Prescribing Support Information

MELATONIN for the treatment of persistent chronic sleep disorders in adults and children

AMBER following specialist initiation

Scope: This information is used to support prescribers in managing patients who have been initiated on melatonin by a specialist for the management of persistent chronic sleep disorder.

Your patient has been identified as being suitable to receive melatonin in accordance with the indications detailed below. They have been started on treatment and have been reviewed to assess the efficacy and adverse effects of the treatment by the specialist team.

Melatonin has been considered as appropriate for prescribing in primary care and the information contained in this document has been provided to support you to prescribe the medicine for your patient in the community. Your patient's dose is now stable and is detailed in the clinic letter.

Background

Paediatric insomnia is a widespread problem, with an overall prevalence of 1% to 6%, but rising to 50% to 75% in children with NDD (neurodevelopmental disorders) or psychiatric comorbidities, and specifically Autistic Spectrum Disorder (ASD and NDD) [1]. Sleep problems often carry on into adulthood. These sleep disturbances exacerbate both cognitive performance deficits and behavioural problems which compound entire-family distress [1].

In adults sleep studies have shown varied results as to the prevalence of insomnia. Some estimates show that about 10% - 30% of adults complain of chronic insomnia. This increases across different demographic populations due to co-morbidities or use of medication [2].

Current practice recommends behavioural sleep interventions (sleep hygiene) as first-line management for insomnia. Pharmacotherapy is often considered when behavioural intervention is insufficient [1].

Melatonin

Melatonin is a hormone secreted by the pineal gland in response to decreased light, mediated through the suprachiasmatic nucleus. The mechanism of action of melatonin is to supplement the endogenous pineal hormone [3].

Available formulations

Melatonin 1mg & 5mg prolonged release tablets (Slenyto ®)

- For children aged 2 years and above
- Patient with sleep disorders associated with ASD or SMS.
- **Slenyto® should only be used in these indications, or for patients unable to swallow conventional tablets with persistent chronic sleep disorder associated with conditions specified in the prescribing statement**
- 2-10mg once at night 30-60 mins before bed with food [3]. Off label doses of up to 12mg have been used.

Melatonin 2mg prolonged release tablets

For children aged 2 years and above who are able to swallow tablets (off label) and for adults (off-label except for short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over).

- Patient with:
    - Attention Deficit Hyperactivity Disorder (ADHD)
    - Cerebral Palsy
    - Chronic fatigue syndrome (CFS)/ myalgic encephalomyelitis (ME) (or encephalopathy)
    - Complex neurodevelopmental disorders (i.e., Angelman's syndrome, Rett's syndrome, tuberous sclerosis complex, fragile X syndrome, foetal alcohol spectrum disorder (FASD))
    - Global developmental delay / learning disability
    - Parkinson's disease (PD) with REM sleep disorder.
- 2-10mg 30-60 mins before bed with food [4]. Off label doses of up to 12mg have been used.

Adaflex® tablets or Ceyesto® oral solution (Immediate release melatonin)

- For children and young people aged 6-17 years and above with insomnia associated with attention deficit hyperactivity disorder (ADHD) or delayed sleep wake phase syndrome where sleep hygiene measures have been insufficient
- 1-5mg once at night 30-60mins before bed. Off label doses of up to 12mg have been used
- Use Adaflex® as preferred brand for immediate release tablet due to variety of strengths available and ability to crush tablet (licensed)
- Use Ceyesto® oral solution as other brands currently not cost effective.

Please note: Some melatonin formulations are off label in patients aged 18 years or above. Patients should be maintained on the same formulation if ongoing pharmacotherapy is required into adulthood.

Behavioral Sleep Intervention (Pending local implementation)

Sleep hygiene must be optimized prior to consideration of melatonin. This is best carried out by someone trained as a sleep practitioner and as part of a structured programme for the family. In certain family or social circumstances i.e. parental ill health, it may not be possible for families to implement behavioral interventions fully to resolve sleep issues. It may be appropriate in these circumstances to commence melatonin to support behavioral interventions. Social support should also be considered. Where the sleep deprivation is severe, it may also be appropriate to commence melatonin to support behavioral interventions. A General Practitioner or specialist should make a clinical judgement around the appropriateness of behavioral sleep intervention. For patients with Parkinson's disease the PD specialist can make the decision to initiate melatonin without referral to a behavioural sleep intervention service. This should be done in accordance with the recommendations within NICE NG17 Parkinson's disease in adults.

Assessment (Specialist to complete)

- Medical history (Rule out medical causes of insomnia i.e. obstructive sleep apnoea, restless legs syndrome, urticaria, pain etc.)
- Sleep history gathered with the use of sleep diaries or actigraphy (if available) if appropriate
- Sleep hygiene must be optimised before consideration of melatonin (Rule out environmental causes of sleep difficulty)
- Appropriate information provided to parents/families (e.g. sleep hygiene, sleep physiology to make parents aware of sleep cycles, partial wakings, the importance of knowing sleep associations and some behavioural advice)
- Support from other professionals considered if available dependant on local CCG commissioning (i.e Behavioural intervention for sleep service)

Initiation & titration [2] (Specialist to complete)

If behavioral sleep intervention is insufficient or inappropriate at this time, or the patient has PD, melatonin should be considered if the patient experiences

- <6 hours of continuous sleep persistently for at least 3 months AND/OR
- >0.5 hour sleep latency on at least 3 out of 5 work/school nights per week for 2 weeks.

Starting doses and titration are suggested as follows:

	Slenyto® tablet (prolonged-release)	Melatonin 2mg tablet (prolonged-release)	Immediate -release melatonin
Starting dose	2mg	2mg	1mg
Dose increment 1[2,3]	5mg	6mg[1]	2mg
Dose increment 2	10mg	10mg[1]	3mg
Dose increment 3	-	-	4mg
Dose increment 4	-	-	5mg[4]

1. Clinical judgement to be used if smaller dose increments more suitable
2. Dose incrementation frequency should be considered after a minimum of 4 weeks for prolonged-release preparations
3. Dose incrementation frequency should be considered after a minimum of 1 week for Immediate -release preparations
4. Higher doses of up to 12mg have been used (off label)

Dose increases should be considered if sleep continues to be a problem as defined by:

- <6 hours of continuous sleep (longest sleep episode)
- >0.5 hour sleep latency on at least 3 out of 5 work/school nights per week

Clinical criteria should also be taken into account for daytime repercussions (fatigue, irritability, attention deficits, challenging (externalising) behaviours and well-being (quality of life)). Sleep hygiene should always be optimised prior to consideration of melatonin or further dose increases.

After at least 3 months of treatment, the specialist will evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be advised to take a drug holiday prior to this review. This can provide evidence of clinical benefit before ongoing need is established.

Drug holidays

To ascertain ongoing need for melatonin a 'drug holiday' should be considered 3 months post initiation (specialist review) and 6 monthly thereafter (discussed at 3 months with specialist and subsequently at annual primary care review). Patients (or their carers) can initiate the drug holiday themselves. Treatment can be stopped abruptly and should be stopped for 2 weeks. A long-term follow-up study showed that discontinuation was not associated with withdrawal effects or rebound insomnia [4]. If sleep improvements are maintained without melatonin, therapy can be stopped. If sleep deteriorates and continues to be an issue, the original dose where sleep improved can be re-instated. Ongoing drug holidays can be considered at the time of annual primary care review. If there is a consistent correlation of sleep deterioration at drug holiday, patients should be advised to continue without break unless they are suspected to be a poor metaboliser of melatonin.

Poor metabolisers of melatonin may find that melatonin efficacy reduces over time. In these patients, melatonin accumulates in the plasma. This leads to an absent peak concentration at bedtime. This is identified through clinical history; patients may report initial benefit with melatonin and then ineffectiveness. These patients may need regular 2-week washout periods if benefit wanes to see continued effect with melatonin. A drug holiday when effect has waned will facilitate washout and patients often see benefit after recommencement. Patients should be counselled regarding this on initiation by the specialist.

Ongoing Review (in primary care)

Monitor sleep and suitability to continue melatonin every 12 months. Review longest sleep episode and sleep latency. See 'initiation & titration' for suggested criteria for increasing melatonin therapy.

No blood monitoring is required. General observation is recommended. A study by Malow et al showed that long term melatonin therapy continues to be effective and has shown that there are no significant effects on growth or pubertal development [4]. This has also been corroborated by Van Geijlswijk et al [5] in an earlier study. These studies followed up children after 2 and 3.1 years of melatonin therapy respectively.

How long the medicine should be prescribed for

The duration of treatment benefit may vary between individuals. Treatment with melatonin should be continued only when considered to be beneficial. If the patient appears to be gaining no benefit from melatonin, treatment should be stopped. Information from drug holidays should be considered as this allows comparison and highlights impact of melatonin pharmacotherapy.

Responsibilities

Specialist service	Primary Care	Patient
Initial assessment	Ongoing review	6 monthly drug holidays
Review until stable	Ongoing prescribing	Annual Sleep diary once stable on and off medication (1 week duration for each)
Prescribe until stable		
Transfer to primary care after stable		

Administration (see patient information leaflet)

Slenyto® tablets should be swallowed whole to maintain the prolonged release properties of the formulation. Tablets can be put into food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance. If the tablets are mixed with food or drink, they should be taken immediately, and the mixture not stored [6].

Melatonin 2mg prolonged release tablet should be swallowed whole to maintain the prolonged release properties of the formulation [7].

Adaflex® is licensed to be crushed and mixed with water to aid administration. Alternatively tablets can be added directly to water and disperse with minimal agitation. Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Melatonin tablets should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meal by persons with significantly impaired glucose tolerance or diabetes [8]

Patient information leaflets

- Medicines for children
- Formulation specific patient information leaflet can be obtained from EMC

Special warnings/cautions [6,7]

Drowsiness

Melatonin may cause drowsiness. Therefore, the medicinal product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety. Note that this may be more likely to occur in patients who are CYP1A2 poor metabolisers [4].

Autoimmune diseases

No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore, melatonin is not recommended for use in patients with autoimmune diseases.

Renal impairment

The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients [3,4].

Hepatic impairment

There is no experience of the use of melatonin in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, melatonin is not recommended for use in patients with hepatic impairment [3,4].

Contra-indications [6,7]

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

Lactose: Melatonin prolonged release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take these medicines.

Interactions with other medicines [6,7]

Interaction studies have only been performed in adults. In the absence of specific studies in children, the drug interactions with melatonin are those known in adults. Melatonin is known to interact with; **fluvoxamine**, **benzodiazepines**, **non-benzodiazepine hypnotics, thioridazine, imipramine, alcohol, 5- or 8-methoxypsoralen, cimetidine, oestrogens, CYP 1A2 inhibitors or inducers, smoking, NSAIDS, beta blockers.**

Adverse effects [6,7]

The most frequently reported adverse reactions with in clinical studies were somnolence, fatigue, mood swings, headache, irritability, aggression, and hangover occurring in 1:100-1:10 children. The following adverse reactions (frequency unknown) have been reported with Circadin®: epilepsy, visual impairment, dyspnoea, epistaxis, constipation, decreased appetite, swelling face, skin lesion, feeling abnormal, abnormal behaviour and neutropenia.

References

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