

**GUIDELINES FOR THE SAFE
PRESCRIBING OF MELATONIN IN
CHILDREN WITH
NEURODEVELOPMENTAL
DISORDERS//NEURODISABILITIES**

Community Child Health

East and North Hertfordshire NHS Trust

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Key points for implementation (practical guidance)

- Before initiating melatonin good sleep hygiene methods should have been tried for more than 6 months and failed in achieving a normal sleep pattern. There is evidence that sleep difficulties is impairing daytime functioning.
**Refer to attached sleep flow chart, check list and sleep pack for parents/carers.
- Melatonin should only be initiated in children/young people with Neurodevelopmental disorders/neurodisabilities with sleep rhythm disturbances.⁷
- Sleep hygiene should be checked regularly (3-6 monthly) in all children commenced on melatonin.
- Children on melatonin should be monitored regularly (3-6 months) for side effects and efficacy.
- Regular trials off melatonin (6 monthly ‘washouts’) are required to review the need for long term use of melatonin use in certain groups of children. ‘Washouts’ should ideally occur during school holidays to minimize disruption to the child and family. Withdrawal of melatonin particularly if the child is on high doses may be considered for a gradual withdrawal, over 2-3 weeks.
- Following withdrawal, sleep pattern should be monitored for improvement. For very small groups of children, withdrawal may be unsuccessful thus necessitating long term use of melatonin.
- Melatonin may be used for short periods (3-6 months) to help establish a normal sleep pattern in certain groups of children e.g. exams/stressful events.
- Parent/Carer information on melatonin should include sleep hygiene, duration of treatment, approximate time and duration of melatonin washouts if applicable and clear instructions on how to return sleep feedback to the CDC and the method of sleep review.
- The licensed product Circadin® 2mg tablets (modified release) should be offered as first line in an off label way whenever possible. Circadin can be crushed to provide an immediate release profile.⁹
- Biomelatonin (Pharmanord) 3 mg tablets (immediate release) licensed in Europe can be used as second line particularly for children who have difficulties with swallowing tablets. Biomelatonin should be prescribed in-house by the hospital pharmacy and not on FP10s.
- Liquid melatonin prescriptions should not be prescribed without discussion with the Paediatric Pharmacist.
- Most melatonin formulations are significantly more expensive than Circadin or Biomelatonin preparations.^{13,14}
- **With effect from 1st May 2014, all melatonin prescriptions including circadin should be prescribed on hospital scripts, not FP10. Exceptions to this include patients travelling a long distance to the hospital e.g. Hertford County clinics or**

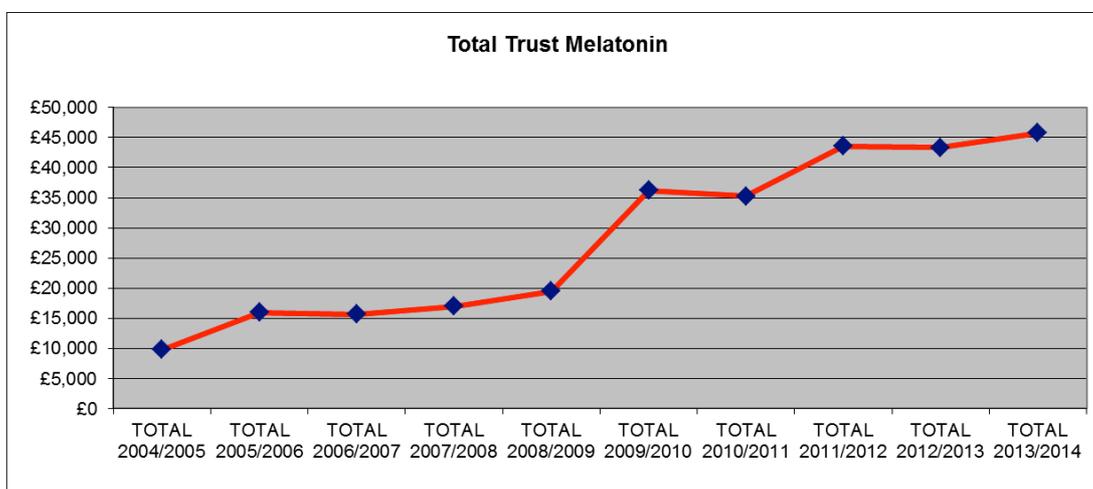
carers with profound disabilities making it difficult to travel to the Hospital pharmacy. Copies of melatonin FP10s should be sent to Sue Briars (Paediatric Pharmacist for monitoring and audit purposes).

Rationale for a Melatonin Guideline:

1. Increase in Melatonin East/North Hertfordshire NHS Trust spend in the last 10 years.

Melatonin annual spend East/North Hertfordshire NHS Trust- £45,000/year.¹²

For Hertfordshire and Hertfordshire Valley, the total annual spend on melatonin products was £344,180 over the same timeframe. Of this £254,257 was accounted for by specials melatonin.¹³



2. Scientific evidence to support long term use of Melatonin (efficacy/safety) is limited.^{1,2,3}

Background: Sleep and Melatonin

Sleep disturbances are common in children with ASD and other neurodevelopmental disorders. They occur in approximately 80% of children with moderate to severe neurodevelopmental disorders. Sleep difficulties have also been reported in children with ADHD, visual impairments, Retts syndrome, epilepsy and brain damaged children. The prevalence of circadian rhythm sleep disorders in children with neurodevelopmental disorders is higher than typically developing children due to an association with abnormal melatonin secretion.^{4,5}

What is Melatonin?

Melatonin is an endogenous substance produced in the pineal gland located in the brain. It has the important role of regulating circadian rhythms. Melatonin responds to decreasing light levels at night and increase in light levels during the day.

In humans endogenous melatonin production starts soon after dark, peaks in the middle of the night (2-4am) and gradually declines during the second half of the night. Half life of natural melatonin is approximately 40 minutes.

Efficacy

There is limited evidence that melatonin can reduce sleep latency, maintain sleep and increase overall sleep efficiency in children with neurodevelopmental disorders. Only few of the studies however have been well designed, controlled and long term ^{1, 2, 3, 6}

Indications⁷

For treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as

- Visual impairment,
- Cerebral palsy,
- Attention deficit hyperactivity disorder,
- Autism,
- Learning difficulties,
- Epilepsy and
Neurodegenerative disorder

* The use of melatonin is supported by NICE in the clinical guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in children.²⁰

Cautions⁷

Autoimmune diseases, hepatic diseases, renal diseases.

Side-effects

The most commonly reported side effects are headaches, nausea, dizziness and drowsiness. Very occasionally children can show a paradoxical reaction of overactivity and irritability. There are also concerns that melatonin may adversely affect seizure control, gonadal

development and asthma control and at present there are no data available to support or refute any of these concerns.

Contraindication⁷

Hypersensitivity to the active substance or to any of the excipients.

Doses and Administration

Child 1 month–18 years initially 2–3 mg daily before bedtime increased if necessary after 1–2 weeks to 4–6 mg daily before bedtime; max. 10 mg daily.

Doses higher than 10mg are not considered to be of greater efficacy and may cause increased side-effects.

Circadin should be taken 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.

Bio-Melatonin should be given 20-30 minutes before desired sleep time. If child is unable to swallow tablets, Bio-Melatonin will dissolve in a small amount of water if broken and stirred.

The dose may be increased to 4-6mg if there is insufficient benefit after 1-2 weeks. If no benefit is seen after 2 weeks on the higher dose then melatonin should be stopped.¹⁶

Be sure to use it along with a good pre-bed routine. The bedroom should be dark and comfortable. It is important that it is free from electronic media (such as TVs, electronic games and phones) which may distract the child and make it difficult to sleep (referred to sleep tool kit)

Duration of Treatment

The duration of treatment is variable. The aim is to establish healthy sleep habits with the lowest effective dose of melatonin. It is suggested that at least six months of an improved sleep pattern should elapse before withdrawal takes place. Withdrawal should occur over a period of 3-4 weeks and change in sleep pattern observed. For some children however withdrawal is not successful and treatment may be necessary long term.

Some clinical experience from the National Child and Adolescent Learning Disability Psychiatry Network suggests that the efficacy may be lost if melatonin is prescribed for longer than two years. It suggests that if the melatonin is withdrawn prior to this, sensitivity may be re-established and melatonin successfully re-introduced at a lower dose.

Reviewing Treatment

If treatment is successful, a trial reduction in the dose should be attempted after 6 months as some patients would have settled into a regular sleep pattern and may not need to continue at the same dose or may even be able to maintain sleep with no medication.

If sleep patterns are maintained, dosage can be reduced by 2 mg every 4-6 weeks. If the difficulties recur the original dose should be reinstated, but a further trial reduction should be attempted 6 months later.¹⁸

Monitoring

Patients should be followed up every three to six months to ensure continuing benefit of melatonin. Standard monitoring of growth and sexual development is recommended i.e. to check height, weight and pubertal development progress as expected.¹⁸

Licensing

There is only one licensed formulation of melatonin in the UK- Circadin® 2mg modified release tablet for short term treatment of primary insomnia in adults over ≥ 55 years.⁷

Circadin should be used first line as an off label indication in children and adolescents with sleep onset insomnia and delayed sleep phase syndromes in children with neurodevelopmental disorders.⁹

Circadin initiation and supervision should be carried out by a Specialist but can be continued by General Practice if shared care arrangements exists.

Unlicensed or off – label use of a licensed product may be prescribed if deemed appropriate by the prescribing clinician.⁸

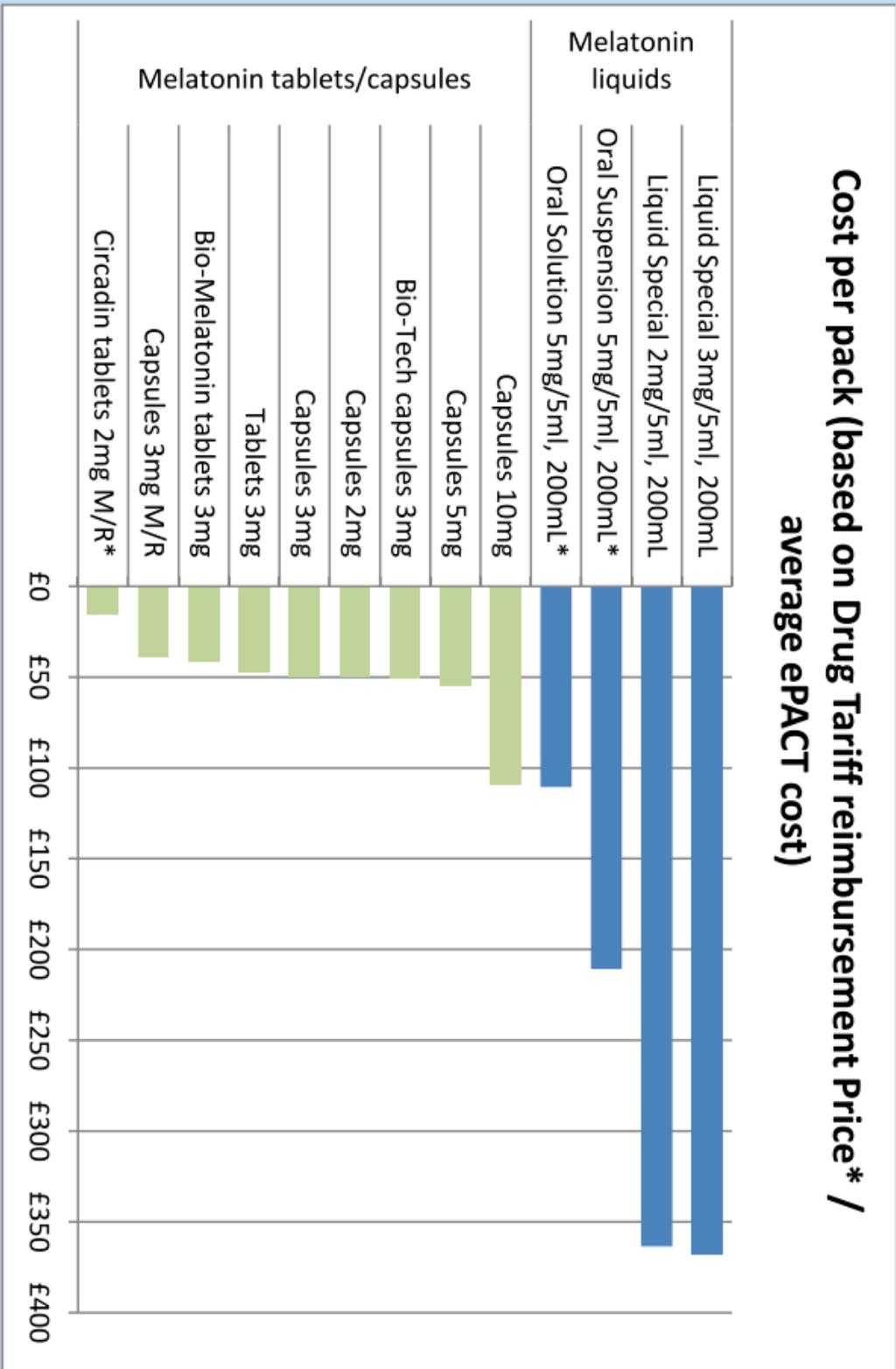
Off label use of a licensed product is preferred to the prescription of an unlicensed product.⁹

Melatonin formulation/Cost¹⁴

Table 1: Cost Breakdown¹³

| Melatonin formulation | Cost (mls/capsule/tablet) |
|------------------------------------|---------------------------|
| Liquid Special 3mg/5ml | Est. £8.20/5ml |
| Capsules Special 5mg | £1.69/ capsule |
| Capsules(special) 10mg | £2.02/capsule |
| Tablets (special) | £2.15/tablet |
| Bio-Melatonin (Pharmanord) Special | £1.21/tablet |
| Circadin | £0.51/tablet |

Figure 1: Cost differences between melatonin formulations



* Pack size calculated as 30.
M/R denotes modified-release.

Specialist Paediatrician responsibilities

- Initiate melatonin and titrate as appropriate.
- Monitor response and adverse effects pre/post titration.
- Regular reviews of sleep pattern and melatonin use.
- Provide adequate carer/parent sleep and melatonin information.
(www.medicinesforchildren.org.uk/search-for-a-leaflet/melatonin-for-sleep-disorders)
- Notification of reviews and changes to GP and all relevant professionals.

GP/ Primary Health Care Professional responsibilities

- *Melatonin shared care arrangements currently do not exist within Hertfordshire.
- Notification of patients with rebound difficulties following discontinuation of melatonin to Specialist Services.
- GP/Health professional to ascertain that good sleep hygiene is established before referral/notification to Specialist Services.

Hospital Pharmacist responsibilities

- Ensure that the Pharmacy holds sufficient stocks of Circadin and Bio-melatonin to meet patients needs
- If there are supply problems to keep patients/carers informed
- Counsel patients on their melatonin prescriptions
- Provide reports for the directorate on melatonin expenditure

Parent/Carer and patient responsibilities

- Continue to implement good sleep hygiene even when the child is on medication.
- Complete a 3 week sleep diary and questionnaire every 3-6 months-ideally during a washout period on school holidays to ascertain the need to continue on melatonin.
- Ensure good compliance with medication and notify the Specialist if child is no longer taking or requiring melatonin.

References:

1. Hoebert M, van der Heijden KB, van Geijlswijk IM et al. (2009) Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *Journal of Pineal Research* 47: 1–7
2. Van der Heijden KB, Smits MG, Someren EJ et al. (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *Journal of the American Academy of Child and Adolescent Psychiatry* 46: 233–41 (5)
3. Appleton R, Jones A, Gamble C, Gringras P et al. The use of melatonin in children with Neurodevelopmental disorders and impaired Sleep: a randomised, double blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess* 2012; 16:1-239.
4. Chamberlein R S, Herman BH (1990) A novel biochemical model linking dysfunctions in brain melatonin, propiomelanocortin peptides and serotonin in autism. *Biological Psychiatry* 28: 773-93.
5. JE et al. Melatonin therapy for circadian rhythm abnormalities in children with multiple disabilities: What we have learned in the last decade. 776-782, s.l. : *Developmental Medicine and Child Neurology*, 2004, Vol.46.
6. Gringras P, Gamble C, Jones AP et al. (2012) Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 345: e6664
7. British National Formulary for Children. July 2013-2014.
8. General medical Council. Good practice in prescribing and managing medicines and devices. Published 31/01/2013. Accessed 21/04.2014. <http://www.gmc-uk.org/guidance/ethical/guidance/14327.asp>
9. Medicines and Healthcare Products Regulatory Agency. Drug procurement advice: Restrictions on the import of unlicensed Melatonin products following the grant of a marketing authorization for Circadin® 2mg tablets 15.08.2008 [http:// www.mhra.gov.uk/News Centre/CONO23251](http://www.mhra.gov.uk/News_Centre/CONO23251). Accessed 21/04/2008.
10. East/North Hertfordshire Melatonin parent/patient information, 2009.
11. Evidence based review of Melatonin for sleep disorders in children with Neurodevelopmental disorders. Flynn Pharma Medical. September 2012.
12. East/North Hertfordshire NHS Trust Pharmacy Department 2014
- 13 Flynn Pharmaceuticals Company drug costs information
- 14 London Procurement Partnership Bulletin (LPP)
15. SPC- Summary of Product Characteristics last updated on the eMC: 02/09/2013
16. Guideline for Safe Prescribing of Melatonin in Children and Adults, Alder Hey Royal Liverpool Children's NHS Trust. Arch 2011.
17. Sleep Health Foundation
18. Melatonin March 2014. Telford and Wrekin CCG
19. London New Drugs group. Melatonin in paediatric use.
20. NICE clinical guideline 53: Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy)

