Ramelteon and Improved Insomnia in Alcohol-Dependent Patients: A Case Series

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In this case series of 5 alcohol-dependent patients with insomnia who had initiated abstinence, a 4-week course of ramelteon 8 mg nightly was associated with markedly improved insomnia scores, increased total sleep time, and decreased time to fall asleep. Given its lack of abuse potential and evidence of low melatonin levels in alcoholism, ramelteon deserves further

study as a treatment for insomnia in this group of patients.

Keywords: Pharmacotherapy, insomnia, alcohol dependence, ramelteon

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Sleep disturbances in alcohol-dependent patients are common, persistent, and increase the risk of alcohol relapse.¹ Benzodiazepine receptor agonists are often avoided in alcohol-dependent patients because of their potential for abuse, so medications for their insomnia have included sedating antidepressants,² anticonvulsants, or antipsychotic medications. Safety and efficacy of these agents have been questioned, however, including their potential for abuse³ and increased drinking during a controlled trial with trazodone.²

Alcohol-dependent individuals have abnormal evening melatonin profiles, including a peak delay of up to 90 min.⁴ Thus, ramelteon, an agonist at central nervous system melatonin receptors with no abuse potential, might be optimal for these patients. Its efficacy in reducing sleep onset latency (SOL) and increasing total sleep time (TST) in chronic insomnia is well-reviewed.⁵ It can also phase advance circadian rhythms,⁶ which may benefit the phase-delayed rhythms reported in alcohol dependence.⁴

We gave ramelteon 8 mg nightly for insomnia to 5 abstinent alcohol-dependent patients to see if it would improve insomnia via effects on SOL and TST. To our knowledge, no studies have reported on ramelteon in these patients.

METHODS

Patients were 4 females and 1 male, ages 32-53 years (Table 1). They met DSM-IV criteria for alcohol dependence during the past year, either primary or alcohol-induced insomnia as determined by semi-structured interview, and scored > 5 on the Pittsburgh Sleep Quality Index.⁷ They all initiated abstinence on their own during the past 2-13 weeks (Table 1), which ensured they had no symptoms of acute alcohol withdrawal when they started ramelteon. None were dependent on other substances except nicotine, and they had negative urine drug screens. None had other psychiatric or medical disorders, or took other medications that could affect sleep.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Insomnia is common and associated with relapse in alcohol-dependent patients. Ramelteon was prescribed because it lacks abuse potential and may target phase-delayed melatonin profiles reported in this patient population.

Study Impact: Although this was an uncontrolled case series with a small sample size, strong effect sizes were found for self-reported measures of insomnia corroborated by actigraphy. Ramelteon may be considered in clinical practice for insomnia in alcohol-dependent patients, and controlled trials would add to these results.

They completed the Insomnia Severity Index (ISI)⁸ both before and after their medication course, and they kept sleep diaries during the pre-medication week and last week of medication. Adherence to ramelteon was monitored by pill counts. In addition, patients recorded the time they took their medication each night in their sleep diaries. Abstinence was assessed initially and monitored using the time-line follow-back interview⁹ and breath tests at each visit. A subset of patients also wore actigraphs during the week prior to starting medication and during the last week of taking medication. Actigraphy provided objective measures of SOL and TST to validate sleep diary data, using the objective sleep time estimated score (OSE).¹⁰ OSE was calculated by dividing each patient's sleep diary measure by the corresponding objective measure and multiplying by 100%, thereby comparing the accuracy of sleep diary measures to actigraphy. An OSE of 100% equals perfect accuracy. Scores above and below 100% indicate overestimates and underestimates of the objective measure, respectively.

RESULTS

The ISI decreased from a mean (SD) of 17.6 (3.6) to 9.8 (7.6) after 4 weeks of ramelteon (Cohen's *d* = 1.31). Patient 1 (Table 1) failed to complete the sleep diary at both time points,

Table 1—Patient characteristics and sleep measures at start and end of ramelteon therapy

Patient	Age	Gender	Weeks Since Last Drink	ISI Scores		TST (h)		SOL (min)	
				Pre	Post	Pre	Post	Pre	Post
1	37	F	2	16	8	7.0	—	45	—
2	32	F	13	16	6	6.4	8.0	21	7
3	45	M	11	17	18	4.1	4.6	50	55
4	53	F	5	24	17	4.2	5.5	68	15
5	50	F	4	15	0	5.3	7.4	62	17

ISI, Insomnia Severity Index; TST, sleep diary Total Sleep Time; SOL, sleep diary Sleep Onset Latency

so sleep diary analyses were conducted in 4 patients only. TST increased from 5.0 (1.0) to 6.3 (1.6) h (Cohen's $d = -0.97$), and SOL decreased from 50.3 (20.9) to 23.5 (21.4) min (Cohen's $d = 1.27$). Actigraphy data were available in 4 patients prior to medication and 3 patients during the medication phase. OSE scores expressed as percentages for TST were 104.1 (37.0) and 110.1 (25.5) for pre- and post-treatment assessments, respectively, indicating that sleep diary reports were reasonably accurate as verified by actigraphy. No drug-related adverse events were reported. Patient 1 (**Table 1**) admitted to drinking during the study for a total of 71 drinks over 12 days (mean of 5.9 drinks per drinking day), meeting generally established criteria for relapse to heavy drinking. When excluded from the analysis, the ISI decreased from 18.0 (4.1) to 10.3 (8.7) (Cohen's $d = 1.13$).

DISCUSSION

Ramelteon improved insomnia over a 4-week period, and exerted some of its effect by increasing TST by more than one hour and decreasing SOL by nearly half an hour on average. Although the small sample size precludes testing for statistical significance, all calculated effect sizes were large. Other limitations include lack of a placebo arm and a very short duration of study. Nevertheless, the magnitude of results despite a small sample size suggests that ramelteon, which was well tolerated and has no abuse potential, is worthy of further study as an alternative treatment option for insomnia in alcohol-dependent patients who have initiated abstinence.

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