Guidelines for Melatonin Prescribing in Children

Author(s)	Sarah Vaukins, Medicines Optimisation Team, Manx Care
Version Number	0.1
Document effective from	27th June 2022
Next review due	27th June 2024

Intended audience	All prescribers across primary and secondary care	
Superseded documents	N/A	
Stakeholders consulted prior to ratification	Primary and Secondary Care Prescribers	
Ratified by	Integrated Medicines Optimisation Group	Date 16/06/2022
Previous reviews	N/A	
Changes made during latest review	N/A	

1. INTRODUCTION

Sleep disturbance in children and young people is common, especially in those with neurological and/or behavioural disorders. Chronic sleep loss causes poor emotional processing, and impaired cognition (difficulties with executive function, attention, working memory and long term memory).

Sleep disturbance for extended periods results in poor motor performance, an increased risk of general health problems and a poorer quality of life generally. Sleep disturbance may include delayed onset of sleep, frequent waking, and early morning waking or day-night reversal of sleep pattern. The resulting daytime sleepiness and associated cognitive impairment affects learning, behaviour and emotional regulation; it also adds considerably to the burden of care.

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 regulate sleep. Melatonin is reported to improve the onset and duration of sleep in people with learning disabilities, in particular those with cortical blindness.
The prevalence of sleep disturbances in children and adolescents with Autism Spectrum Disorder (ASD) range from 30-53% and up to 70% in those with ADHD. If untreated, such sleep disturbances can negatively impact children, adolescents, and their families with respect to physical and mental health, social, academic, and cognitive functioning.

Children with Smith-Magenis syndrome have a reverse day - night sleep pattern due to abnormal melatonin secretion and children with autism have lower melatonin levels. The first licensed preparation of Melatonin for use in children was released in 2018 (Slenyto 1mg and 5mg tablets). Slenyto 1mg and 5mg prolonged release tablets are

licensed for the treatment of insomnia in the children and adolescents aged 2 to 18 with ASD and/or Smith-Magenis Syndrome (SMS). It is a prolonged release formulation with a tablet size of 3mm which is easy to swallow for the paediatric population. Switching from unlicensed to licensed medication should be considered for safety and quality reasons.

A licensed modified release melatonin 2mg tablet has been available since June 2008. Circadin® is only licensed for patients aged 55years and over, and in response to guidance issued by MHRA on melatonin in 2008, its use in children is off-licence.

1.1 Purpose

- To ensure that melatonin prescribing is safe and clinically appropriate for the age of the patient, and the indication prescribed for is evidence based
- To ensure that melatonin treatment is reviewed within the recommended intervals and the duration of treatment is within licensed recommendations
- To ensure that melatonin formulations and doses are optimised for the ease of the patient and to avoid unnecessary costs

1.2 Scope

All prescribers who work within or contracted to Manx Care.

1.4 Definitions

Off-License – Off-label' use means that the medicine has a license for treating some conditions, but that the manufacturer of the medicine has not applied for a license for it to be used to treat your condition. In other words, the medicine may not have undergone clinical trials to see if it is effective and safe in treating your condition.

Unlicensed – An unlicensed medicine is one that does not have a product license in the UK.

2. GUIDELINES

Melatonin has very strict indications for its use; for example it should not be prescribed for sleep disorders associated with ADHD without a concomitant disorder of Autistic Spectrum Disorder (ASD)[1].

Melatonin should not be used long term in children (over two years)[2]. The review of the effectiveness of the melatonin should be at 3 months and then at intervals of 6 months up to 2 years. A review of withdrawing treatment should be trialled after treatment has reached 2 years, as there is very little data of efficacy and safety data beyond this. Alder Hey also suggest that a drug holiday should occur every 6 to 12 months to ensure that the medication is still required[3].

Patients who have a learning disability and behavioural challenges (where sleep hygiene measures have been insufficient) can have melatonin prescribed up to 10mg per day all other criteria would still apply.

2.1 Safety concerns

Melatonin 1mg/ml oral solution should not be used in children and adolescents due to safety and efficacy concerns. This is due to the excipients being problematic in children[4,5] :

- Propylene glycol 150.37mg per 1ml per dose (Safe limit 50mg/kg)
- Ethanolol 0.00045mg per 1 ml per dose (Safe Limit 500mg/kg)
- Sorbitol 140mg per 1ml per dose (Safe Limit 140mg/kg)

The total daily dose of excipients needs to be calculated and checked whether they are within the safety limits for age and weight of the child (see above).
Patients with swallowing difficulties should be prescribed the following licensed melatonin preparations off-label, in preference to using an unlicensed melatonin preparation.

- Immediate release – halve, quarter or crush melatonin prolonged release (P/R) tablets, or melatonin 3mg tablets or use of melatonin 5mg/5ml oral solution.
- Prolonged Release – mix whole prolonged release tablets with yoghurt orange juice or ice cream and take immediately to aid swallowing. Do not break, crush or chew them. If not suitable change to immediate release preparations.

Melatonin 1mg/ml oral solution is licensed for short-term treatment of jet lag in adults, however safety concerns regarding its excipients mean it should not be prescribed off-license in children and young people (see above).

Growth and puberty must be monitored in children and adolescents taking melatonin as it has been suggested that it may affect the reproductive system by inhibiting the hypothalamic-pituitary-gonadal axis.

Several strengths of melatonin capsules, tablets and liquids are available via 'Specials' manufacturers. These products are unlicensed and should not be prescribed if there is a licensed or off-license alternative according to advice from the General Medical Council. [6]

Liquid preparations should only be prescribed for selected patients that cannot tolerate solid dosage form, have swallowing difficulties, or because of the drug release characteristics. The Standard Operating Procedure 'How to swallow tablets' [7]will support you with this process.

Melatonin preparation choice and dose need to be optimised to manage any safety issues, or potential cost increases when considering switching melatonin preparations.

2.2 Isle of Man Melatonin Formulary: Advised Choices

- First line – Slenyto 1mg P/R or 5mg P/R tabs
- Second line – Melatonin 2mg M/R tabs (off license)
- Third line – Melatonin 5mg/5ml oral solution (unlicensed)

2.3 Patients currently prescribed melatonin

All patients currently prescribed melatonin should be reviewed.

2.4 Liquids

All patients to be reviewed whether a liquid preparation is still required or a tablet alternative could be given.

Patients who have difficulty swallowing tablets should not be changed to tablets. Patients prescribed other non-tariff strengths (i.e. 2.5mg/5ml or 10mg/5ml) or formulations (i.e. suspension), should be changed (with equivalent volume of dose amendment) to the tariff listed strength and formulation. If any help is needed please contact the medicine optimisation team.

2.5 Tablets and Capsules

When the dose of melatonin capsules is equivalent to a dose of melatonin M/R tablets then this can be changed to the same dose e.g. 6mg of unlicensed melatonin capsules to 3 x 2mg of melatonin M/R tablets.

For patients not on an equivalent dose, this can be changed to the next nearest dose e.g. 2.5mg capsules to 2mg tablets or 3mg capsules to 1 x 2mg plus 1 x half a 2mg tablet of melatonin M/R tablets.

Monitoring of side effects should be carried on a regular basis and reviewed at each appointment. If GPs review the side effects, this information should be relayed back to the specialist.

The aim is to establish healthy sleep habits with the lowest effective dose. Tolerance is characterised by the administration of a drug in higher doses to achieve the same effect. 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[8]. It suggests that if melatonin is withdrawn prior to this, sensitivity may be re-established and melatonin successfully re-introduced at a lower dose. Alder Hey support this and suggest melatonin holidays every 6 to 12 months. Therefore 2 week drug holidays should occur every 6 months to confirm continued need.

Patients who fail to attend their appointments should not have further prescriptions issued until reviewed.

2.6 New Patients

All melatonin for children should be initiated by a specialist in secondary or tertiary care.

Before starting melatonin treatment consider the use of a sleep diary; the use of a sleep diary is crucial in establishing the sleep routine and in determining the pattern of sleep difficulties.

Signposting to the relevant sleep management websites for Information regarding sleep is essential (Appendix 1) .

Parents should keep a sleep diary for their child, both prior to commencing medication and once medication has started. Review of the diary should occur at follow-up appointments to assist with decisions regarding dosage and continuation. Effectiveness of interventions should be documented in the clinical notes at review[9].

Consider initiating treatment with melatonin only when non-pharmacological measures have been tried and failed. Behavioural therapies should be continued alongside medication as the combination has been found to be more effective than medication alone[10].

Dose - The usual starting dose of melatonin for sleep disorders is 2-3 mg each night in children above the age of two. The dose may be doubled if there is insufficient benefit after 1-2 weeks. The maximum daily dose – is 10 mg. If no benefit is seen after 2 weeks, then melatonin should be stopped.

3. REFERENCES AND/OR RESOURCES

1. Joint Formulary Committee (2020) British National Formulary for Children. Available at: http://www.medicinescomplete.com (Accessed: 05 May 2022)
2. Prescqipp Community Interest Company (2020) Melatonin (245) Available at https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f4920%2f245-melatonin-22.pdf. Accessed on 4th May 2022
3.Wong, SM (2017) A retrospective Audit of Melatonin Prescribing. Available at http://nppg.org.uk/wp-content/uploads/2017/06/P15-See-Mun-Wong.pdf Accessed on 4th May 2022
4.Summary of Product Characteristics Melatonin 1mg/ml oral solution. Colonis Pharma Limited. Available at: www.medicines.org.uk Accessed 19/05/2020
5.Arthur S, Burgess A. How to identify and manage 'problem' excipients in medicines for children. The Pharmaceutical Journal 2017; 299 (7903) online | DOI: 10.1211/PJ.2017.20203121. Available at: https://www.pharmaceutical-journal.com/learning/learning-article/how-to-identify-and-manageproblem-

excipients-in-medicines-for-children/20203121.fullarticle?firstPass=false Accessed 08/07/2019
6. General Medical Council (2022) Prescribing Unlicensed Medicines. Available at https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines
7. Medicine Optimisation Team (2022) How to Swallow tabs (IMOG)
8. Cambridgeshire and Peterborough (2020) Melatonin prescribing for Paediatric Patients (formulation Choice). Available at https://www.cambridgeshireandpeterboroughccg.nhs.uk/easysiteweb/getresource.axd?assetid=21809&type=0&servicetype=1 Accessed on 4th May 2022
9. General Medical Council (2022) Keeping Records, Available at https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/protecting-children-and-young-people/keeping-records Accessed on 4th May 2022
10. Shropshire Community Health (2021) Guidance for use of melatonin in children and young people with severe sleep disorders. Available at https://www.shropscommunityhealth.nhs.uk/content/doclib/11223.pdf Accessed on 4th May 2022

4. RESOURCES

- https://www.medicinesforchildren.org.uk/medicines/melatonin-for-sleep-disorders/
- https://www.thurrockccg.nhs.uk/docman/our-key-documents/medicines-management/formulary-and-prescribing-guidelines/chapter-04-nervous-system/6195-melatonin-for-children-and-adolescents/file
- https://mm.wirral.nhs.uk/document_uploads/sharedcare/Melatonin(Circadin)forchildren4713.pdf
- https://www.bcpft.nhs.uk/documents/policies/c/768-camhs-melatonin-prescribing/file

5. APPENDICES

See following pages

Appendix 1

Useful patient resources

- 10 Steps to a Quiet Night available from “Ten Steps to a Quiet Night” (cchp.nhs.uk)
- Healthy sleep tips for children www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tipsfor-children/
- Taking Melatonin information leaflet download from medicines for children https://www.medicinesforchildren.org.uk/melatonin-sleep-disorders
- Sleep advice websites-www.cerebra.org.uk www.thesleepcharity.co.uk
- Good sleep habits booklet can be downloaded at: www.autism.org.uk
- What is enough sleep?
- Below are the approximate hours of sleep needed by children of different ages (How much sleep do children need? - NHS (www.nhs.uk)).
- Babies 4 to 12 months old • 12 to 16 hours including naps
- Toddlers 1 to 2 years old • 11 to 14 hours including naps
- Children 3 to 5 years old • 10 to 13 hours including naps
- Children 6 to 12 years old • 9 to 12 hours
- Teenagers 13 to 18 years old • 8 to 10 hours
- Sleep hygiene in children and young people | Great Ormond Street Hospital (gosh.nhs.uk)