Ramelteon

A Novel Hypnotic Lacking Abuse Liability and Sedative Adverse Effects

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Context: Ramelteon is a novel MT₁ and MT₂ melatonin receptor selective agonist recently approved for insomnia treatment. Most approved insomnia medications have potential for abuse and cause motor and cognitive impairment.

Objective: To evaluate the potential for abuse, subjective effects, and motor and cognitive–impairing effects of ramelteon compared with triazolam, a classic benzodiazepine sedative-hypnotic drug.

Design: In this double-blind crossover study, each participant received oral doses of ramelteon (16, 80, or 160 mg), triazolam (0.25, 0.5, or 0.75 mg), and placebo during approximately 18 days. All participants received each treatment on different days. Most outcome measures were assessed at 0.5 hours before drug administration and repeatedly up to 24 hours after drug administration.

Setting: Residential research facility.

Participants: Fourteen adults with histories of sedative abuse.

Main Outcome Measures: Subject-rated measures included items relevant to potential for abuse (eg, drug liking, street value, and pharmacological classification), as well as assessments of a broad range of stimulant and sedative subjective effects. Observer-rated measures included assessments of sedation and impairment. Motor and cognitive performance measures included psychomotor and memory tasks and a standing balance task.

Results: Compared with placebo, ramelteon (16, 80, and 160 mg) showed no significant effect on any of the subjective effect measures, including those related to potential for abuse. In the pharmacological classification, 79% (11/14) of subjects identified the highest dose of ramelteon as placebo. Similarly, compared with placebo, ramelteon had no effect at any dose on any observer-rated or motor and cognitive performance measure. In contrast, triazolam showed dose-related effects on a wide range of subject-rated, observer-rated, and motor and cognitive performance measures, consistent with its profile as a sedative drug with abuse liability.

Conclusion: Ramelteon demonstrated no significant effects indicative of potential for abuse or motor and cognitive impairment at up to 20 times the recommended therapeutic dose and may represent a useful alternative to existing insomnia medications.

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Insomnia is the inability to fall or remain asleep or the experience of nonrestorative sleep, resulting in clinically significant distress or adverse consequences on daytime functioning.¹ This disorder is prevalent, with 10% to 15% of adults having chronic insomnia and another 25% to 35% experiencing occasional insomnia.²³ The most common pharmacological agents used in the treatment of insomnia are γ-aminobutyric acid type A (GABA_A) modulators acting at the benzodiazepine recognition site (ie, benzodiazepine receptor agonists) (eg, zolpidem tartrate, eszopiclone, temazepam, and triazolam).⁴⁵ These compounds produce several problematic effects that increase the risk of inappropriate use and restrict the populations in which they may be safely prescribed.⁶ First, benzodiazepine receptor agonists are known to be used nonmedically (ie, abused), particularly by individuals with a history of substance abuse.⁶⁻⁸ Second, these compounds can engender cognitive impairments, most prominently anterograde amnesia.¹⁰⁻¹⁴ Third, these agents can produce motor impairments (eg, poor driving performance¹⁵,¹⁶ and falls in older persons¹⁷,¹⁸). Fourth, benzodiazepine receptor agonists can produce a withdrawal syndrome on discontinuation of long-term use of therapeutically or higher doses.⁸,¹⁵,¹⁹ Withdrawal symptoms include rebound insomnia, anxiety, irritability, headache, gastrointestinal disturbance, depersonalization, perceptual changes, and, in severe cases, seizures and delirium.⁹ Pharmacological agents without such problematic effects

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could provide a valuable alternative for the treatment of insomnia.

Because of concern about abuse, dependence, and withdrawal, physicians are frequently discouraged from prescribing benzodiazepine receptor agonists to patients with a history of substance abuse or dependence.28-32 The 2005 Physicians’ Desk Reference, for example, provides the following caution to physicians when prescribing the benzodiazepine receptor agonist zolpidem: “Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or any [italics added] other hypnotic.”28(p892) Compliance with such recommendations is difficult considering that 46% of the US population reports some use of illicit drugs during their lifetimes and 9% meet criteria for past-year abuse of or dependence on any illicit drug or alcohol.23 Furthermore, patients may not disclose such histories of nonmedical use.

Ramelteon, an agent recently approved for the treatment of insomnia characterized by difficulty with sleep onset, is a novel MT1 and MT2 melatonin receptor selective agonist and has minimal affinity for other sites implicated in potential for abuse and impairment, such as benzodiazepine receptors, dopamine receptors, opiate receptors, ion channels, and various receptor transporters.24 The MT1 and MT2 receptors are located in the suprachiasmatic nucleus of the hypothalamus and are involved in maintaining the circadian sleep-wake cycle.25 In double-blind studies26-28 analyzing doses from 4 to 64 mg, ramelteon was efficacious in reducing latency to persistent sleep and, although less consistently, in increasing total sleep time in individuals with and without chronic insomnia.

Evidence to date suggests that ramelteon administration may lack several of the problematic effects associated with benzodiazepine receptor agonists used in treating insomnia. In preclinical studies of rhesus monkeys, ramelteon was found to have no reinforcing effect in an intravenous drug self-administration procedure,29 was similar to the vehicle in a benzodiazepine vs vehicle drug discrimination procedure,30 and showed no evidence of withdrawal symptoms during intermittent abstinence periods throughout 1 year of administration.31 In clinical trials in subjects with chronic insomnia, ramelteon treatment was not associated with rebound insomnia or with withdrawal symptoms after 5 weeks of treatment.27,29 Furthermore, in studies26,28 of subjects with and without chronic insomnia, ramelteon did not produce cognitive or memory impairment when assessed about 9 hours after administration.

The potential for abuse and motor- and cognitive-impairing effects of ramelteon at supratherapeutic doses has not been evaluated in humans. The present study used well-developed methods for assessing potential for abuse and impairing effects of novel agents at supratherapeutic doses in persons with histories of substance abuse.31 Specifically, subjects who abused sedative drugs were studied using a double-blind, placebo-controlled, dose-effect, crossover design, with triazolam as a positive control.
Five tablets, 3 capsules, and 180 mL of solution were administered in each experimental session. Drugs and placebos were identical in appearance and were supplied by Takeda Pharmaceuticals North America, Lincolnshire, Ill. Ramelteon was supplied as 0.25-mg of triazolam each. Placebo capsules contained microcrystalline cellulose. Alprazolam (1 mg/mL) (manufactured by Roxane Laboratories, Inc, Columbus, Ohio) was supplied in capsules as colorless, oral solution. Cherry-flavored water was added to the alprazolam solution. The placebo solution was cherry-flavored water.

Except as indicated herein, subject-rated, observer-rated, and motor and cognitive performance measures were assessed at 0.5 hours before drug administration and at 1, 2, 3, 4, 6, 8, 12, and 24 hours after drug administration. Subject-rated and observer-rated measures were also obtained at 0.5 hours after drug administration. The following measures were assessed at a single time point after drug administration: Addiction Research Center Inventory, Word Recall and Recognition Task, Next-Day Questionnaire, and Drug vs Money Choice Procedure.

SUBJECT-RATED AND OBSERVER-RATED MEASURES

Unless otherwise stated, all questionnaires regarding subject-rated and observer-rated measures were administered on a desktop computer. The subject or staff member used a computer mouse to point to and select one of the various response options displayed on the screen.

Subjective Effect Questionnaire

and Pharmacological Class Questionnaire

The Subjective Effect Questionnaire consisted of 2 parts. The first part asked subjects to rate their present level of alertness or sleepiness on a visual analog scale. The second part asked subjects to rate 34 subjective effect items using a 5-point scale. The Pharmacological Class Questionnaire asked subjects to categorize the drug effect as being most similar to 1 of 14 classes of psychoactive drugs.

Next-Day Questionnaire

The 7-item Next-Day Questionnaire, completed approximately 24 hours after drug administration, asked subjects to rate the overall effects of yesterday's drug. One item was a pharmacological class question similar to the Pharmacological Class Questionnaire.

Drug Effect Questionnaire

and Addiction Research Center Inventory

The Drug Effect Questionnaire asked subjects to rate drug strength on a 5-point scale and drug liking on a 9-point bidirectional scale. The Addiction Research Center Inventory (short form) questionnaire, completed 2 hours after drug administration, asked subjects 49 true-or-false questions and resulted in 5 scales of drug effects.

Drug vs Money Choice Procedure

and Observer-Rated Questionnaire

The Drug vs Money Choice Procedure, a contingency-based paper questionnaire, assessed the monetary value of each drug condition. The Observer-Rated Questionnaire asked a trained research staff member to rate 7 aspects of a subject's gross behavior on a 5-point scale. The observer also estimated the number of minutes the subject slept during the past hour. The research staff member making the rating generally observed the subject for the entire time frame being rated, although for brief periods the participant was not observed.

MOTOR AND COGNITIVE PERFORMANCE MEASURES

Digit Symbol Substitution Test, Balance Task, and Circular Lights Task

A computerized version of the Digit Symbol Substitution Test (DSST) assessed subjects' ability to use a numeric keypad to enter a geometric pattern associated with 1 of 9 digits displayed on a video screen. The Balance Task, a motor task, assessed subjects' ability to stand upright on 1 foot with the eyes closed and arms extended to the side at shoulder height. The Circular Lights Task, a motor task, assessed subjects' ability to make hand-eye coordinated movements. Subjects pressed a series of 16 buttons as rapidly as possible in response to a randomly sequenced illumination of lights.

Enter and Recall Task

and Word Recall and Recognition Task

The Enter and Recall Task short-term memory task assessed subjects' recall of 8 randomly selected digits. The Word Recall and Recognition Task explicit memory task assessed recall and recognition 6 hours after drug administration of words presented 2 hours after drug administration.

STATISTICAL ANALYSIS

Motor and cognitive performance measures were analyzed as a percentage of the predrug score, except for the Word Recall and Recognition Task, which was measured at a single time point. Subject-rated and observer-rated measures, as well as the Word Recall and Recognition Task, were analyzed as absolute scores (ie, not as percentages of the predrug scores). For each measure assessed at multiple time points, peak effect data were determined for each participant by selecting the highest postdrug score among all postdrug time points. For motor and cognitive performance measures, the lowest score served as the peak effect score. For the Subjective Effect Questionnaire and the Next-Day Questionnaire, separate drug-liking and drug-disliking scores were analyzed as described previously. Time-course data were analyzed by repeated-measures 2-factor analysis of variance with condition (7 drug conditions) and time (postdrug time points) as factors. Tukey honestly significant difference tests were used to compare each active drug condition with placebo at each time point. Other analyses consisted of 1-factor analyses of variance using drug condition as a factor. These analyses were performed on Addiction Research Center Inventory scales, Next-Day Questionnaire items, Word Recall and Recognition Task measures, Drug vs Money Choice Procedure, and peak effects for other measures. Tukey honestly significant difference tests were then used to compare each of the 7 drug conditions with each other. For all statistical tests, P≤.05 was considered significant.
Figure 1. Time-course and dose-response functions for triazolam and ramelteon for representative measures. Representative subject-rated measures are ratings on the Drug Effect Questionnaire items drug strength and drug liking. Representative motor and cognitive performance measures are Digit Symbol Substitution Test (DSST) number correct and Circular Lights Task score, expressed as percentage of predrug score. 0 Indicates predrug rating. Data are presented as means. Solid symbols indicate a significant difference from the corresponding placebo value at the same time point ($P<.05$, Tukey post hoc test).
The subjects enrolled were 14 adult volunteers (1 woman; 2 black and 12 white), with a mean age of 28 years (age range, 19-50 years) and a mean weight of 77 kg (range, 56-109 kg). Subjects reported a history of recreational use of a wide range of substances, including sedatives, during the previous year. Eleven subjects reported regular use of tobacco cigarettes.

**TIME COURSE OF DRUG EFFECTS**

Triazolam, but not ramelteon, produced orderly dose-related and time-related effects. Figure 1 shows time-course data for the following 4 representative measures: drug strength (from the Drug Effect Questionnaire), drug liking (from the Drug Effect Questionnaire), the DSST, and the Circular Lights Task. For most measures significantly affected by triazolam, the highest dose (0.75 mg) resulted in scores that were significantly different from placebo at the first time point measured (0.5 or 1 hour after drug administration). The mean maximal effects for measures significantly affected by triazolam typically returned to baseline (ie, were not significantly different from placebo) at 3 or 4 hours after drug administration for some measures. Measures significantly affected by triazolam usually returned to baseline (ie, were not significantly different from placebo) at 3 or 4 hours after drug administration, although the maximal effects were observed at 2 hours after drug administration for some measures. Measures significantly affected by triazolam typically returned to baseline (ie, were not significantly different from placebo) at 3 or 4 hours after drug administration, although some measures returned to baseline at 6 hours after drug administration. In contrast, for no measure did any dose of ramelteon result in scores significantly different from placebo at any time point.

**SUBJECT-RATED MEASURES**

The Table summarizes significant subject-rated measures based on post hoc comparisons. For 19 of 20 subject-rated measures, at least 1 triazolam dose resulted in significant differences from placebo in the direction of greater drug strength, potential for abuse, or typical sedative drug effects. An exception was that the 0.5-mg dose significantly decreased ratings for the Subjective Effect Questionnaire item regarding headache. No dose of ramelteon resulted in scores that were significantly different from placebo for any subject-rated measure. Furthermore, for 14 of the subject-rated measures in the Table, the highest dose of triazolam (0.75 mg) resulted in significantly greater ratings of drug strength, potential for abuse, or typical sedative drug effects compared with the highest dose of ramelteon (160 mg). The top 4 graphs in Figure 2 show that triazolam, but not ramelteon, resulted in dose-related peak effects for the 2 representative subject-rated measures (drug strength and drug liking) in Figure 1.

The pharmacological class question in the Next-Day Questionnaire revealed that subjects generally classified ramelteon as placebo at all doses, whereas classifications of triazolam as placebo decreased with increasing dose. The highest dose of ramelteon (160 mg) was classified by 11 (79%) of 14 subjects as placebo, whereas the highest dose of triazolam (0.75 mg) was rated as placebo by only 2 (14%) of 14 subjects. Placebo was classified as placebo by 12 (86%) of 14 subjects. When not rated as placebo, triazolam and ramelteon were most often classified as a muscle relaxant, benzodiazepine, or barbiturate or sleeping drug. Single–time point assess-
ments based on the Pharmacological Class Questionnaire during peak drug effects yielded similar results.

**OBSERVER-RATED MEASURES**

The Table provides a summary of significant observer-rated effects based on post hoc comparisons. For all 8 of the observer-rated measures, at least 1 triazolam dose showed significantly greater drug effect than placebo. Furthermore, in 6 of 8 measures, the highest dose of triazolam (0.75 mg) resulted in significantly greater increases in observer-rated measures than the highest dose of ramelteon (160 mg).

**MOTOR AND COGNITIVE PERFORMANCE MEASURES**

The Table provides a summary of significant motor and cognitive performance effects based on post hoc comparisons. For all 7 motor and cognitive performance measures, at least 1 triazolam dose resulted in significantly lower scores (ie, greater drug effect) than placebo. More-

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**Figure 2.** Dose effects for peak magnitude for triazolam and ramelteon for representative measures. Representative subject-rated measures are ratings on the Drug Effect Questionnaire items drug strength and drug liking. Representative motor and cognitive performance measures are Digit Symbol Substitution Test (DSST) number correct and Circular Lights Task score, expressed as percentage of predrug score. Data points show mean ± SEM. Solid symbols indicate a significant difference from placebo (P<.05, Tukey post hoc test).
over, the highest dose of triazolam (0.75 mg) resulted in significantly lower scores than the highest dose of ramelteon (160 mg) for all of these performance measures. The bottom 4 graphs in Figure 2 show that triazolam, but not ramelteon, resulted in dose-related peak effects for the 2 representative motor and cognitive performance measures (DSST and Circular Lights Task) in Figure 1.

The objective of this study was to provide information relevant to the potential for abuse and the impairing effects of ramelteon at supratherapeutic doses relative to those of triazolam, a classic benzodiazepine sedative-hypnotic drug with known potential for abuse and impairing effects. A range of ramelteon doses (16, 80, and 160 mg) resulted in no statistically significant effects on several measures. These doses were up to 20 times the recommended therapeutic dose (8 mg) that has been shown to be efficacious for improving sleep outcomes in adult and older adult subjects with chronic insomnia. In contrast, triazolam resulted in significant dose-related changes indicative of potential for abuse and motor and cognitive impairment, consistent with the findings of previous studies in subjects with histories of sedative drug abuse and healthy volunteers, demonstrating the dose-dependent sensitivity and validity of the procedures used.

The apparent lack of potential for abuse of ramelteon stands in contrast to the abuse liability of existing hypnotic agents that are benzodiazepine receptor agonists. Studies similar in design to the present study have documented potential for abuse for many of these compounds (eg, zolpidem, lorazepam, triazolam, oxazepam, and zaleplon). Abuse liability is an important consideration for physicians that may sometimes be overlooked. Recreational abuse of benzodiazepine receptor agonists occurs most frequently among polydrug abusers and is generally characterized by the motivation to “get high,” use of supratherapeutic doses, ingestion in combination with other drugs (eg, opioids and alcohol), and procurement from illicit sources. Associated problems include the legal and health risks associated with involvement in the illicit drug culture, as well as motor and cognitive impairment and withdrawal syndrome. Findings from the present study suggest that recreational abuse and associated adverse consequences are unlikely with ramelteon.

The absence of motor and cognitive impairment after ramelteon ingestion in the present study contrasts with findings from previous studies demonstrating impairing effects after administration of a range of hypnotic drugs, including benzodiazepine receptor agonists (eg, zolpidem, lorazepam, triazolam, oxazepam, and zaleplon) and other compounds (eg, pentobarbital sodium, diphenhydramine hydrochloride, and trazodone hydrochloride). Previous results of sleep efficacy investigations of ramelteon are consistent with the present study in finding no motor or cognitive–impairing effects. One study that investigated the effects of up to 64 mg of ramelteon found no effect on next-morning (9 hours after drug administration) DSST scores; an unexplained finding is that next-morning subjective ratings of alertness and ability to concentrate were significantly reduced at the highest dose (64 mg). Another study, which investigated the effects of up to 32 mg of ramelteon, found no effect on next-morning (about 9 hours after drug administration) DSST scores, memory recall, and subjective ratings of alertness and ability to concentrate. The apparent absence of potential for abuse and the lack of impairing effects of ramelteon compared with other hypnotic agents likely relate to differences in mechanisms of action. The localized effect of ramelteon on MT1 and MT2 receptors contrasts with the widespread effects throughout the central nervous system of GABA–mediated hypnotic agents.

In conclusion, the present results demonstrated no significant effects indicative of potential for abuse or motor and cognitive impairment for ramelteon at doses up to 20 times the recommended therapeutic dose of 8 mg. In combination with findings from previous studies supporting its efficacy in reducing sleep latency, increasing total sleep, and limiting interference with sleep architecture, as well as its apparent lack of rebound insomnia and withdrawal symptoms, our study results (indicating no evidence of potential for abuse or impairing effects) suggest that ramelteon may fill an unmet need in the treatment of insomnia. Although further clinical trials are warranted, ramelteon may be particularly useful for the treatment of insomnia in individuals with histories of substance abuse, in older subjects (who are especially susceptible to the impairing effects of benzodiazepine receptor agonists), and in persons requiring minimal interference with arousal response (eg, on-call workers and patients with chronic obstructive pulmonary disease). Furthermore, ramelteon may be a safe first-line medication even in individuals not reporting substance abuse, given that some individuals may not admit to such misuse. Finally, the selective pharmacological action of melatonin receptor agonists represents a novel target for a new class of hypnotic agents that may be devoid of potential for abuse and impairment.

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