

Melatonin (Circadin): a novel hypnotic for use in older patients

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KEY POINTS

- melatonin is a hormone produced by the pineal gland that plays a role in regulating circadian rhythms such as the sleep-wake cycle
- Circadin is a modified-release formulation of melatonin licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over
- available as 2mg tablets (21, £10.77), 2mg taken two hours before bedtime for three weeks
- melatonin significantly improves sleep quality and morning alertness in about 25 per cent of patients compared with 14 per cent with placebo
- it appears to reduce sleep latency by about as much as other hypnotics
- the frequency and nature of adverse events associated with melatonin in clinical trials were similar to those with placebo
- absence of effects on motor function makes melatonin a particularly suitable hypnotic for older patients



Melatonin is a new hypnotic with a novel mode of action for the short-term treatment of insomnia in older patients. In this New products review, Steve Chaplin discusses the clinical trial evidence for its efficacy, and Professor David Nutt describes its place in treatment.

Approximately one-third of adults in the UK report one or more sleep problems at night – of these, two-thirds have persistence of sleep problems 12 months later.¹ The National Institute for Health and Clinical Excellence (NICE) estimates that the prevalence of sleep problems that meet the diagnostic criteria for insomnia is 6 per cent.² Risk factors for persistent problems include old age, anxiety, depression and pain.¹ Management options include addressing co-morbidities, education about realistic expectations of sleep and advice on optimising sleeping.³

NICE published guidance on the use of nonbenzodiazepine hyp-

notics in 2004, noting that ‘although GPs and pharmacists can deliver appropriate advice and education, access to many nonpharmacological therapies is restricted through a combination of a lack of trained providers, cost and a poor understanding of available options’.²

Drug treatment should be considered for the short-term treatment of severe short-term insomnia that interferes with daily life.^{2,4} Alternatives include self-medication with an over-the-counter medicine, used by 40 per cent of people reporting insomnia,² or prescription of a benzodiazepine or ‘Z’ drug, *ie* zaleplon (Sonata), zolpidem or zopiclone.

Objective measurements show that hypnotics reduce sleep onset latency by a mean of 10-13 minutes.⁵

The technology

Melatonin is a hormone produced by the pineal gland that plays a role in regulating circadian rhythms such as the sleep-wake cycle. It is secreted during the night, with peak output occurring between 2 and 4am. Melatonin secretion declines with age.

Circadin is a modified-release formulation of synthetic melatonin 2mg licensed as monotherapy for the short-term treatment of primary insomnia characterised by

	Melatonin		Placebo	
	n	%	n	%
Improvement of ≥ 10 mm on the Leeds QOS and BFW scales				
yes	44	26	25	15
no	124	73	139	84
missing	1		1	
odds ratio for melatonin versus placebo = 1.97 (95% CI 1.14-3.41) chi-square test = 6.04, $p=0.014$ QOS = quality of sleep, BFW = behaviour following waking				

Table 1. Response to melatonin and placebo in two components of the Leeds Sleep Evaluation Questionnaire in patients aged 55-80 with primary insomnia⁷

poor quality of sleep in patients who are aged 55 or over. Primary insomnia is defined as sleeplessness not attributable to a medical, psychiatric or environmental cause persisting for at least one month causing clinically significant distress or impairment in social, occupational or other important areas of functioning.⁶

Melatonin is taken once daily after food one to two hours before bedtime for three weeks. It is not recommended for patients with hepatic impairment or autoimmune disease. There is insufficient experience to offer guidance

on its use in patients with renal impairment.

Clinical trials

Two pivotal trials provide the main evidence of the efficacy of melatonin. The larger was a double-blind trial involving 354 individuals in primary care aged 55-80 with primary insomnia confirmed by the Leeds Sleep Evaluation Questionnaire (LSEQ).⁷ After a two-week placebo run-in period, they were randomised to placebo or melatonin 2mg two hours before bedtime.

The primary end-point was clinically significant improvement, *ie*

10mm on a 100mm linear scale, in both of two subscales of the LSEQ, *ie* quality of sleep and behaviour following waking (BFW; a measure of alertness), after three weeks' treatment. Mean baseline scores were 54-55mm for quality of sleep and 52mm for behaviour following waking.

By intent-to-treat analysis, the primary end-point was reached by 25 per cent of participants taking melatonin and 14 per cent with placebo (odds ratio 2.01, CI 95% 1.17-3.46; $p=0.011$; see Table 1); number needed to treat (NNT) = 9. However, the size of effect was

small – from baseline, 3 or 4mm improvement over placebo on a 100mm scale.⁶ The response rate was greater among patients with very severe insomnia (29 *vs* 10 per cent; NNT=5).⁶

Secondary end-points (in the per-protocol population) showed a reduction in sleep latency and improvement in overall sleep quality and quality-of-life scores, but no significant difference in overall clinical assessment or participants' sleep diaries for day or night.

The smaller study was of a similar design and included 170

outpatients randomised to placebo or melatonin 2mg nightly.⁸ The primary end-point was the change in quality of sleep component of the LSEQ (mean baseline score 65mm⁶); behaviour following waking (mean baseline score 57-60mm) was analysed separately.

After three weeks, quality of sleep (treatment difference 6mm) and behaviour following waking (treatment difference 9mm) scores improved significantly more with melatonin. Patients' diaries recorded significant improvement with melatonin for quality of night but there was no difference between the groups' daytime scores, quality-of-life scores, sleep latency or waking from sleep.

In a *post-hoc* analysis of a subgroup of 87 patients with worse insomnia (mean baseline quality of sleep score 69mm), melatonin was associated with a greater treatment difference (9mm over placebo).

An analysis of pooled data showed that, after adjustment for placebo, melatonin reduced sleep latency by about nine minutes overall but by 19 minutes in subjects with low endogenous melatonin.

In a study of similar design conducted to provide an indirect comparison, zolpidem reduced sleep latency by 17 minutes;⁶ this is more than reported elsewhere.⁵ Melatonin and zolpidem had similar effects on quality of sleep.⁶ The response to melatonin is not affected by prior use of benzodiazepine hypnotics.⁶

Adverse effects

There was no evidence of dependence, withdrawal effects or rebound insomnia associated with melatonin.⁶ The commonest adverse events reported in all clinical studies of this formulation of melatonin were headache, pharyngitis, back pain and asthenia. The frequency and nature of adverse events were similar to those reported with placebo.⁶

References

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Two separate large studies, one in Scotland and one in France and Israel, have demonstrated statistically significant improvement in subjective quality of sleep and daytime function in older insomnia patients given modified-release synthetic melatonin.

The efficacy of melatonin reported in these three-week trials is modest – less than 10 per cent change on the LSEQ compared to 4-5 per cent after placebo – but is in a

similar range to that reported with the benzodiazepine hypnotics and is, nevertheless, an important finding.

Insomnia is a hugely prevalent problem, affecting between 7 and 15 per cent of the adult population depending on the criteria used, and prevalence increases with age to around 30 per cent. Its negative impact on day-to-day living and quality of life is enormous.

Pharmacological treatment of insomnia at present is usually with benzodiazepines or 'Z' drugs, which are safe and effective when used correctly. However, older patients do

tend to get up in the night and even short-acting GABAergic drugs can compromise balance and cognition early in the night.

Thus melatonin, which does not have effects on motor function, should be less likely to predispose to unsteadiness and falls during the night, and is a welcome addition to the pharmacopoeia, especially as there was no evidence of withdrawal effect in the clinical trials.

By David Nutt, professor of psychopharmacology at the University of Bristol