NHS LINCOLNSHIRE in association with UNITED LINCOLNSHIRE HOSPITALS TRUST SHARED CARE GUIDELINE:
The use of melatonin in the treatment of severe sleep disorders in children and adolescents with neurological or neuro-developmental disorders.

This shared care protocol covers the initiation of treatment in children and adolescents including those with learning disabilities. THIS PROTOCOL DOES NOT COVER THE INITIATION OF NEW TREATMENT IN ADULT AND ELDERLY PATIENTS OVER THE AGE OF 55 YEARS.

This protocol however can be extended to cover the on-going therapy for existing patients once they have reached 18 years of age who are retained in services.

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.
(BNF 76, September 2018 – March 2019, pg.5)

Aims:

1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.
2) Specific shared care guidance should be available for any high cost or high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.
3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.
4) Shared care guidelines will ensure that the GP has sufficient information available to undertake the prescribing for a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe for such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless, the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber1 on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies of any guidelines in this series are available from members of the Optum Medicines Management and Optimisation Team.
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Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018. Key recommendations from the guidance:

1.0 Introduction

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.

1.4 Where possible shared care should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared care policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER1 for Lincolnshire) through the traffic light system.

However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

2.3 Reasonable predictable clinical situation

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

2.4 Agreement of shared care between consultant and GP

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP.

2.7 Clear definition of responsibility

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

2.8 Clinical responsibility

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

2.9 Communication network & emergency support

2.9.1 Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.

2.9.2 People who are being treated on the advice of a secondary care team, but are no longer being seen in that setting, may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

6.0 Monitoring

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

Introduction

Sleeps disorder may affect 20–30% of children aged 1 to 5 years and can often persist in later childhood. Disorders include problems getting to sleep (dyssomnias) or undesirable phenomena during sleep (parasomnias), such as sleep terrors and sleepwalking. Children with neurodevelopmental or psychiatric comorbidities are at greater risk of sleep disorders.

Melatonin is prescribed as a licensed or an 'off-label' or 'unlicensed' indication for the treatment of sleep-wake disorders in children and adolescents with developmental and psychiatric disorders. NICE states if a prescriber decides to prescribe an unlicensed or off-label medicine, they must follow their professional guidance. For doctors this is the General Medical Council's good practice guidelines. This guidance includes giving information about the treatment and discussing the possible benefits and harms so that the patient, and their parent or carer if appropriate, has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Melatonin is a naturally occurring hormone produced by the brain. It is involved in regulating a person's body clock and helping to regulate sleep patterns. The following are the currently licensed melatonin products in the UK and they are all POMs (Prescription Only Medicines):

i. Slenyto® MR (1mg or 5mg) tablets (Flynn Pharma Ltd), licensed for the treatment of insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

ii. Circadin® MR 2mg tablets (Flynn Pharma Ltd), licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over.

    The use of Circadin® in children and adolescents is therefore known as "off-label". .

iii. Melatonin 3mg film coated tablet and melatonin 1mg/1ml oral solution (Colonis Pharma Ltd), licensed for short-term treatment of jet-lag in adults.

    According to Colonis Pharma Ltd, the safety and efficacy of their melatonin 3mg tablet and 1mg/1ml oral solution in children and adolescents aged 0 – 18 years have not been established and should not be used in children and adolescents due to safety and efficacy concerns.

Other melatonin products, often described as "immediate-release" capsules, tablets or liquids, are available from specialist suppliers and on the internet. These are not licensed for use in any patient group in the UK and so are known as 'unlicensed'.

Licensed indications and recommended preparations

The aim of treatment is to improve the onset and duration of sleep unresponsive to behavioural therapy and establish a regular nocturnal sleep pattern.
Melatonin is not usually considered first line for the treatment of sleep disorders. Behavioural interventions and good sleep hygiene measures should be considered first line. If these are unsuccessful consider melatonin.

Diagnosis should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with training and expertise in the diagnosis of sleep and developmental disorders. Diagnosis should be made according to DSM-5 criteria or the guidelines in ICD-10.

- Drug treatment should only be recommended by a healthcare professional with expertise in sleep-wake disorders.
- Treatment should be based on comprehensive assessment.
- Drug treatment should always be part of comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.
- GPs may continue prescribing and monitoring drug treatment under shared care arrangements.
- The option to share care is an 'invitation' to the GP, not an 'expectation' hence they retain the right to refuse to prescribe. The consultant also retains the right to refuse to prescribe. In this status quo the GP will be solely responsible for prescribing and monitoring an alternative medicine.
- Drug choice is the responsibility of the healthcare professional with expertise in sleep-wake disorders and should be based on:
  - Co-morbidities
  - Different adverse effects of drug treatments
  - Potential problems with compliance
  - Potential risk of misuse and diversion
  - Preferences of child/young person and their parent/carer.
- NICE advises:
  A licensed medicine meets acceptable standards of efficacy; safety, and quality. Clinical situations will arise where the use of unlicensed medicines or the use of medicines to treat conditions for which they are not licensed (off-label) may be judged by the prescriber to be in the best interest of the patient.

In accordance with this shared care protocol, the following are the options for prescribing melatonin for children and adolescents:

Option A:
Prescribe Slenyto® MR (1mg or 5mg) tablets if the indication meets Slenyto® licensed indication and dose; and patient can take tablets.
Indication: Insomnia in children and adolescents with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures are insufficient.
Dose: 2mg, 5mg or 10mg at night (30-60 minutes before bedtime).

Option B:
Prescribe Circadin® MR 2mg tablets if the indication does not meet Slenyto® licensed indication and dose; and patient can take tablets. This is an off-label use.
Dose: The usual starting dose is between 2-3mg daily in all ages of children given before bedtime and increased if necessary after 1-2weeks to 4-6mg.
The posology for Circadin in ≥55 is 1-2 hours before bedtime and after food (to delay absorption). There is no data on timing of the dose in children. The maximum dose is 10mg at night. Circadin® should be swallowed whole.
Circadin® has both an immediate release component and a delayed release component which combined offer the 'prolonged release' property. Circadin® can be halved using a tablet cutter. Careful halving may preserve some of the modified-release characteristics.

At the discretion of the clinician, Circadin® can be crushed and dispersed in water if an immediate release profile is desired.

Option C:
Prescribe unlicensed "Melatonin **10mg/5ml** oral suspension (Alcohol and Sugar Free)" if the indication does not meet Slenyto® licensed indication and dose; but patient cannot take tablets or Circadin® MR tablets.
Dose: Please add "Alcohol and Sugar Free" to the dose (e.g. 2.5ml ON, alcohol and sugar free). This is an unlicensed use.

Melatonin can be stopped abruptly should the need arise. There should be no adverse effects associated with this. There are no monitoring requirements associated with melatonin apart from continued therapeutic benefit and checking for side-effects.

Specialist Responsibilities

The specialist will:

1. Assess suitability of the patient for the recommended treatment.
2. Discuss treatment options with the patient, their parent(s) or carer(s). The discussion should include an explanation of the unlicensed or off-label use of melatonin (where applicable) and the risks and benefits of the proposed treatment. Provide the patient/parent/carer with all necessary information on their condition and treatment.
3. Send a letter to the GP requesting that the GP participates in shared care. As part of the communication the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website www.lincolnshire.nhs.uk
4. Prescribe melatonin clearly stating strength and formulation to be used (see page4).
5. Should continue to prescribe melatonin until GP has agreed to the shared care agreement.
6. Should assess and monitor the patient's response to treatment and the need to continue therapy on a 6-12 monthly basis.
7. Respond to any request from the GP to review the patient due to adverse effects of therapy.
8. Report any adverse effects of therapy to the Medicines and Health care products Regulatory Agency (MHRA) via the yellow card process.
9. Advise the GP on continuing or stopping the medication following medical review of the patient and associated drug therapy.

Community Pharmacist Responsibilities

The community pharmacist:

1. Has a responsibility to ensure any unlicensed medication ordered (where applicable) is of good quality
2. Provide the appropriate measuring device e.g. spoon, or oral syringe, with the medication (where applicable).

GP Responsibilities

The GP will:

1. Notify the specialist in writing, within two weeks, if they agree to share care.
2. Ensure that the patient, their carer(s) has understood and consented to unlicensed use of melatonin.
3. Prescribe melatonin as directed by specialist. Medication should be prescribed at the lowest effective dose within dose range outlined by specialist.
4. Switch from one form of melatonin to another (where appropriate) as agreed with the patient (and/or carer); seek specialist advice if needed.
5. Monitor the patients' general health and wellbeing.
6. Monitor the patient for adverse drug reactions and report any to the specialist and to the MHRA via yellow card process.
7. Liaise with the specialist regarding any complications of treatment.
8. Contact the specialist and refer patient back should unmanageable problems arise.

Referral Criteria

1. Patients will have been assessed by the specialist service.
2. Patients will either have received at least one month's supply of melatonin, or the GP will have reached a prior agreement with the specialist to initiate treatment on the required brand and dose.
3. The specialist will either have carried out an assessment of efficacy or the GP will be notified as to the planned follow-up for the patient.

Recommended dose

The BNF for Children states the dose of melatonin is initially 2-3mg daily for 1-2 weeks, then increased if necessary to 4-6mg daily, dose to be taken before bedtime.
Maximum dose is 10mg daily.

Treatment should be stopped in those that fail to demonstrate a response to the maximum dose.
Melatonin can be stopped suddenly without any side effects.

Adverse Drug Reaction (ADR)

For further information on adverse effects please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/ or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk

Common
Arthralgia, headaches, increased risk of infection, pain.

Uncommon
Anxiety, asthenia, chest pain, dizziness. Drowsiness, dry mouth, gastrointestinal discomfort, hyperbilirubinaemia, hypertension, menopausal symptoms, mood altered, movement disorders, nausea, night sweats, oral disorders, skin reactions, sleep disorders, urine abnormalities, weight increased.

Rare or very rare
Aggression, angina pectoris, arthritis, concentration impaired, crying, depression, disorientation, electrolyte imbalance, excessive tearing, gastrointestinal disorders, haematuria, hot flush, hypertriglyceridaemia, leucopenia, memory loss, muscle complaints, nail disorder, palpitations, paraesthesia, partial complex seizure, prostatitis, sexual dysfunction, syncope, thirst, thrombocytopenia, urinary disorders, vertigo, vision disorders, vomiting.

Frequency not known
Angioedema, galactorrhoea.

Table below details the management of some of the adverse effects

ADR details	Management of ADR
Uncommon: Irritability, nervousness, restlessness, insomnia, abnormal dreams, anxiety, Migraine, lethargy, psychomotor hyperactivity, dizziness, somnolence	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral
Uncommon: Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral
Uncommon: Hypertension	Refer to specialist service and discontinue medicine prior to referral
Uncommon: Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, hyperbilirubinaemia	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral

Drug Interactions

For detailed information on drug interactions, please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/ or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk

Below is a summary of some of the key interactions.

Fluvoxamine & Cimetidine

Fluvoxamine & cimetidine have been shown to increase melatonin levels by inhibiting cytochrome P450 (CYP) isozymes CYP1A2 and CYP2D respectively and these combinations should be avoided

CYP1A2 inhibitors
Theoretical risk that any CYP1A2 inhibitor (e.g. oestrogens, quinolones) could increase melatonin levels.

CYP1A2 inducers
CYP1A2 inducers (e.g. carbamazepine & rifampicin) may give rise to reduced plasma melatonin levels.

Alcohol
Use should be avoided as reduces effect of melatonin on sleep.

Sedatives and hypnotics
Melatonin may enhance effects of sedatives and hypnotics e.g. benzodiazepines.

Precautions and Contraindications

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via https://bnf.nice.org.uk/ or from the Summary of Product Characteristics which can be accessed via: www.medicines.org.uk

Contraindications

Known hypersensitivity to melatonin or any of the excipients.

Precautions

- Patients with autoimmune diseases- not recommended.
- Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose- galactose malabsorption – not recommended
- Pregnancy – no information available – avoids.
- Breast feeding - present in milk- avoid.
- Hepatic impairment – clearance reduced – avoid
- Renal impairment – no information available – use with caution

Monitoring

Standard monitoring of growth and sexual development is recommended i.e. to check that height, weight and pubertal development progress is as expected.

Indication of Likely Cost of Therapy in Primary Care

Melatonin product Strength, Cost per pack

- Slenyto® MR 1mg tablets (60= £41.20)
- Slenyto® MR 5mg tablets (30= £103.00)
- Circadin 2mg MR tablets (30= £15.39)
- Unlicensed Melatonin 10mg/5ml oral suspension (100ml= £41.61)

Information given to patient - Contact Details

Pre-treatment information sheet may be provided.

COMMUNITY PAEDIATRICIANS

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