BSW Guidelines for use of melatonin in children

NHS
Bath and North East Somerset, Swindon and Wiltshire
Clinical Commissioning Group

These guidelines apply to children treated by NHS BSW commissioned services; HCRG care group, GWH community services and CAMHS.

Part 1 – Background for use of melatonin in children within BSW (approved indications)
Part 2 – Criteria for use and recommendations for treatment review
Part 3 – Transition of patients at age 18
Part 4 – Preferred formulary melatonin products (includes advice for community pharmacists)

Part 1 – Background for the use of melatonin in children

- **The approved indication for paediatric NHS BSW patients is Autistic Spectrum Disorder (ASD) and ASD with Attention Deficit Hyperactivity Disorder (ADHD).** Melatonin is used by some local services for patients with ADHD alone but it is recognised that it should not be *routinely* used for ADHD on its own due to limited evidence base.
- **Melatonin has a RED traffic light status (TLS) across NHS BSW for paediatric (<18years) use.**
- Sometimes NHS BSW patients will be seen by services outside of our area where they might have different TLS for melatonin such as an AMBER with Shared Care Arrangement (SCA). In this scenario, a GP can take on such prescribing, if they agree with the SCA and are happy to take on the prescribing responsibility.

Melatonin has been used in children by specialist paediatric services for > 25 years to treat sleep disorders without significant adverse effects becoming apparent. Like a lot of medicines used in children, there wasn't any licensed melatonin products available for use in children until recently.

- **Adaflex®** has recently (2022) been licensed for insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. In BSW, routine prescribing for this indication is not supported (see page 2) but Adaflex does provide melatonin in a cost-effective formulation that is specifically licensed for children[1], and can be used in an off-label manner for children with ASD.
- **Slenyto®**, was launched in the UK in 2019 with a very specific license[2] as follows: *indicated for the treatment of insomnia in children and adolescents aged 2-18 with ASD and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.* Slenyto has not been considered locally for formulary inclusion and is an expensive version of melatonin. NICE have not considered this product for England, so we have no NICE directive to fund this treatment. The Scottish Medicines Consortium[3] (SMC) and the All Wales Medicines Strategy Group[4] (AWMSG) have however done a full review of this product twice. SMC did not approve it for use in Scotland stating it is not cost-effective for use on the NHS. AWMSG have approved it after a second review (March 2021).

Safety of melatonin in children

The phase 3 trials for Slenyto® highlighted to the European Medicines Agency (EMA) gaps in terms of longer-term safety data. Data is only available for use in children for up to 2 years duration and so the EMA asked the manufacturers (Flynn Pharma Ltd) to do further safety clinical trials. Specifically, the EMA want trial data on the use of melatonin in pregnancy & lactation and also regarding the potential risk of delay of sexual maturation and development.[5] The EMA state that "*the fact that melatonin plasma levels are high in pre-pubertal children and is dramatically reduced during puberty, has led to the suggestion that administration of exogenous melatonin leading to supraphysiological levels in pre-pubertal and pubertal children may lead to pubertal abnormalities*."

The phase 3 trial data has led the NHS funded organisation PresQIPP to suggest new criteria for using melatonin in children which keep usage within the realms of the available evidence base.[6] Their criteria should reduce the use of melatonin as it is currently being used far more widely than the available evidence base would support.

Advice to young people/parents/carers about melatonin should include a discussion about the current lack of studies that rigorously examine the long-term safety of melatonin. However, this would also need to be set within the context that melatonin has been used to treat sleep disorders in this age group over a period of ~25 years without significant adverse effects becoming apparent. Until robust trial data draws firm conclusions about long term safety, the best advice is to: **use the lowest effective dose, for the shortest amount of time necessary, and monitor for pubertal maturation in pre-pubertal children. Local clinicians are asked to review their use of melatonin to ensure that moving forwards it is used as per the criteria in Part 2.**

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Part 2 – Criteria for use of melatonin within the current evidence base and recommendations for treatment review

Specialists should aim to use at the lowest effective dose, for the shortest amount of time necessary, and monitor for pubertal maturation in pre-pubertal children.

As a RED TLS drug in BSW, melatonin prescribing and monitoring in children is retained by the specialist.

1.) Ensure that children have undergone a trial of parent-directed behavioural sleep interventions for 3 months before considering prescribing melatonin within licensed indications.
2.) Do not routinely prescribe melatonin for sleep disorders associated with ADHD without a concomitant disorder of (ASD).
3.) Be aware that little is known about the long-term effects of melatonin (data is available for up to 6 months in adults and 2 years in children). Hence we would expect the usual maximum duration of use to not extend beyond these time points.
4.) Review the continued need for and effectiveness of melatonin in children after the first 3 months, then annually.
5.) *Consider* a trial withdrawal of treatment after 2 years melatonin treatment in children as efficacy and safety data are not available beyond 2years treatment.
6.) Monitor children for a possible impact of melatonin on their pubertal development.

If treatment is beneficial, at least 6 months of improved sleep pattern should elapse before attempting to withdraw treatment. **The specialist will review the appropriateness of the melatonin at least every 12 months, possibly by initiating melatonin-free breaks. In those who require long term treatment, a melatonin-free break should be introduced at least annually to assess the continued need for treatment, unless the specialist considers this inappropriate.** This could take place in the 2 weeks before annual review. When a break is planned, the specialist will have provided a written plan to the patient and/or the parent/carer, to include keeping a sleep diary which can be reviewed by the specialist to assess efficacy of the melatonin. A melatonin-free break should also be taken in those who stop responding to melatonin. If/when melatonin is restarted, consideration should be given to starting at the lowest dose of melatonin (usually 2 – 3 mg, depending on the formulation used) and titrating back up to the original dose only if indicated. Adaflex® is available in a variety of strengths that allows greater flexibility when titrating patients off melatonin or reducing down to the least effective dose. The outcome of any melatonin-free breaks must be recorded in the patient's notes and communicated with the GP.

Use of melatonin in ADHD:

NICE published an evidence summary on the use of melatonin in children and young people with ADHD with sleep disorders in January 2013.[7] No high-quality studies were identified that provided evidence for the efficacy of prolonged-release melatonin tablets (licensed in the UK) used off-label in children with sleep disorders and ADHD. NICE summarised that the evidence to support the use of melatonin in children and young people with ADHD is **very limited**. Although this review is dated, the PresQIPP evidence base review from May 2020[6] also did not support the use of melatonin in children with ADHD on its own based on the published evidence available. Although it is recognised that specialist services have used melatonin widely in patients with ADHD, if a specialist wishes to use melatonin in a patient with ADHD they should be aware of the limited evidence base to support using this **routinely** if there is no concomitant diagnosis of ASD.

Part 3 - Transition of young people turning 18: AMBER TLS

The proportion of patients continuing to take melatonin at age 18 is likely to be relatively small. All patients who remain on melatonin at 17 years old MUST have a planned trial off melatonin in the 6-12 month period prior to their 18th birthday. It is anticipated that a small proportion of patients treated with melatonin will continue to benefit and require treatment beyond age 18. To clearly determine who these patients are, and to provide guidance to the GP when the patient is discharged from specialist paediatric services, the following must be carried out by the specialist:

1. Arrange with the patient/parent/carer for melatonin to be stopped at a time that is least disruptive to the young person (e.g. summer break/school holiday) for a period of at least 2weeks.
2. Provide a written plan for the treatment break, including the use of a sleep diary.
3. Review the patient at the end of the treatment break and only reinstate treatment with melatonin if there was a clear deterioration in sleep resulting in a significant impact on quality of life.
4. If the treatment break indicates that melatonin –

a. **is no longer required**: write to the GP to explain that melatonin has been discontinued and the patient is no longer being treated.

b. **continues to be beneficial**: write to the GP confirming that a withdrawal in treatment has been attempted and that melatonin remains indicated beyond age 18. The letter should include recommendations about how long melatonin is likely to continue to be useful for the individual, and when a further trial off medication should be considered (e.g. annually following a similar approach as described above). **The GP may continue treatment with melatonin beyond age 18 if a trial off medication has been confirmed and once the patient is discharged from specialist paediatric services, if they feel it is appropriate to do so. Note that such prescribing is off-label.**

NICE Key Therapeutic Topic (KTT6): Hypnotics Oct 2020 update[8]: https://www.nice.org.uk/advice/ktt6/ states: *The risks associated with hypnotics, such as falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised. Recent data also suggest that risks such as falls are associated with melatonin.* **NICE do not clarify which age group this statement applies to.** The KTT also refers to an observational study discussed in NICE's medicines evidence commentary on fracture risk associated with melatonin and other hypnotics which has found that in people aged 45 years and over, receiving 3 or more melatonin prescriptions was associated with an increased risk of fracture compared with no use of any hypnotic drugs. **It is not clear whether this finding is relevant to children using melatonin.**

Part 4a - Preferred Formulary Products for BSW

Please also see chapter 16 (paediatric) of http://www.bswformulary.nhs.uk

- There have been several newly licensed melatonin products launched recently, including some licensed in adults for treatment of jet lag[9] as well as various paediatric products (e.g. Slenyto®). This has caused increased confusion as to which product should be prescribed and supplied when used in children.
- Prescribers should be aware of the MHRA position on the use of off-label and unlicensed products[10] and ensure that any use of such products is in the best interests of the patient.
- **Melatonin for paediatric use is RED on the BSW formulary and is prescribed by the local specialist paediatric services across NHS BSW on FP10 prescriptions.**

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1st line option: Adaflex® 1mg, 2mg, 3mg, 4mg, 5mg standard tablets (not prolonged release) used OFF-LABEL for ASD. It is licensed for insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. However, it should be noted that it should not routinely be used for this indication (see page 2). It also represents a cost-effective option compared to other products. See table below and SPC

1st line alternative: Melatonin 2mg m/r tablets (generic) Note that these are not licensed for use in children but has been used successfully by specialist services for many years without apparent major adverse effects. It also represents a cost-effective option compared to other products. See SPC

2nd line option: Melatonin oral suspension or solution See table on swallowing problems below. Unlicensed. Various strengths available[11] (*don't use 4mg/5ml strength which is prohibitively expensive*) priced as per Drug Tariff Part VIIIB plus £20 specials fee that community pharmacists can charge per item. Any liquid melatonin prescribed will be more expensive than a solid dosage form. Specialists can consider a liquid formulation **only if crushed Adaflex® has been tried and is unsuitable**. To supply unlicensed medications in line with Specials supplier policies, community pharmacists may need a letter from the prescriber confirming why the patient requires an unlicensed product where there are licensed alternatives.

Dose adjustment of Adaflex® and how to deal with swallowing problems	
Aim	**Establish healthy sleep habits with the lowest effective dose. (updated with SPC)**
Initial dose	Adaflex® tablets 1-2 mg (2mg if using generic M/R melatonin) given 30 - 60 minutes before bedtime.
Dose titration (Adaflex®)	If no improvement after 1-2 weeks, incr. dose by 1mg (2mg if using generic M/R melatonin) every week to max 5mg (6mg if using generic M/R melatonin).
Maximum dose (Adaflex®)	Dose may be increased up to 5mg/day (6mg if using generic M/R melatonin). Where no benefit seen after titration to max dose, treatment should be stopped. No need to taper the dose down.
Usual administration	Oral; the tablet can be crushed and mixed with water directly before administration; it is recommended that food is not consumed 2 h before and 2 h after intake. For generic M/R melatonin tablets should be swallowed whole. Halved generic M/R melatonin retains MR properties; quartering or crushing make them immediate release. [12]
Administration via enteral feeding tubes	Adaflex® is soluble in water. However, there is no specific data on administration via enteral feeding tubes so would advise that it is an individual clinical decision. Note that alternatively, Circadin® can be crushed to a fine powder and added to 15 - 30ml water, mixed well, then use immediately via enteral tube and flush tube after administration.[13] (Unlicensed). This makes the formulation an immediate-release product.
Administration via small-bore enteral feeding tubes (gauge less than 9)	Melatonin oral solution or suspension (alcohol free, unlicensed), bottle size 200ml (comes in different strengths see Drug Tariff Part VIIIB)[11] may be prescribed for patients with feeding tubes (gauge ≤9) where there is risk of tube occlusion.
Severe oral sensitivity preventing the use of crushed medication	Patients unable to tolerate a trial of crushed medication due to severe oral sensitivity may be prescribed melatonin oral suspension or solution 200ml (unlicensed).

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Part 4b– Melatonin products not to be prescribed or supplied

Please also see chapter 16 (paediatric) of http://www.bswformulary.nhs.uk

Do not prescribe or supply the following NON-FORMULARY products:

Colonis melatonin 3mg film-coated tablets and 1mg/mL oral solution[9] (Non-formulary):

Colonis 3mg tablets are licensed for the treatment of adults with jet lag for up to 5 days at a time. The SPC specifically states: *The safety and efficacy of this product in children and adolescents aged 0-18 years has not been established* and so should not be used in children and adolescents.

Colonis melatonin 1mg/1mL oral solution is licensed for adults. The SPC states safety and efficacy of Colonis melatonin 1mg/mL oral solution in children and adolescents aged 0 – 18 years have not been established and so should not be used in this group. It is not suitable for all children due to the levels of propylene glycol exceeding the recommended safety limits for some children based on their weight. To prevent the inappropriate supply of Colonis oral solution against a generically written prescription for melatonin liquid, prescribers can annotate in the dosage instructions when Colonis is not clinically suitable for their patient due to these safety concerns and that there is a clinical need for an unlicensed special formulation.

Slenyto® 1mg and 5mg tablets [2] (Non-formulary):

These are licensed for children aged 2-18 years for insomnia with ASD and/or Smith-Magenis Syndrome (SMS) where sleep hygiene measured have been insufficient. These are not included on the local BSW formulary and no application has been received for it to be considered. See part 1 of this guidance for info on recommendations of national groups SMC and AWMSG. **Local specialist services may prescribe Slenyto for patients that have been initiated on it by tertiary providers (e.g. Southampton).**

Syncrodin (Pharma Nord) 3mg film-coated tablets [14] (Non-formulary):

Only to be used for patients currently using this product. No new patients (use Adaflex® instead). These are licensed for the treatment of adults with jet lag for up to 5 days at a time. The SPC specifically states: *The safety and efficacy of this product in children and adolescents aged 0-18 years has not been established* and so should not be used in children and adolescents due to safety and efficacy concerns.

References and Useful Resources

1. Summaries of Product Characteristics, Adaflex® MHRA Products | Home Accessed March 2022
2. Summaries of Product Characteristics, Slenyto®. https://www.medicines.org.uk/emc/search?q=slenyto Accessed April 2021
3. SMC [Slenyto® - Sep 2019 and Jan 2021] https://www.scottishmedicines.org.uk/search/?keywords=slenyto Accessed April 2021
4. AWMSG [Slenyto® – Nov 2019 and Mar 2021] https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/melatonin-slenyto1/
5. EMA Slenyto® EPAR Nov 2019 https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto
6. PrescQIPP Bulletin 245 May 2020 https://www.prescqipp.info/our-resources/bulletins/bulletin-245-melatonin/
7. NICE ESUOM2 Jan 2013 https://www.nice.org.uk/advice/esuom2/chapter/Key-points-from-the-evidence
8. NICE KTT6 Hypnotics Jan 2015, Updated Sep 2019 https://www.nice.org.uk/advice/ktt6
9. Summaries of Product Characteristics. Colonis melatonin products https://www.medicines.org.uk/emc/search?q=melatonin
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11. Drug Tariff Specials Drug Tariff Part VIIIB Accessed April 2021
12. Chua HM et al. Dissolution of Intact, Divided and Crushed Circadin Tablets: Prolonged vs. Immediate Release of --Melatonin. Pharmaceutics 2016, 8, 2; https://pubmed.ncbi.nlm.nih.gov/26751472/
13. Summaries of Product Characteristics. Circadin https://www.medicines.org.uk/emc/product/2809 Accessed April 2021
14. Summaries of Product Characteristics, Syncrodin. https://www.medicines.org.uk/emc/product/11772 Accessed April 2021

Also see - MTRAC Commissioning Support Melatonin (Circadin) for treatment of primary insomnia Oct 2013 https://bit.ly/3w5onQq
Oxford CAMHS SCA: Melatonin Shared Care Protocol.pdf (sitekit.net) [parts of this SCA adapted into BSW guidance with permission]
NEWT Guidelines http://www.newtguidelines.com/ (requires subscription) Accessed March 2022