New Medicine Assessment

Melatonin prolonged release tablets (Circadin®)

For the Treatment of Rapid Eye Movement (REM) Sleep Behaviour Disorder (RBD) in Parkinson's Disease and Lewy Body Dementia

Recommendation: AMBER0

Melatonin prolonged release tablets are suitable for prescribing in primary care following recommendation or initiation by a specialist when clonazepam is not considered to be appropriate.

- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.

Summary of supporting evidence:

- NICE and the American Academy of Sleep Medicine both suggest melatonin as a treatment option for the management of RBD.
- Randomised controlled trials have demonstrated improvement in sleep measures (not directly related to RBD) for PD patients using melatonin.
- A review identified a randomised controlled trial and several case series demonstrating beneficial effects of melatonin in RBD.
- Clonazepam tablets appear to be more effective than melatonin although patients tend to experience greater numbers of adverse events when using clonazepam.
- The number of reported adverse events is low and comparable to placebo in patients with RBD using melatonin. Reports of adverse events were more common in clonazepam, the main comparator treatment for RBD.

Date: June 2020

Details of Review

Name of medicine (generic & brand name)**:**

Melatonin prolonged release tablets (Circadin®) [1]

Strength(s) and form(s):

2mg prolonged release tablets

Dose and administration:

3-12 mg [2] orally once daily, 1-2 hours before bedtime and after food.

BNF therapeutic class / mode of action:

Non-benzodiazepine hypnotics and sedatives/ agonist at melatonin (MT1, MT2 and MT3) receptors.

Licensed indication(s):

Short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. [1]

Proposed use (if different from, or in addition to, licensed indication above):

Treatment of Rapid Eye Movement (REM) Sleep Behaviour Disorder (RBD) in Parkinson's disease.

Course and cost:

Dose range = 3-12 mg, £15.39 for a pack of 30 x 2mg tablets.

Cost for 30-day supply = £23.09 to £92.34

Annual cost (£23.09 to £92.34) x 12 = £277.02 to £1,108

Current standard of care/comparator therapies:

- Clonazepam tablets, dose range = 0.5 – 2 mg (taken before bed)
  100 x 0.5 mg tablets = £31.79
  100 x 2 mg tablets = £34.46
  Assuming 2 mg tablets can be halved the annual cost range for treating RBD with clonazepam is:
  Cost of single 1 mg dose (cheapest dosage regimen) = (34.46 ÷ 100) ÷ 2 = £0.1723

  Annual cost of 1 mg dose = £0.1723 x 365 = £62.89

  Cost of single 1.5 mg dose (most expensive regimen) = ((34.46 ÷ 100) ÷ 2) + (31.79 ÷ 100) = £0.4902

  Annual cost of 1.5 mg dose = £0.4902 x 365 = £ 178.92

Relevant NICE guidance:

NICE guideline (NG 71): Parkinson's disease in adults [3] states the following:

Rapid eye movement sleep behaviour disorder

1.5.4 Take care to identify and manage restless leg syndrome and rapid eye movement sleep

behaviour disorder (RBD) in people with Parkinson's disease and sleep disturbance. **[2017]**

1.5.5 Consider clonazepam or melatonin to treat RBD if a medicines review has addressed possible pharmacological causes[2]. **[2017]**

Background and context

Rapid eye movement sleep behaviour disorder (RBD) is a parasomnia. RBD is typically characterised by abnormal or disruptive behaviours emerging during rapid eye movement sleep having the potential to cause injury or sleep disruption such as talking, laughing, shouting, gesturing, grabbing, flailing arms, punching, kicking, and sitting up or leaping from bed. Vigorous, violent episodes may occur rarely or up to several times nightly. RBD occurrence is associated with several neurodegenerative conditions including Parkinson disease (PD), but even more extensively dementia of Lewy body (DLB) type and multiple system atrophy (MSA). [2]

Once RBD has been diagnosed patients are advised to modify their sleeping environment to protect themselves and their bed partner e.g. removing sharp objections from the immediate environment, placing mattresses on the floor to provide padding, and in some cases it may be prudent for bed partners to sleep in a separate room. A range of pharmacological interventions have been trialled to manage the symptoms of RBD, the most recognised treatments being clonazepam and melatonin.

Melatonin for the treatment of RBD in Parkinson's Disease was prioritised for review by the Lancashire and South Cumbria Medicines Management Group (LSCMMG) following a request by the Fylde Coast CCGs to review.

Summary of evidence

Summary of efficacy data in proposed use:

Ahn et al RCT (2020) [4]

This was a randomised, double-blind, placebo-controlled, multi-centre trial to evaluate the efficacy and safety of prolonged-release melatonin (PRM) in Parkinson's disease (PD) patients with poor sleep quality. The 34 patients included in the study were 55–80 years of age, had a diagnosis of PD (as defined by the UK Parkinson's Disease Brain Bank Criteria) and had a global Pittsburgh Sleep Quality Index (PSQI) score > 5 (PSQI involves a questionnaire including assessment of sleep quality, latency, disturbance and daytime disruption). Participants with changes in medication during the previous 6 months, or taking benzodiazepines, sedative antidepressants, or antipsychotics which could affect sleep, were excluded. Patients with dementia, other significant clinical conditions (e.g. malignancy) or obstructive sleep apnoea were also excluded.

The primary outcome measure was change in the PSQI with changes in the RBD screening questionnaire (questionnaire assessing clinical features of RBD) included as a secondary outcome measure. After 4 weeks of treatment, PSQI score was improved in the PRM group compared with baseline and the placebo group. The mean change in PSQI score was 1.75 (18.4%) in the PRM group (CI95% 0.33; 3.17, p = 0.049). However, the post-treatment RBD screening score did not change significantly from baseline (37.5% vs 43.8% of participants, p = 0.464).

Kakhaki et al RCT (2020) [5]

A 12-week randomised, double-blinded, placebo-controlled clinical trial assessed 60 people, aged 50‑90 years with PD, diagnosed according to clinical diagnostic criteria of the UK PD Society Brain Bank. In addition, all patients had rapid eye movement behaviour disorder or restless leg syndrome. The only listed exclusion criterion was an unwillingness to cooperate. The primary

outcome of the trial was the unified Parkinson's Disease rating stage (USPDRS) although sleep quality was measured as a secondary outcome using the PSQI. Melatonin supplementation significantly improved the PSQI score (difference −1.82; [CI95%, −3.36; 0.27; p = 0.02]).

Gilat et al RCT (2019) [5]

A randomised, double-blind, placebo-controlled, parallel-group trial with an 8-week intervention and 4-week observation pre- and postintervention assessed 30 PD patients with rapid eye movement sleep behaviour disorder. Patients were randomised to 4 mg of prolonged-release melatonin (Circadin) or matched placebo, ingested orally once-daily before bedtime. Primary outcome was the aggregate of rapid eye movement sleep behaviour disorder incidents averaged over weeks 5 to 8 of treatment captured by a weekly diary. Excluded patients included those with untreated obstructive sleep apnoea; any significant liver, kidney, psychiatric or autoimmune disease; current use of benzodiazepines or other non-benzodiazepine hypnotics or excessive alcohol consumption (>25 Unit/week); pregnancy or lactation; use of light therapy (for treatment of sleep-wake disorders) within the last 6 months.

No reduction in RBD was found between groups (3.4 events/week melatonin vs. 3.6 placebo; absolute difference: 0.2 [CI95% –3.2; 3.6, p = 0.92]). Secondary outcomes also revealed no difference for the number of nights in which RBD was reported (2.1 nights/week melatonin vs. 1.8 placebo; difference, 0.35; [CI95% –0.8; 1.5, p = 0.56]) or change in the frequency of vivid dreams (2.4 dreams/week melatonin vs. 2.9 placebo; difference, – 0.6; [CI95% –2.2; 1.1, P = 0.49]).

Videnovic systematic review (2017) [7]

This review was funded by the National Institutes of Health and involved an analysis of published studies relating to the management of sleep dysfunction in PD and multiple system atrophy. The review analysed several types of sleep dysfunction and sleep disorders including RBD. The author identified several case series reported beneficial effects of melatonin for RBD with daily doses up to 12 mg. Also, the review found a double-blind, placebo-controlled, cross-over trial of melatonin performed in 8 male patients with mild RBD. In this study treatment with 3mg of melatonin resulted in complete resolution of dream enactment behaviours in 4/8 patients, partial resolution in 3/8 and no change in 1 patient.

The review also identified a study of comparative efficacy of melatonin and clonazepam in a survey of 45 patients with RBD, half of whom had a co-existent neurodegenerative disorder. The survey revealed effectiveness of both agents with some superiority of clonazepam. The main reason for discontinuation of two agents was lack of efficacy among melatonin users and adverse events among those taking clonazepam.

Summary of safety data:

There are currently no licensed treatments for RBD. It is anticipated that off-label prolonged release melatonin (Circadin®) would be the preferred melatonin treatment option for RBD as this is the preparation used most commonly in clinical studies.

The Summary of products characteristics for Circadin® states that the most common adverse reactions associated with the use of Circadin® were headache, nasopharyngitis, back pain, and arthralgia. The full list of adverse events are tabulated below: [1]

NB there were no reports of very common (≥ 1/10), common (≥ 1/100 to < 1/10) or very rare (< 1/10,000) adverse events.

Class	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**	**Not known:** (Cannot be established from the available data)

Infections and infestations		Herpes zoster	
Blood and lymphatic system disorders		Leukopenia, thrombocytopenia	
Immune system disorders			Hypersensitivity reaction
Metabolism and nutrition disorders		Hypertriglyceridaemia, hypocalcaemia, hyponatraemia	
Psychiatric disorders	Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	Mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression	
Nervous system disorders	Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence	Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	
Eye disorders		Visual acuity reduced, vision blurred, lacrimation increased	
Ear and labyrinth disorders		Vertigo positional, vertigo	
Cardiac disorders		Angina pectoris, palpitations	
Vascular disorders	Hypertension	Hot flush	
Gastrointestinal disorders	Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea	Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis	
Hepatobiliary disorders	Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders	Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	Eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder	Angioedema, oedema of mouth, tongue oedema
Musculoskeletal and connective tissue disorders	Pain in extremity	Arthritis, muscle spasms, neck pain, night cramps	
Renal and urinary disorders	Glycosuria, proteinuria	Polyuria, haematuria, nocturia	
Reproductive system and breast disorders	Menopausal symptoms	Priapism, prostatitis	Galactorrhoea
General disorders and administration site conditions	Asthenia, chest pain	Fatigue, pain, thirst	
Investigations	Liver function test abnormal, weight increased	Hepatic enzyme increased, blood electrolyes abnormal, laboratory test abnormal	

Circadin® should not be taken by patients who have a hypersensitivity to the active substance or any of the medicine's excipients. Circadin® contains lactose. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take Circadin®. Due to a lack of clinical data, Circadin® is not recommended in pregnant patients or patients with autoimmune disorders. As exogenous melatonin is probably excreted in human breast milk, breast-feeding is not recommended in women under treatment with melatonin. [1]

Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible (e.g. fluvoxamine, nicotine, oestrogens in HRT and the combined oral contraceptives, quinolones, carbamazepine and rifamipicin). Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism

and in patients on cimetidine a CYP2D inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism. [1]

Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep. Circadin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics. Circadin co-administration with imipramine or thioridazine resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone. [1]

Strengths and limitations of the evidence:

Strengths

- NICE and the American Academy of Sleep Medicine both suggest melatonin as a treatment option for the management of RBD.
- Randomised controlled trials have demonstrated improvement in sleep measures (not directly related to RBD) for PD patients using melatonin. [4] [5]
- A review identified a randomised controlled trial and several case series demonstrating beneficial effects of melatonin in RBD.
- The number of reported adverse events is low and comparable to placebo in patients with RBD using melatonin. Reports of adverse events were more common in clonazepam, the main comparator treatment for RBD. [7]
- No very common or common adverse events were reported for a licensed preparation of melatonin according to its SPC. [1]

Limitations

- Clinical trials data for the treatment of RBD in PD is limited by small numbers; heterogeneity of study design and patient selection; and the use of wide range of melatonin preparations and doses.
- In studies using outcome measures more specific to RBD symptoms, no benefit was demonstrated in the melatonin patient groups. However, these studies only assessed the use of lower doses of melatonin. [4] [6]
- The RBD screening questionnaire score was used to assess outcomes in some studies, however given that this score is a measure of the incidence of RBD rather than severity, these outcomes should be interpreted with caution.
- Clonazepam tablets appear to be more effective than melatonin although patients tend to experience greater numbers of adverse events when using clonazepam. [7]

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

Melatonin should only be considered for the treatment of RBD following a medication review to address possible pharmacological causes of RBD. Melatonin may cause drowsiness and should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex

			VAT)
Melatonin 2mg prolonged release tablets (Circadin®)	3-12 mg before bed	£15.39 for 30	£277.02 to £1,108
Clonazepam 0.5 and 2 mg tablets	0.5 – 2 mg before bed	£31.79 for 100 0.5 mg tablets £34.46 for 100 2 mg tablets	£62.89 to £178.92
Costs based on MIMS list prices June 2020. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

The prevalence of RBD is much higher in patients with Parkinson's disease than in the general population (one study referencing prevalence rates as high as 42.3%) [8] There is currently no licensed treatment for RBD.

Financial implications of the intervention:

Parkinson's disease (PD) affects approximately 1 in every 350 adults in the UK. This equates to approximately 3,700 patients in Lancashire and South Cumbria. In PD patients the reported prevalence of RBD ranges from 13-50% [9] Based on NICE guidance suggesting low prevalence of RBD and the small number of local requests for melatonin in this indication the lower end of the prevalence range is used in the patient number assumptions. 13% of the 3,700 PD patients with RBD would give a potential patient cohort of approximately 480 patients.

A number of patients with RBD may be managed through non-pharmacological strategies and medication reviews to mitigate pharmacological causes. Patients still requiring treatment after a medication review may be treated with either melatonin or clonazepam. Therefore the number of patients requiring melatonin treatment is likely to be a small proportion of the total patient cohort. Assuming that 25% of the 480 patients were treated with melatonin this would lead to a potential annual cost burden of:

£277.02 to £1,108 x 120 = **£33,242 to £132,960**

NB. The estimated cost burden does not take it account the cost of alternative treatments for the management of RBD and therefore may be lower than value stated above.

Service Impact Issues Identified:

No significant impact to service provision is expected. No additional patient attendance at specialist service is anticipated.

Equality and Inclusion Issues Identified:

None identified.

Cross Border Issues Identified:

No border issues have been identified as both Pan Mersey APC and GMMMG do not have a RAG position for the use of melatonin in the proposed indication.

Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] Electronic Medicines Compendium, “Summary of Product Characteristics Circadin 2mg Prolonged Release tablets,” Flynn Pharma Ltd, 20 April 2012. [Online]. Available: https://www.medicines.org.uk/emc/product/2809. [Accessed 15 June 2020].

[2] R Aurora et al, “Best Practice Guide for the Treatment of REM Sleep Behavior Disorder (RBD),” *Journal of Clinical Sleep Medicine,* vol. 6, no. 1, pp. 85-95, 2010.

[3] National Institute for Health and Care Excellence, “Parkinson's disease in adults: NICE guideline (NG 71),” 19 July 2017. [Online]. Available: https://www.nice.org.uk/guidance/ng71/chapter/Recommendations#pharmacological-management-of-non-motor-symptoms. [Accessed 15 June 2020].

[4] JH Ahn et al, “Prolonged-release melatonin in Parkinson's disease patients with a poor sleep quality: a randomized trial,” *Parkinsonism and Related Disorders,* vol. 75, pp. 50-54, 2020.

[5] RD Kakhaki et al, “Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: A randomized, double-blind, placebo-controlled trial,” *Clinical Neurology and Neurosurgery,* vol. 195, p. 105878, 2020.

[6] M Gilat et al, “Melatonin for Rapid Eye Movement Sleep Behavior Disorder in Parkinson's Disease: A Randomised Controlled Trial,” *Movement Disorders,* vol. 35, no. 2, pp. 344-349, 2019.

[7] A Videnovic, “Management of sleep disorders in Parkinson’s disease and Multiple System Atrophy,” *Movement Disorders,* vol. 32, no. 5, pp. 659-668, 2017.

[8] X Zhang et al, “Prevalence of Rapid Eye Movement Sleep Behavior Disorder (RBD) in Parkinson's Disease: A Meta and Meta-Regression Analysis,” *Neurological Science,* vol. 38, no. 1, pp. 163-170, 2017.

[9] U Vyas and R Franco, “REM Behavior Disorder (RBD) as an Early Marker for Development of Neurodegenerative Diseases,” *British Journal of Medical Practitioners,* vol. 5, no. 1, p. a506, 2012.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality