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Ramelteon and It's use in Treatment of Insomnia: A Systematic Review

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ABSTRACT :

Ramelteon is a tricyclic synthetic analogue of melatonin that acts in particular on the MT1 and MT2 melatonin receptors. Ramelteon is the first melatonin receptor agonist approved by the Food and Drug Administration (FDA) to treat insomnia, characterized by difficulties at onset of sleep. Ramelteon is both chronobiotic and hypnotized, and has been shown to promote sleep initiation and calculation in variety of preclinical and clinical studies. The efficacy and security of ramelteon in patients with chronic insomnia was first confirmed in a short-term placebo-controlled study. These showed little evidence of residual effects, withdrawal symptoms, or rebound insomnia for the next day. Other studies have shown that ramelteon has no potential for abuse and has, minimal risk of creating dependency or adverse effects on cognitive or psychomotor performance. A 6-month placebo-controlled international study and one-year open label study in the US showed that ramelteon is effective and well tolerated.

Keywords: insomnia, melatonin receptors, ramelteon

INTRODUCTION

Insomnia is a frequent disorder defined as difficult to start or maintain sleep, or an experience of intolerant sleep, leading to a clinically significant burden or impairment of social, professional, or other important functional areas. Insomnia affects approximately 30 to 35% of general population, with an estimated 10% suffering from chronic insomnia. Insomnia is an important health problem that requires treatment, as its high prevalence and potentially unwanted outcomes related to daily function productivity and quality of life. In 2005, he received FDA approval for the treatment of insomnia, characterized by difficult in inserting sleep, and is in the United States in development of phases 2 for the treatment of circadian rhythm sleep disorders. The elderly are generally the largest consumers of OTC drugs. Changes in pharmacodynamics and pharmacokinetics with increased polypharmacy and increased age make older people more susceptible to side effects from OTC drugs consumption. Therefore, approaches to treating insomnia in older adults should be carefully assessed in relation to possible unwanted effects, cognitive impairment, psychomotor disorder, and potential for abuse and tolerance. Ramelteon is selective MT1/MT2 receptor agonist approved for the treatment of insomnia. MT1 and MT2 receptor are strongly focused on the brain's hyperliteracy nuclei (SCN) and are intended to assist in the regulation of normal sleep-wake cycles and other functions regulated by circadians. Due to its effects on SCN, ramelteon is sometimes called a chromosomal or chronosolid agent.

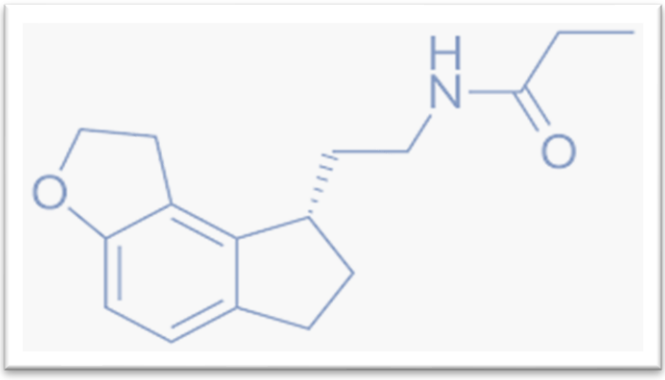

Fig 01 – Structure of Ramelteon

Clinical Trials of Ramelteon

In a clinical study with 107 patients with insomnia (mean age 37.7 years), ramelteon was administered at various doses ranging from 4 mg to 32 mg. Drug therapy was received 30 minutes before habitual sleep were monitored at 8-hour polygon. Ramelteon significantly reduced sleep decline for 13 minutes and increased overall sleep duration by 12 minutes at all doses. The next day, no remaining hangover effects were found. Similar results were also conserved in a large study in which 375 patients, age 35 years old, were given 16 mg or 64 mg of ramelteon daily. Sleep stats were reduced by 9 to

10 minutes, and total sleep time increased by 11 and 14 minutes. Higher doses did not lead to greater improvement. No withdrawal effect or rebound insomnia was found.

In a randomized, double-blind placebo-controlled study in which 829 elderly patients with insomnia (341 men and 488 women, age 64 to 93) received a ramelteon N dose of either 4 mg or 8 mg for 5 weeks, patients reported a decrease in sleep lenses and an increase in overall sleep duration. Ramelteon led to a drop of about 13 minutes on the sleeper landing. This effect was demonstrated from the first week and became increasingly pronounced until the fifth week. These results were similar for both ramelteon administration regimes. Overall sleep duration for older insomnia was greater than overall sleep duration for control personnel. However, increasing the dose from 4 mg to 8 mg did not significantly increase sleep duration.

EFFICACY FOR TRANSIENT INSOMNIA

Two clinical studies examined the effectiveness of ramelteon in the treatment of temporary insomnia, a temporary sleep disorder that often occurs in unknown settings such as sleep rooms. These studies used (First Night Effect). This is phenomenon that usually makes it more difficult for an individual to maintain sleep in their new environment.

In the first attempt, Roth et al. (2005) administered 375 healthy subjects at doses of 16 and 64 mg, in addition to placebos that did not report existing sleep problems. Polysomnographic records, which provide detailed measurement of sleep architecture, showed that both ramelteon doses significantly reduced latency, relying on sustained sleep (times drawn and fell asleep), significantly reducing overall sleep time compared to placebo. Interestingly, the similarity of sleep latin between doses of 16 and 64 mg indicates a flat dose-effect curve.

Zammit et al. (2005) compared ramelteons to 8 and 16 mg doses and placebo in relation to 289 healthy subjects. According to previous studies, polysomography data showed that both ramelteons significantly reduced sleep waiting times and prolonged overall sleep duration compared to the placebo group. In particular, subjects receiving 8 mg doses of ramelteon experienced a moderate delay due to ongoing sleep of 12.2 minutes, compared to 19.7 minutes in the placebo group. These results jointly show that ramelteon effectively considers temporary insomnia by promoting faster sleep and prolonging sleep time even at relatively low dosses.

EFFICACY FOR CHRONIC INSOMNIA

This section describes several studies that investigate the effectiveness of ramelteon in treatment of chronic insomnia in adults and elderly people.

- **Effectiveness in adult**

Ramelteon has the ability to shorten the time to sleep (sleeping slats) and significantly increase the total duration of sleep compared to placebo. This effect has been observed in several studies the enhance its reliability. Interestingly, the researches discovered a flat dose-effect curve. In other words, increasing the dose of ramelteon dose does not necessarily increase the benefits of sleep in proportion. This indicate that lower doses are just as effective as higher doses.

Additionally, participants persecuted ramelteon for up to 12 months to maintain a positive on sleep duration and overall sleep duration for up to 12 months. This indicate that this drug is still effective for long-term use.

Critical, after stopping ramelteon, participants did not experience rebound insomnia. This is great advantage over other sleeping pills.

- **Effectiveness in elderly**

Ramelteon has been found to be equally effective in the elderly, significantly improving both the sleep lens and overall sleep duration.

Both 4 mg and 8 mg doses of ramelteon showed positive results in older adults, providing flexibility in the dose.

SAFETY AND ADVERSE EFFECTS OF RAMELTEON

Ramelteon generally have a preferred security profile, especially for short-term use. This will reflect unwanted events as placebo events. Avoid the most common problems such as addiction, withdrawal, and rebound insomnia observed in other hypnosis. Research has confirmed its effectiveness and security profile, even for long-term use for up to one year with improved sustainable sleep. Several toxicity studies have shown that there is a risk of potential mutations and carcinogenicity, particular with regard to M-II metabolites.

CONCLUSION

This summarize ramelteon's potential as a safe and effective hypnotic for chronic primary insomnia, based on preclinical and clinical studies.

Key points include:

- **Efficacy:**

Ramelteon consistently reduces sleep onset latency and increases total sleep time (TST) in clinical trials.

- **Safety:**

The incidence of adverse effects is similar to that of a placebo.

No evidence of physical dependence or abuse liability has been reported.

Minimal adverse effects on learning, memory, and motor coordination.

Minimal rebound or withdrawal effects.

- **Mechanism:**

Its hypnotic and chronobiotic effects are attributed to its action on G protein-coupled melatonergic receptors in the suprachiasmatic nucleus (SCN).

- **Potential Beyond Insomnia:**

Ramelteon's ability to promote phase advances in sleep/wake rhythms suggests potential therapeutic value for circadian rhythm sleep disorders (C

REFERENCES

1. Primary insomnia. In: Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, DC: American Psychiatric Association, 2000:599-604.
2. Silber MH. Chronic insomnia. N Engl J Med 2005; 353:803-10.
3. Prescribing information. Rozerem (ramelteon). Deerfield, IL: Takeda Pharmaceuticals America, Inc., April 2006.
4. Ramelteon (TAK 375). Drugs R D 2005; 6:186-8.
5. 5.Dubocovich ML, Yun K, Ghoul WM, et al. Selective MT2 melatonin receptor antagonists block melatonin-mediated phase advances of circadian rhythms. Fed Am Soc Exp Biol J 1998; 12:1211–20
6. 6.Roth T, Seiden D, Weigand S, et al. Phase III study to determine the efficacy of ramelteon in elderly patients with chronic insomnia [abstract]. Proceedings of new clinical drug evaluation unit; June 6–9, 2005, Boca Raton, FL. Available from: http://www.nimh.nih.gov/ncdeu/index.cfm. Accessed, 10-20-2005
7. 7.Erman M et al. (2006) An efficacy, safety, and dose response study of ramelteon in patients with chronic primary insomnia. Sleep Med 7: 17–24
8. 8. Roth T, Stubbs C, Walsh JK. 2005. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. Sleep, 28:303–7.
9. 9. Roth T, Seiden D, Sainati S, et al. 2006. Effects of ramelteon on patient reported sleep latency in older adults with chronic insomnia. Sleep Med, 7:312–18.
10. 10. Zammit G, Erman M, Wang-Weigand S, et al. 2007. Evaluation of the efficacy, and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med, 3:495–504.
11. 11. DeMicco M, Wang-Weigand S, Zhang J. 2006. Long-term therapeutic effects of ramelteon treatment in adults with chronic insomnia: A 1-year study. Sleep, 29(Abstract Suppl): A234
12. 12. Erman M, Seiden D, Zammit G, et al. 2006. An efficacy, safety, and dose response study of ramelteon in patients with chronic primary insomnia. Sleep Med, 7:17–24.
13. 13. Richardson GS, Wang-Weigand S, Zhang J, et al. 2006a. Long-term safety of ramelteon treatment in adults with chronic insomnia: A 1-year study. Sleep, 29(Abstract Suppl): A233
14. 14. Wang-Weigand S, Mayer G, Roth-Schechter B. 2007. Long-term efficacy, and safety of ramelteon 8 mg treatment in adults with chronic insomnia: results of a six-month, double-blind, placebo-controlled, polysomnography trial. Sleep Biol Rhythms, 5(Suppl 1): A156. Abstract PO525.