

Ramelteon

A Viewpoint by Göran Hajak

Department of Psychiatry, Psychosomatics and Psychotherapy, University of Regensburg, Regensburg, Germany

Physicians and experts dealing with the problem of disturbed sleep have recently woken up from a period of sleep that had lasted for years. Over a period of two decades, pharmacotherapy of insomnia was dominated by the use of pharmacological agents acting at benzodiazepine receptor sites in the human brain. These benzodiazepines and modern benzodiazepine receptor agonists, such as zolpidem, zaleplon and zopiclone, as well as old fashioned over-the-counter products of heterogeneous pharmacology (e.g. antihistamines, herbal drugs), were approved by health authorities for the treatment of insomnia. Additionally, physicians prescribed antidepressants (e.g. trazodone, doxepin) or antipsychotics (e.g. olanzapine, quetiapine) for off-label use as sleep-promoting agents.

In the last few months, there has been remarkable change in the area of insomnia treatment. Ramelteon, a selective melatonin MT_1/MT_2 receptor agonist was approved in the US for the treatment of insomnia characterised by difficulty with sleep onset. For the first time, a drug is now available by prescription that is believed to mediate circadian biological functions, which are part of the sleep regulation process. The pharmacodynamic profile of ramelteon suggests an influence on components of the internal clock, specifically by binding to receptors in the

central nervous suprachiasmatic nucleus. By not having significant binding affinities for MT_3 and other receptors in the mammalian brain, ramelteon promises a favourable adverse event profile. In fact, a series of studies showed ramelteon to significantly improve most relevant sleep parameters in patients with chronic insomnia, with an incidence of adverse events similar to that of placebo.

Will this change the treatment of patients with insomnia in daily practice? Yes, if the unique pharmacology of ramelteon will address patients' needs. Probable absence of abuse potential, lack of cognitive impairment, and no negative effects on muscle tone and respiratory functions are promising advantages in a market that increasingly monitors adverse events of newly developed drugs.

However, some questions remain, which the available data in the public domain do not answer. The vast majority of patients with insomnia are chronically ill and suffer from difficulties in initiating and maintaining sleep that persist over months or years. While ramelteon has been shown to significantly improve sleep onset during short-term treatment up to 5 weeks, its effect on sleep maintenance was inconsistent and data on long-term treatment are missing. This suggests that clinical practice rather than present scientific data will show whether this melatonin MT_1/MT_2 agonist is different from prescribed benzodiazepine receptor agonist hypnotics or melatonin products that are available as over-the-counter hypnotics or nutrition supplements. ▲