NSW Medicines Formulary Information 04/23

Issue date: 04/12/23

Use of melatonin in NSW Health facilities

Summary

Melatonin is not listed on the NSW Medicines Formulary (the Formulary).

There is a lack of high-quality evidence demonstrating a meaningful clinical benefit to patients in improving sleep or delirium in inpatient settings. Use of melatonin without high-quality evidence demonstrating patient benefit is not in line with quality use of medicine principles.

Approval to use compounded and Special Access Scheme (SAS) melatonin formulations remains under the governance of the local Drug and Therapeutic Committee (DTC).

Evidence based strategies for the management of insomnia and delirium in inpatient settings are available in the NSW Therapeutic Advisory Group guidance 'Getting it right for sleep at night' and Australian Commission on Safety and Quality in Health Care Delirium Clinical Care Standard.

Australian regulatory status

In Australia, **melatonin 2 mg prolonged release (PR) tablets** are Therapeutic Goods Administration (TGA) registered for use as 'monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over'.[1] The use of this melatonin formulation in other indications is off label.

Melatonin 1 mg and 5 mg PR tablets are TGA registered for 'the treatment of insomnia in children and adolescents aged 2-18 with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient'.[2] The use of these melatonin formulations in other indications are off label.

A variety of melatonin formulations are available via SAS, including immediate release tablets, syrups, and lozenges.

Melatonin containing products are not listed on the Pharmaceutical Benefits Scheme.

Evidence for effectiveness

There is limited high quality evidence demonstrating a clinically meaningful benefit with melatonin in improving sleep, delirium, or facilitating benzodiazepine discontinuation in the inpatient setting. Study findings are inconsistent, and those that do show improvement are of small/questionable clinical benefit. A summary of the evidence for effectiveness by indication is presented below.

Indication	Summary of available evidence for effectiveness	Additional information
Management of insomnia in palliative care patients	No demonstrated improvement in sleep quality with melatonin use in adult inpatients receiving a palliative approach to care.[3-5]	Melatonin did not improve other symptoms including fatigue, pain, loss of appetite, or quality of life.[3-5] Level I-II evidence, low certainty, low quality (high heterogeneity, some concerns of bias).
Prevention of delirium in geriatric patients	Melatonin use has not shown effectiveness in preventing delirium in geriatric inpatients compared with placebo.[6-8]	No beneficial effects on secondary outcomes including delirium duration, length of hospital stay or mortality.[6, 8] In studies showing an efficacy benefit, both melatonin and ramelteon were evaluated together.[6, 9, 10] Subgroup analysis was not conducted by drug type in some studies.[9, 10] Where subgroup analysis by drug was completed, melatonin did not show benefit in reducing delirium compared with ramelteon.[6] Pre-disposing risk factors for delirium (for example, pre-existing cognitive impairment, medications, clinical characteristics of patients) were not accounted for. Level I-II evidence, low certainty, low quality (high heterogeneity, some concerns of bias).
Prevention of delirium in intensive care patients	Melatonin has not been shown to reduce the prevalence of delirium when used in patients in intensive care settings.[8, 11-14]	A multicentre randomised controlled trial across 12 Australian ICUs found that enteral administration of melatonin (4 mg every night for 14 days) did not reduce the prevalence of delirium, ICU length of stay, hospital length of stay, mortality, nor the quality or quantity of sleep, compared to placebo.[12] In a study showing an efficacy benefit, both melatonin and ramelteon were evaluated together.[6] Subgroup analysis was not conducted by drug type.[6] Pre-disposing risk factors for delirium (for example, pre-existing cognitive impairment, medications, clinical characteristics of patients) were not accounted for. Level I-II evidence, low certainty, low quality (high heterogeneity, some concerns of bias).

Indication	Summary of available evidence for effectiveness	Additional information
To facilitate benzodiazepine tapering/ discontinuation in benzodiazepine dependence	Melatonin use has not improved benzodiazepine discontinuation rates or withdrawal symptoms in adults with benzodiazepine dependence.[15-19]	Inconsistent evidence on the effect of melatonin on sleep quality during benzodiazepine tapering/discontinuation.[15-17, 20] Level I-IV evidence, low certainty, low quality (high heterogeneity, some concerns of bias).
Management of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over	There is some evidence that short term melatonin improves sleep in healthy adults aged at least 55 years with primary insomnia. This benefit has not been demonstrated in hospital settings or other patient groups as they were excluded from the pivotal clinical trial.	The pivotal trials supporting the TGA registration of melatonin 2 mg PR for use in primary insomnia showed only modest improvements in sleep quality (clinical significance uncertain), with a substantial proportion (74%) experiencing no improvement in sleep quality.[21] Clinical trials were not of optimal design. People with severe neurological, neurosurgical, and psychiatric conditions, those taking CNS medicines, and people aged under 55 years were not included in the pivotal clinical trials.[21] The outcomes from controlled clinical trials may not apply to real-world patients in hospital settings, where pre-existing comorbidities and multiple concomitant medicines are common.
Management of insomnia in adult inpatients who have failed non-pharmacological strategies	There is limited and inconsistent evidence that melatonin has a clinically meaningful benefit in improving sleep in adult inpatients.[22-24]	Study findings are inconsistent. Several studies found no improvement in sleep parameters with melatonin use in the inpatient setting.[12, 13, 25-27] Some studies showing a benefit grouped melatonin and ramelteon together for the efficacy outcome and it is unclear which drug the benefit was attributed to.[15, 28] In studies that did show statistical improvements in sleep, the benefit was small and of questionable clinical significance.[28, 29] Level I-II evidence, low certainty, low quality (high heterogeneity, some concerns of bias).
Management of primary insomnia in paediatrics/ adolescents	There is limited and inconsistent evidence for a clinically meaningful benefit in improving sleep in paediatrics/adolescent inpatients with primary insomnia.	Study findings are inconsistent. In studies that do show improvement, the benefit was small and of questionable clinical significance.[30, 31] Level I-II evidence, low certainty, low quality (high heterogeneity, some concerns of bias).

Indication	Summary of available evidence for effectiveness	Additional information
Management of insomnia in patients with psychiatric disorders	There is limited and inconsistent evidence that melatonin has a clinically meaningful benefit in improving sleep in adults with psychiatric disorders.	Study findings are inconsistent. Some studies found no improvement in sleep parameters with melatonin in patients with psychiatric disorders.[32-34] In studies that do show improvement, study design was suboptimal (for example, small sample size, lack of a control group or the use of subjective outcome measures).[34-38] Level II-IV evidence, low certainty, low quality (high heterogeneity, some concerns of bias). Small sample sizes.
Management of insomnia in patients with substance use disorders	There is insufficient evidence to establish the role of melatonin in improving sleep quality among patients with substance use disorders. Available evidence of benefit are mixed and inconsistent.	Study findings in benzodiazepine dependence and opioid addiction are inconsistent. Some studies observed no benefit with melatonin on sleep outcomes[15, 20] or withdrawal symptoms[16, 18, 19, 39] in patients withdrawing from opioids or benzodiazepines. Others reported improved sleep quality with melatonin in opioid or benzodiazepine dependence.[20, 40-42] Paucity of data in nicotine addiction or alcohol use disorder. Level II-IV evidence, low certainty, low quality (high heterogeneity, some concerns of bias).

Red, indications with evidence of no benefit; orange, indications where evidence for benefit is uncertain.

Evidence for safety

There is limited data on the safety of melatonin when used for non TGA registered indications in the inpatient setting. Although melatonin is generally well tolerated and very rarely associated with serious adverse events, there is variability in the incidence and nature of adverse events reported in published literature.

Formulary review

Melatonin 2 mg PR tablets are not listed on the Formulary due to a lack of high-quality evidence supporting safe, efficacious, and cost-effective use in inpatient settings.

- Use of pharmacological interventions without quality evidence for efficacy (for example, the use of melatonin as a "safe placebo") is contrary to the quality use of medicines principles in Australia's National Medicines Policy.
- Use of interventions that contribute to the health system's carbon footprint without evidence for efficacy does not align with the NSW Health environmental sustainability plan.

Melatonin 1 mg and 5 mg PR tablets were considered for the treatment of sleep problems in children and adolescents with neurodevelopmental disorders.

Consultation with paediatric specialists highlighted that the immediate release formulations available via the SAS were preferred for initiation due to their onset of action, lower cost, and improved patient accessibility in community settings. For this reason, melatonin 1 mg and 5 mg PR tablets were not listed on the Formulary. Approval to use compounded and SAS melatonin formulations remains under the governance of the local DTC.

Further information

Non-pharmacological interventions are recommended as first-line treatment of insomnia and for the prevention of delirium. Many factors known to disrupt sleep in hospitalised patients are modifiable (for example, environmental noise, awakening by hospital staff). Refer to the following resources for evidence based strategies:

- NSW Therapeutic Advisory Group guidance 'Getting it right for sleep at night'
- Australian Commission on Safety and Quality in Health Care Delirium Clinical Care Standard

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Review date: 11/24