20 - 29.20 Melatonin Agonists Ramelteon and Melato

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consensus and controversies. Bipolar Disord. 2005;7:5. 29.20 Melatonin Agonists: Ramelteon and Melatonin There are two melatonin receptor agonists commercially available in the United States: (1) melatonin, a dietary supplement available in various preparations in health food stores, and not under Food and Drug Administration (FDA) regulations; (2) and ramelteon (Rozerem), an FDA-approved drug for the treatment of insomnia characterized by difficulties with sleep onset. Both exogenous melatonin and ramelteon are thought to exert their effects by interaction with central melatonin receptors. RAMELTEON Ramelteon (Rozerem) is a melatonin receptor agonist used to treat sleep-onset insomnia. Unlike the benzodiazepines, ramelteon has no appreciable affinity for the γaminobutyric acid (GABA) receptor complex.

Pharmacological Actions Ramelteon essentially mimics melatonin's sleep-promoting properties and has high affinity for melatonin MT1 and MT2 receptors in the brain. These receptors are thought to be critical in the regulation of the body's sleep–wake cycle. Ramelteon is rapidly absorbed and eliminated over a dose range of 4 to 64 mg. Maximum plasma concentration (Cmax) is reached approximately 45 minutes after administration, and the elimination half-life is 1 to 2.6 hours. The total absorption of ramelteon is at least 84%, but extensive first-pass metabolism results in a bioavailability of approximately 2%. Ramelteon is metabolized primarily through the cytochrome P450 (CYP)1A2 pathway and eliminated principally in urine. Repeated once-daily dosing does not appear to result in accumulation, likely because of the compound's short halflife. Therapeutic Indications Ramelteon was approved by the FDA for the treatment of insomnia characterized by difficulty with sleep onset. Potential off-label use is centered on application in circadian rhythm disorders, predominantly jet lag, delayed sleep phase syndrome, and shift work sleep disorder. Clinical trials and animal studies have failed to demonstrate evidence of rebound insomnia of withdrawal effects. Precautions and Adverse Events Headache is the most common side effect of ramelteon. Other adverse effects may include somnolence, fatigue, dizziness, worsening insomnia, depression, nausea, and diarrhea. The drug should not be used in patients with severe hepatic impairment. It is also not recommended in patients with severe sleep apnea or severe chronic obstructive pulmonary disease. Prolactin levels may be increased in women. The drug should be used with caution, if at all, in nursing mothers and pregnant women. Ramelteon has been found to sometimes decrease blood cortisol and testosterone and to increase prolactin. Female patients should be monitored for cessation of menses and of galactorrhea, decreased libido, and fertility problems. The safety and effectiveness of ramelteon in children has not been established. Drug Interactions CYP1A2 is the major isozyme involved in the hepatic metabolism of ramelteon. Accordingly, fluvoxamine (Luvox) and other CYP1A2 inhibitors may increase side effects of ramelteon. Ramelteon should be administered with caution in patients taking CYP1A2 inhibitors, strong CYP3A4 inhibitors such as ketoconazole, and strong CYP2C inhibitors such as fluconazole (Diflucan). No clinically meaningful interactions were found when

ramelteon was coadministered with omeprazole, theophylline, dextromethorphan, midazolam, digoxin, and warfarin. Dosing and Clinical Guidelines The usual dose of ramelteon is 8 mg within 30 minutes of going to bed. It should not be taken with or immediately after high-fat meals. MELATONIN Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced mainly at night in the pineal gland. Ingested melatonin can reach and bind to melatonin-binding sites in the brains of mammals, and produce somnolence when used at high doses. Melatonin is available as a dietary supplement and is not a medication. Few well-controlled clinical trials have been conducted to determine its effectiveness in treating such conditions as insomnia, jet lag, and sleep disturbances

related to shift work. Pharmacological Actions Melatonin’s secretion is stimulated by the dark and inhibited by the light. It is naturally synthesized from the amino acid tryptophan, which is converted to serotonin and finally converted to melatonin. The suprachiasmatic nuclei (SCN) of the hypothalamus have melatonin receptors, and melatonin may have a direct action on SCN to influence circadian rhythms, which are relevant for jet lag and sleep disturbances. In addition to the pineal gland, melatonin is also produced in the retina and gastrointestinal tract. Melatonin has a very short half-life of 0.5 to 6 minutes. Plasma concentrations are a function of the dose administered and the endogenous rhythm. Approximately 90 percent of melatonin is cleared through first-pass metabolism by way of the CYP1A1 and CYP1A2 pathways. Elimination occurs principally in urine. Exogenous melatonin interacts with the melatonin receptors that suppress neuronal firing and promote sleep. There does not appear to be a dose–response relationship between exogenous melatonin administrations and sleep effects. Therapeutic Indications Melatonin is not regulated by the FDA. Individuals have used exogenous melatonin to address sleep difficulties (insomnia, circadian rhythm disorders), cancer (breast, prostate, colorectal), seizures, depression, anxiety, and seasonal affective disorder. Some studies suggest that exogenous melatonin may have some antioxidant effects and antiaging properties. Precautions and Adverse Reactions Adverse events associated with melatonin include fatigue, dizziness, headache, irritability, and somnolence. Disorientation, confusion, sleepwalking, vivid dreams, and

nightmares have also been observed, often with effects resolving after melatonin administration was suspended. Melatonin may reduce fertility in both men and women. In men, exogenous melatonin reduces sperm motility, and long-term administration has been shown to inhibit testicular aromatase levels. In women, exogenous melatonin may inhibit ovarian function and for that reason it has been evaluated as a contraceptive, but with inconclusive results. Drug Interactions As a dietary supplement preparation, exogenous melatonin is not regulated by the FDA and has not been subjected to the same type of drug interaction studies that were performed for ramelteon. Caution is suggested in coadministering melatonin with blood thinners (e.g., warfarin [Coumadin], aspirin, and heparin), antiseizure medications, and medications that lower blood pressure. Laboratory Interference Melatonin is not known to interfere with any commonly used clinical laboratory tests. Dosage and Administration Over-the-counter melatonin is available in the following formulations: 1, 2.5, 3, and 5 mg capsules; 1 mg/4 mL liquid; 0.5 and 3 mg lozenges; 2.5 mg sublingual tablets; and 1, 2, and 3 mg timed-release tablets. Standard recommendations are to take the desired melatonin dose at bedtime, but some evidence from clinical trials suggests that dosing up to 2 hours before habitual bedtime may produce greater improvement in sleep onset. Agomelatine (Valdoxan) Agomelatine is structurally related to melatonin and is used in Europe as a treatment for major depressive disorder. It acts as an agonist at melatonin (MT1 and MT2) receptors. It also acts as a serotonin antagonist. Analysis of agomelatine clinical trial data raised serious questions about the efficacy and safety of the drug. The drug is not being marketed in the United States. REFERENCES Calvo JR, Gonzalez-Yanes C, Maldonado M. The role of melatonin in the cells of the innate immunity: A review. J Pineal Res. 2013;55(2):103–120. Scharf MB, Lankford A. Melatonin receptor agonists: Ramelteon and melatonin. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3145. Srinivasan V, Ohta Y, Espino J, A Pariente J, B Rodriguez A, Mohamed M, Zakaria R. Metabolic syndrome, its

Revision #1
Created 2026-01-04 19:51:48 UTC by Omar Ayman

Updated 2026-01-04 19:51:48 UTC by Omar Ayman