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

The 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.

The 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 74, September 2017 – March 2018, 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 to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe 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 amber 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.

Date of Issue: November 2018
Review Date: November 2020

Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018.
Key recommendations from 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 acre should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared acre policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER (AMBER 1 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 patiet 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 acre 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 an 'unlicensed' or 'off-label' indication for the treatment of sleep-wake disorders in children and young people 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. Although one melatonin product - Circadin® Flynn Pharma Ltd - is licensed for use in treating sleep disorders in the UK, it is not licensed for use in people less than 55 years of age. Its use in children and young people is therefore known as "off-label". It is available as a prescription-only prolonged-release preparation. 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

Melatonin is unlicensed for the treatment of severe sleep disturbances in children with neurological or neuro-developmental disorders. 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 may be judged by the prescriber to be in the best interest of the patient.

If there is a choice of more than one drug use the drug with the lowest overall cost. Where ever possible, Circadin®, the UK licensed formulation of melatonin should be used. This also includes using it for clinical indications not covered by the UK product license e.g. off – label or unlicensed use. The MHRA have since clarified this advice stating that the off label use of a medicine with a UK product license carries less risk than that of un- assessed unlicensed products.

Circadin® is a modified release formulation and is only available as a 2mg MR (prolonged release) tablet. 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 (40%) component and a delayed release component (60%) 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 Cricadin® can be crushed and dispersed in water if an immediate release profile is desired.

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.

The MHRA have issued further advice in 2008 on suitable alternatives in terms of the quality, safety and efficacy of the preparations available.

This can be summarised as:

- 1st line treatment - off label use of Circadin 2mg MR tablets. This decision is on the basis of licensing, cost and quality assurance of the product.
- 2nd line treatment –Bio-melatonin 3 mg tablets manufactured by Pharma –Nord if an immediate release preparation is required. This tablet can be crushed immediately before administration.
- 3rd line – Liquid formulations and strengths specified in the Drug Tariff, section VIIIB.

For details of all these products please refer to preparations section on page 4

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 use of melatonin and

the risks and benefits of the proposed treatment. Provide the person/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. Circadin should be used first line. Melatonin oral solution 5mg/5ml could be considered as an alternative if circadin does not meet the clinical needs of the patient. (See preparations page 6).
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 is of good quality
2. Provide the appropriate measuring device e.g. spoon, or oral syringe, with the medication.

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. Monitor the patients' general health and wellbeing.
5. Monitor the patient for adverse drug reactions and report any to the specialist and to the MHRA via yellow card process.
6. Liaise with the specialist regarding any complications of treatment.
7. 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 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.

Preparations Available

1st line product
Melatonin prolonged release 2mg tablets (Circadin®) UK product licensed for the short term treatment of primary insomnia in adults aged over 55 years.
Prescribe by brand as Circadin 2mg prolonged release tablets.
For patients who cannot take whole tablets or for patients who require a more immediate effect the MR tablets should be crushed. These can be administered with a spoonful of milk, yoghurt or jam. Crushing destroys the costing on the tablets and removes their prolonged release properties.
N.B. Crushing the MR tablets is out of the terms of their product license

2nd line product
Consider melatonin oral solution 1mg/ml (as per Drug tariff). Only use if the licensed form on melatonin m.r. Circadin cannot meet the clinical needs of the patient.
Any other preparation not included on the shared care protocol may be considered on a case by case basis.

Adverse Effects

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 compex 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.

Cautions for melatonin 2mg MR tablets (Circadin®):

Circadin may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.
No clinical data exist concerning the use of Circadin in individuals with autoimmune diseases. Therefore Circadin is not recommended for use in patients with autoimmune diseases.
Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 (pack size)
Circadin 2mg m.r tablet £15.39 (30 tabs)
Melatonin 5mg/5ml oral solution £29.74 (100ml)

Information given to patient

Pre-treatment information sheet may be provided.

Contact Details

COMMUNITY PAEDIATRICIANS

Dr F Johnson – Consultant Community Paediatrician
Lincoln County Hospital
Tel 01522573177

References

1. MHRA Drug procurement advice EL (08) A/11 Restrictions on the import of unlicensed melatonin products following the grant of marketing license for Circadin 2mg tablets. 15th August 2008.
2. MHRA. Supply of melatonin – MHRA's position. September 2008.
3. BNF for Children 2013-14.
4. BNF 68 September 2014.
5. Leicestershire Medicines Strategy Group, Melatonin Guidelines in Primary and Secondary Care, accessed 20.09.13

References used for revision of protocol November 2018

6. Shared care guideline, Melatonin for the management of Sleep – wake disorders in children and young people. Implemented November 2017- review date November 2019.Sunderland CCG, City Hospitals Sunderland, Northumberland Tyne and Wear.
7. BNF for children accessed online November 2018
8. BNF accessed online November 2018.
9. Summary of Product Characteristics Circadin , Flynn Pharma Ltd. Last updated on emc 7th June 2018.
10. Shared Care Protocol Melatonin. Oxfordshire University Hospitals and Oxford Clinical Commissioning Group. Updated November 2017.

Authors revision December 2014

Cathy Johnson – Interface Lead Pharmacist, GEMSCU in consultation with:
Shiraz Haider, Chief Pharmacist, Lincolnshire Partnership NHS Foundation Trust
Dr Folasade Johnson, Consultant Community Paediatrician, Lincoln County Hospital
Dr Enrique Bonell, Consultant Psychiatrist, Lincolnshire Partnership NHS Foundation Trust

Authors revision November 2018

Cathy Johnson, Support Services Pharmacist- Optum MMO team
Dr Folasade Johnson, Consultant Community Paediatrician, Lincoln County Hospital

Approved at meeting of Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) November 16th 2018.