



MELATONIN REVISITED

by Frank Roman MD JD

It is a very exciting time to be in sleep medicine as our field grows exponentially both in scientific knowledge and practitioners. In the last few years there has been an increase in the type and number of medications available to treat specific sleep disorders including insomnia. The latest compound to enter the marketplace is Rozerem, a melatonin agonist receptor. In years past our choices of medications were very limited. Case in point, one day while window shopping at Ethan Allen with the intent of looking at what was in style only to later buy the knockoffs in a discount furniture outlet, I found a book on display in one of their fancy bookcases: *Pharmacology of Sleep*, Robert L. Williams and Ismet Karacan, Editors, from 1976. To make a long story short, I ended up buying a bookcase to get what I really wanted, the book. As far I could tell from a cursory inspection there was no mention of melatonin let alone melatonin agonist receptor compounds over thirty years ago. The medications mentioned prominently in 1976 included among others, Flurazepam, triazolam, chloral hydrate, amylobarbitone, methaqualone, glutethimide, pentobarbital, methypylone, secobarbital, tryptophan, meprobamate, and the old standby, diphenhydramine.

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Legend has it that approximately 40 years ago a dermatologist, Dr. Aaron Lerner, isolated and identified a substance from the bovine pineal gland which he named melatonin. Dr. Lerner had a special interest in vitiligo, the skin

pigmentation disease. In an effort to alter the skin pigmentation in his patients he administered this newly discovered endogenous substance. One prominent side effect from this trial was the subjective sleepiness reported by many of his patients.

Melatonin is a methoxyindole synthesized by the pineal gland at night under normal environmental conditions. It is the main hormone secreted by the pineal gland. However there are secondary sources of melatonin in the retina, gut, skin, platelets, and bone marrow. The melatonin is synthesized from tryptophan taken up from the circulation, which is then transformed to serotonin. The serotonin in turn is converted into melatonin by a two-step process. In general, melatonin plasma levels are high in mammals during darkness at night and low during the day. Even when time cues are removed from the environment and light is maintained dim, melatonin continues to express its circadian rhythm. Light exposure during the night can acutely suppress melatonin levels. On the other hand, darkness does not stimulate melatonin.

Melatonin has been shown to phase-shift and entrain the circadian timing system in a variety of species. There is also some evi-

dence that melatonin stabilizes and strengthens coupling of circadian rhythms; especially of core temperature and sleep wake rhythms. Melatonin reinforces the nocturnal decrease in core temperature, which in turn facilitates sleep propensity.

What one may not be aware of is that melatonin is also a potent free radical scavenger; more potent than vitamin E. Melatonin directly scavenges the highly toxic hydroxyl radical and other oxygen centered radicals. Preliminary data in one study showed decreased nocturnal plasma melatonin in patients with coronary heart disease. It was speculated in the study that the presence of melatonin as an antioxidant could be beneficial to prevent the adverse effects during myocardial ischemic perfusion. Melatonin may also be involved in the control of the circadian rhythm of blood pressure. Another preliminary study showed that nocturnal melatonin secretion is impaired in non-dipper hypertensive patients and daily nighttime administration of melatonin for three weeks in patients with essential hypertension reduced blood pressure without alteration of the heart rate.

Other patient subsets where melatonin is of interest include (1) the blind, where the use of melatonin improved sleep in blind patients suffering from non 24 hour sleep wake schedule, (2) the elderly due to the decline in melatonin production where some studies have demonstrated melatonin to improve both subjective and objective sleep parameters with doses ranging from 0.5 to 6 mgs. taken nightly and (3) Delayed Sleep Phase Syndrome which is a very prevalent sleep disorder in the younger population and most of the time under recognized and or poorly addressed.

Preliminary data on children suffering from severe insomnia secondary to multiple neurological disorders showed that administration of pharmacological melatonin doses would substantially improve their sleep patterns and increase sleep duration. Moreover, children with normal development but struggling with chronic insomnia also demonstrated increased total sleep time after receiving melatonin. The data also suggests that children are more sensitive to the effects of melatonin than the elderly. This could be a result of increased functional sensitivity of melatonin receptors at younger ages and or their higher density. Maternal melatonin can cross the placenta and may be one of the maternal rhythmic signals synchronizing the fetal biological clock. Breast milk containing melatonin could take over the synchronization in the newborn. Rhythmic melatonin production reaches the highest level at the age of 3-6 years. Nocturnal peaks in melatonin drops progressively by 80% until reaching adult levels.

Despite these positives regarding melatonin, there are some areas of concern. Most important is the lack of FDA regulation,

The Old Hag... Continued from page 40

native" experience the problem more than others or why some of us don't experience it at all. However, there are theories and hypotheses being put forward. One author, Florence Cardinal in her book "The Terror of Sleep Paralysis" writes: "Episodes of paralysis can occur when the body is in any position, but happen most frequently when the sleeper is lying flat on his or her back." So here is another clue that the disorder and the Old Hag may be related to sleep apnea. As all sleep specialists and techs know REM supine is the most likely position and sleep state that favors greater oxygen desaturations respiratory event counts. Cardinal goes on to say: "Intense fear is common, but sometimes other strong emotions such as sadness or anger are present." Lack of restful sleep associated with OSA often causes such emotions including stress, irritability, inability to focus and depression. Sleep paralysis (SP) also occurs in individuals who don't get enough sleep or folks that have disruptive sleep schedules and circadian rhythm disorders. And it may be no coincidence it also shows up more frequently in those with severe anxiety or bipolar disorder.

Researchers have discovered that statistically SP is five times more likely to occur in those who are prescribed anti-anxiety or anti-depressants such as Xanax or Valium. Another clue, as these drugs may also make some more prone to OSAHS. Another study found that 35% of the subjects with identifiable isolated SP report a history of panic attacks while awake.

So does the available evidence such as it is, weigh in favor of adding the Old Hag to the symptoms that suggest the possibility of OSAHS? It would seem that way.

Melatonin Revisited... Continued from previous page

the lack of safety data regarding long term use, the lack of knowledge regarding potential drug to drug interactions, and more importantly evidence based research regarding the best dose, formulation, timing, and duration of treatment using melatonin.

In October 2005, Rozerem (ramelteon) was approved by the FDA as the first and only non-scheduled prescription medication for insomnia. At this time it is important that the author declare a potential conflict of interest as a member of the Speakers Bureau for Takeda Pharmaceuticals. Rozerem is different than the benzodiazepines and non-benzodiazepines hypnotic agents that we have become accustomed to. Rozerem is a unique molecule with high selectivity for the MT1/MT2 receptors in the suprachiasmatic nucleus. It is FDA approved for sleep onset insomnia. Compared to melatonin, Rozerem has an approximately 3-5 time times greater affinity for human MT1/MT2 receptors and is up to 17 times more potent. In vitro studies, Rozerem demonstrated no significant ligand binding to GABA receptor complex, dopamine, serotonin, acetylcholine, glutamate, noradrenaline, cytokines, or opiates. Of special interest is Rozerem is not expected to exhibit rebound insomnia, memory impairment, respiratory depression, drug abuse, dependence, and withdrawal as by some of the benzodiazepine receptor agonists.

Research still is required in this area. Space constraints limit the amount of meaningful analysis of this topic. The reader is strongly encouraged to investigate further and formulate his or her own conclusions regarding this treatment modality.

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