Melatonin: a new therapy for insomnia

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In the sleep medicine field, melatonin has been investigated for the treatment of phase shift sleep disorders (such as jet lag syndrome), some parasomnias and primary insomnia, the latter of which is discussed in this article.

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THE SLEEP–WAKE CYCLE

The human sleep–wake cycle is driven by two primary physiological processes: the homeostatic drive (likely to be neurochemically mediated and dependent on the duration of prior wakefulness and the quality and duration of prior sleep episodes) and the circadian process.

Endogenous melatonin secretion by the pineal gland during the dark/night phase of the sleep–wake cycle is under direction from the circadian pacemaker (the suprachiasmatic nucleus) in the anterior hypothalamus and is closely associated with the human endogenous rhythm of sleep propensity. Other factors such as core body temperature are also driven by this circadian influence and are associated with sleep propensity.

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PHARMACOLOGICAL AGENTS FOR INSOMNIA

Pharmacological hypnotics have long been used for the short-term treatment of insomnia. Such agents have a less well-defined role for the chronic treatment of insomnia. The range of pharmacological sleep-promoting agents include (in recent times) benzodiazepines, the more selective benzodiazepine receptor agonist agents (the 'Z' drugs, such as zolpidem and zopiclone) and melatonergic agents.

Some other psychotropic drugs are used for their sleep-promoting effects although are not primarily classified as hypnotics (e.g. antidepressants), and some barbiturates have a historical role as sleep-promoting agents.

MELATONIN

There has been an explosion of interest in the clinical use of exogenous melatonin across a diverse range of medical conditions.[1-2] In the sleep medicine field, melatonin has been investigated for the treatment of phase shift sleep disorders (such as jet lag syndrome and delayed sleep phase syndrome) and primary insomnia, and recent evidence suggests a possible role in treating some parasomnias (such as rapid eye movement sleep behaviour disorder).[3-5] Primary insomnia is the only use that is discussed in this article.

Exogenous melatonin ($C_{13}H_{16}N_2O_2$) is presumed to act like endogenous melatonin as an agonist on the MT_1 and MT_2 melatonin receptors in specific brain locations, thereby promoting increased sleep propensity and more stable, consolidated sleep.

Melatonergic agonists other than melatonin have been developed in recent years and marketed in some countries but not in Australia. These include ramelteon developed as a sleep-promoting agent and egomelatine developed as an antidepressant.

What have studies shown?

Some studies have suggested that melatonin levels in humans decline with age,[6-8] and this gradual decline has been associated with other senescent biological changes, including reduced sleep efficacy. This has been posited as a rationale for exogenous melatonin therapy in some sleep disorders. However, the putative age-related fall in melatonin secretion has not been confirmed in all studies.[9-10]

Recent studies suggest that administration of exogenous melatonin over a relatively short time frame to older otherwise well subjects with primary insomnia promotes improved sleep.[11-12] There have been no head-to-head comparative studies of melatonin versus other commonly used hypnotics. In some but not all clinical studies, varying dosages of exogenous melatonin have been shown to improve sleep latency in a modest fashion in different experimental and clinical scenarios,[13,14] and there does not seem to be an important dose–response relation in the range of 0.5 to 10 mg.[15-17] In addition to its modest effect on sleep latency, exogenous melatonin consolidates sleep in a way that manifests as improved sleep quality and morning alertness.[12,18]

A meta-analysis has shown quite modest improvements with melatonin treatment in sleep efficiency (3.1%) and total sleep duration (13.7 minutes) compared with placebo.[19] No data has attributed daytime impairment or withdrawal effects to oral exogenous melatonin.

What are its approved indications in Australia?

On the basis of the above published data, melatonin (Circadin) as a 2 mg prolonged-release tablet has been approved for the short-term monotherapy of primary insomnia characterised by poor quality of sleep in patients aged 55 years or older. As melatonin is a prolonged-release formulation, the tablet should be swallowed whole and taken one to two hours before planned bedtime. Concurrent food consumption delays absorption therefore melatonin should not be taken with food.

What are the precautions, interactions and side effects?

Melatonin has a high first-pass metabolism (approximately 85%) and is metabolised in the liver via the CYP1A enzyme system. Its use in patients with liver impairment has not been studied therefore it should not be used in patients with significant liver impairment. Its inactive metabolite 6-sulfatoxymelatonin is excreted in the urine. Various other medications also interact with the CYP1A enzyme system so some caution is advised when coadministration is contemplated (see the full product information). Generally, however, exogenous melatonin is well tolerated across a wide dose range.

Alcohol taken at the same time as melatonin should be avoided because it may interfere with the prolonged-release characteristics of the tablet and reduce effectiveness. Coadministration of other hypnotics is best avoided. Other psychotropic drugs (e.g. fluvoxamine, thioridazine and imipramine) may also interact unfavourably with oral melatonin.

Melatonin is found in breast milk and its safety as an exogenous agent in human pregnancy is unknown, therefore melatonin should be avoided in these situations (however, this is an unlikely scenario in a woman over 55 years of age). Driving and operating heavy machinery should be avoided for an appropriate time after taking melatonin.

The risks of protracted use of exogenous melatonin are unknown but no obvious public health risks have been identified to date. Some commercial sources of melatonin have in the past been reported as containing iodine contaminants at low levels, but this concern is presumed not to apply to Circadin.

The overall level of side effects with melatonin treatment during short-term use is low and comparable with placebo. Headache has been noted (but also reported with placebo). There is limited evidence for caution using oral melatonin in some patients with hypertension.[20]

PSYCHOLOGICAL THERAPY FOR INSOMNIA

Generally, nondrug therapies should be the first consideration for primary insomnia. One such modality for the treatment of chronic insomnia is psychological therapy, particularly cognitive behavioural therapy, which may impart more long-term benefits than pharmaceutical aids can provide.[22] There are at present, however, practical difficulties in providing timely adequate delivery of psychology-based insomnia therapies to the perceived needs of large communities.

CONCLUSION

Oral melatonin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients aged 55 years or older. It may have a useful role in those older patients with insomnia in whom sedating hypnotics are better avoided. Although not approved for this indication at this time in Australia, a recent industry-sponsored clinical trial has shown safety and efficacy for longer periods of treatment (six months) with melatonin.[21] MT

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A list of references is available on request to the editorial office.

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