# NHS BSW ICB Primary care guidance for the use of melatonin for sleep disorders in Adults with Learning Disability & behaviour that challenges

NHS
Bath and North East Somerset, Swindon and Wiltshire
Integrated Care Board

**Approved indication:** Specialist initiated (AMBER) off-label for insomnia in patients with learning disabilities where sleep hygiene measures have been insufficient, ***who also have*** a co-morbid mental illness (for example Depression, Mania, Psychosis, Dementia etc.) OR disorder (for example Autism or Autistic Spectrum, Anxiety Disorders, Adult ADHD etc.).
**Local BSW traffic light status:** AMBER initiation and stabilisation by specialist (3 months).

## Background

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 the induction of sleep.
People with learning disability frequently suffer with poor sleep, which can be multi-factorial, complex, and more difficult to treat than in the general population. Low nocturnal melatonin levels have been found in Angelman syndrome, Rett syndrome, Smith-Magenis syndrome and in autism spectrum disorder (Braam, 2009; Potocki et al, 2000; De Leersnyder et al, 2001). The complications of poor sleep can be significant and diverse, including an increase in challenging behaviour, drowsiness with an inability to undertake daytime activities, and in people with autism, mood disorders, gastrointestinal problems, poor social interaction, problems in communication and increased stereotypy (Rossignol and Frye, 2011). These problems can affect quality of life and risk placement breakdown.

## Melatonin products and use

Melatonin was previously only available as licensed MR tablets (Circadin®), unlicensed tablets and unlicensed liquids. In 2019, several new formulations of melatonin gained a marketing authorisation (product licence); however, most of its use remains off-label.
Generic 2mg modified-release melatonin tablets are now available (£3.96 for 30 in June Drug Tariff) and are the product to use for this cohort. Generic melatonin has the licensed indication of short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. Therefore their use in this cohort of patients will be off-label. The BSW formulary 04.01.01 has full information about which products are available to use in NHS BSW ICB.
The BNF recognises the off-label of melatonin for insomnia in patients with learning disabilities where sleep hygiene measures have been insufficient, for initiation under specialist supervision and NICE guideline **Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges** NG11 recommends that its use should be "considered" for sleep problems.

**1st line option:** Melatonin 2mg m/r tablets (generic, do not prescribe as the brand name Circadin®) used OFF-LABEL. See SPC.

## Evidence base for use in this cohort of patients

Meta-analyses:
Braam et al. (2009) analysed 9 randomised double-blind placebo-controlled studies, with a total of 183 individuals with learning disability. The conclusion was that in this population, melatonin treatment decreased sleep latency by a mean of 34 minutes ($p<0.001$), increased total sleep time by a mean of 50 minutes ($p<0.001$), and significantly decreased the number of wakes per night ($p<0.05$). Heterogeneity was noted in the patient groups, the dosing schedules, preparations, and study protocols.
Rossignol and Frye (2011) analysed 5 randomised, double-blind placebo-controlled trials of melatonin for people with autism spectrum disorder reporting quantitative data on sleep parameters. Significant effects on sleep onset latency and sleep duration with melatonin compared with baseline and placebo were found. A further review of 18 studies (not meta-analyses) reported that 67-100% of 349 individuals (children and adults) experienced an improvement in sleep with melatonin.

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## Safety & adverse effects

Little is known about the long-term effects of melatonin (data is available for up to six months in adults and two years in children).

Gringras (2008) described an open-label longer study in which 44 children with neurodevelopmental disability continued with treatment – there were no adverse reactions, including no indication that therapy was implicated in a seizure in the 19 children diagnosed with epilepsy, and no new seizures witnessed. A recent Cochrane review found no increase in seizure frequency in patients with epilepsy given melatonin (Maudsley Prescribing Guidelines, 2018).

In contrast to other sedative hypnotics, melatonin is not generally believed to produce tolerance, rebound insomnia or dependence (Bramble & Kiani, 2015). See Summary of Product Characteristics for further information regarding adverse effects. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

## Patient advice

- Where melatonin is being prescribed off licence or off-label this must always be explained to patients and carers and the discussion documented in the clinical record.
- Give a warning regarding sedation for those driving or using machinery.
- Give advice about good sleep hygiene.

## General prescribing advice

Use with caution in renal and hepatic dysfunction. Metabolism is 90% via CYP1A (decreased activity in Angelman syndrome referred to by Rossignol & Frye, 2011) and renal excretion.

**Dosing**

Effective dosing varies significantly between individuals and there is no evidence to support a direct relationship between dose and response. The recommended starting dose is 2mg, increased to a maximum 10mg per day (BNF). Increasing above 5mg is likely to be utilising the sedative effects of melatonin, rather than its sleep-phase shifting properties (Maudsley Prescribing Guidelines).

**Timing**

BNF recommends 1-2 hours before bedtime, though clinical experience suggests flexibility in dose timing may be required. Adjust timing according to response.

**Crushing tablets**

Crushing generic or Circadin® tablets removes their prolonged release profile, creating an immediate release dose of melatonin. For this reason, it is not recommended by the manufacturer. However, there is information to support crushing tablets where patients are unable to swallow tablets whole, for example patients with swallowing difficulty.

## Prescriber's responsibilities

**Secondary care specialist responsibilities**

**Assessment of sleep disorder:**

- Any of the following: early insomnia, delayed sleep phase, night-time waking, low duration of sleep, reversal of circadian rhythms
- Sleep diary to be completed by the carer for at least 2 weeks
- Lack of response to sleep hygiene measures including: keeping a regular time to go to bed and get up in the morning, no daytime napping, established and calm bedtime routine, bedroom conditions (temperature, light, noise) to be optimised, no late afternoon or evening caffeine or excessive evening drinking, minimising access to blue light emitting screens 2 hours before bedtime

**Assessment and treatment of co-morbidities:**

- Mental health associations with poor sleep: autism spectrum disorder, attention deficit hyperactivity disorder, depression, anxiety, delirium, dementia, bereavement

- Specific syndrome associations with poor sleep: Angelman syndrome, Rett syndrome, Williams syndrome, Smith Magenis syndrome
- Physical health associations with poor sleep: pain, epilepsy, obstructive sleep apnoea (high prevalence in Down syndrome)
- Cautions or contraindications for melatonin: kidney and liver disorders; manufacturer advises avoid in auto-immune disease.

**Assessment of medication:**

- Check concurrent medications for interactions and/or cautions.
- Plasma levels may be reduced in smoking.
- Give warning to those driving or using machinery about drowsiness.
- Initiate treatment and determine minimal effective dose.

**At second and subsequent consultations:**

- Ensure that sleep hygiene advice and strategies are consistently being applied and monitored.
- Assess for side-effects.
- If no response after 14 days, then discontinue.
- Consider appropriateness of switching from non-preferred or other unlicensed melatonin formulations to an alternative formulation for quality, safety, and cost-effectiveness reasons.
- Melatonin doses should be optimised to ensure that use is within licensed dose ranges and to manage additional cost pressures.
- If a lower treatment effect is seen with melatonin after titration to a higher dose, first consider a lower dose before deciding on discontinuation of treatment.
- In adults, a trial withdrawal period or stopping treatment should be considered after 13 weeks. It should be noted that safety data is available up to six months only.
- If continuing treatment, review ongoing need for melatonin every 6-12 months and consider trial of withdrawal.

**Primary care responsibilities:**

- **Will be responsible for prescribing the melatonin long-term, but the medication will be reviewed for its appropriateness and that it is efficacious for the patient by the AWP specialist.**
- Raise any concerns during treatment with the AWP specialist.

## References & further reading:


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- Rossignol, D.A. & Frye, R.E. 2011. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Developmental Medicine & Child Neurology. 53. 783-792.
- Taylor, D.M., Barnes, T.R.E. & Young, A.H. 2018. Melatonin in the treatment of insomnia in children and adolescents. pp517-520. *In* The Maudsley Prescribing Guidelines in Psychiatry. 13th Edition.

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## AWP Specialist contact information:

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The ICB Medicines Optimisation team can be contacted on bswicb.formulary@nhs.net or bswicb.prescribing@nhs.net

BSW guidance on the use of melatonin in *children* can be found here: https://bswtogether.org.uk/medicines/wp-content/uploads/sites/3/2023/11/BSW-Melatonin-use-in-children-guidance-Oct-23-minor-update-v0.3-FINAL-licensed-liquid-melatonin-and-circadin.pdf

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