for queries regarding treatment/side effects, and concerns about compliance or suspected drug misuse.
- Ensure compatibility of melatonin with concomitant prescribed medication.
- Stopping treatment on the advice of the Consultant/Specialist team.
- Continuation without specialist review is not recommended.

- Reporting noted adverse events to the Consultant/Specialist Team.

8. Summary of cautions, contra indications, side-effects

[1] [6]

Cautions

- The bioavailability of orally administered melatonin varies widely between individuals; dosing should begin at a low level and increase gradually according to clinical response. [8]
- Unlicensed preparations made in laboratories may vary considerably in their bioavailability. If an unlicensed product is prescribed, the same manufacturer and brand should be specified on every prescription.

Contraindications

Melatonin should not be used:

- In patients with auto-immune disease or hereditary galactose intolerance disorders, LAPP lactase deficiency, or glucose-galactose malabsorption.
- In patients with hepatic or real impairment.
- In patients who are pregnant or breastfeeding.

Side effects

- Melatonin is generally well tolerated but long term side effects have not been evaluated.
- The most common side effects are headache, nasopharyngitis, back pain, and arthralgia.
- Other side effects include abdominal pain, constipation, dry mouth, weight gain, drowsiness, dizziness, migraine, asthenia, sleep disorders, restlessness, nervousness, irritability and sweating.

Interactions

- Fluvoxamine
- Cimetidine
- Oestrogens
- Carbamazepine
- Rifampicin
- Quinolones e.g. ciprofloxacin

Please also check the latest list of interactions contained within the current edition of the cBNF.

9. Special considerations

- Handover for shared care largely by written agreement. Individual consideration of patients to occur when issues of tolerance, inconsistent response to treatment, pre-existing medical conditions or issues of patient compliance.

- Obtaining melatonin may take up to 14 days. Therefore patients/carers should request repeat prescription from their GP in advance.

10. Back-up care available to GP from Hospital, including emergency contact procedures and help line numbers

- Written correspondence following Consultant/ Specialist Team appointments, specifically detailing the next review date and any dose adjustments.

- Telephone advice/ information from the Consultant / Specialist Team during office hours, and plans for earlier review by team if necessary.

- Out of hours on call/ emergency service contactable through hospital switchboards.

11. Statement of agreement

- Shared care is an agreement between the GP and the Consultant. This Shared Care Guideline is a request by the consultant to share the suggested care pathway of your patient.
- If you are unable to agree to the sharing of care and initiating the suggested medication, please make this known to the consultant within 14 days of receiving the document stating the nature of your concern.

References

1. British National Formulary for Children 2010-2011, London: BMJ Group and Pharmaceutical Press.

2. NICE Clinical Guideline CG 53 Chronic fatigue Syndrome/myalgic encephalomyelitis (or encephalopathy) 2007.

3. London New Drugs Group, Melatonin in paediatric sleep disorders, 2008. Accessed 14th Feb 2011. http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Drug-Specific-Reviews/

4. Joint Royal College of Paediatrics and Child Health/Neonatal and Paediatric Pharmacists Group Standing Committee on Medicines, 2000.

5. Brzezinski, A., Melatonin in Humans, The New England Journal of Medicine, 336 (3), 186-195, 1997.

6. Circadin 2mg prolonged release tablets, Summary of Product

Chracteristics, Lundbeck Ltd. Accessed 14th Feb 2011. http://www.medicines.org.uk/EMC/medicine/20878/SPC/Circadin+2mg+prolonged-release+tablets/#tableOfContents

7. Personal correspondence with Lundbeck UK and PharmaNord UK. March 2011.

8. Sweetman, S., (ed) Melatonin in *Martindale: The Complete Drug Reference* [online] London: Pharmaceutical Press. http://www.medicinescomplete.com/ Accessed 14th Dec 2010.

9. MHRA Drug procurement advice: Restrictions on the import of unlicensed Melatonin products following the grant of a marketing authorisation for Circadin® 2mg tablets. 15 August 2008

Appendix 1 Useful Information for Community Pharmacists

For contact details and further product information:

For **Circadin®**

Lundbeck Limited
Lundbeck House
Caldecotte Lake Drive
Caldecotte Lake
Milton Keynes
MK7 8LG

Tel + 44 1908 649966
Fax + 44 1908 647888

For **Bio-Melatonin®**

Pharma Nord (UK) Ltd.
Telford Court
Morpeth
Northumberland
NE61 2DB

Tel: 01670 519989
Fax: 01670 534903
E-Mail:
uksales@pharmanord.com

The 2mg SR Circadin® tablet can be halved using a tablet cutter and it will retain its slow release characteristics.

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.
Once crushed, the tablet will not retain its slow release characteristics.
Therefore the prescription should state that the medication is to be crushed prior to administration.
(Personal correspondence with Lundbeck – manufacturers of Circadin®)

The 3mg Bio-Melatonin® tablet can be crushed and mixed in cold soft food such as yoghurt.
(Personal correspondence with PharmaNord – manufacturers of Bio-Melatonin®)