A Double-Blind, Randomized, Placebo Controlled Trial of Ramelteon for the Treatment of Insomnia and Mood Stability in Patients with Euthymic Bipolar Disorder (Poster)

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Purpose

Abnormalities in circadian rhythms are prominent features of bipolar I disorder (BPD). Literature suggests that disrupted 24-hour sleep-wake circadian rhythms are associated with an increased risk of relapse in bipolar disorder. Bipolar patients have shorter, and more variable, circadian activity patterns even when not acutely ill. It is proposed that normalizing the circadian rhythm pattern of bipolar patients will improve their sleep; and consequently, also lead to fewer mood exacerbations. Ramelteon offers a mechanism to re-synchronize the suprachiasmatic nucleus. The administration of ramelteon for bipolar patients will improve sleep and will cause fewer mood exacerbations.

Methods

This single-site, double-blind, randomized, placebo-controlled study evaluated the efficacy of ramelteon in the treatment of insomnia and mood stability in patients with euthymic bipolar disorder for up 6 months of maintenance treatment. Men and women aged 18 to 65 who were currently experiencing sleep difficulties were randomized to receive ramelteon or placebo in double blind fashion. Sleep (PSQI) and mood symptoms (MADRS, YMRS) were evaluated at 4 week intervals.

Results

90 individuals signed informed consent and 83 participants were enrolled in the study and were randomized to receive ramelteon (n = 42) or placebo (n = 41). There was no evidence of group differences on background variables; nor were there differences between groups on any of the measures used to monitor disease progression, including PSQI, YMRS, MADRS, or CGI. Overall, there were 40 patients who relapsed (48.2%). The results of the Cox regression analyses indicated that the ramelteon group (Odds Ratio 0.48, p=.024) was significantly less likely to relapse over the course of the 24 week study than patients in the placebo group. Kaplan Meier curves also indicated significantly longer median survival times in the drug group (Mdn = 188 days since baseline) versus the placebo group (Mdn=84 days since baseline) X2(1) = 5.33, p = .02. There were no serious adverse events in this study.

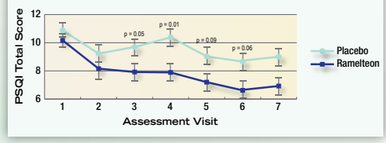
Background Characteristics by Study Assignment

	Placebo (n=41)	Drug (n=42)	Total			
	n (%)	n (%)	n (%)	x2	df	p
Gender:				.02	1	1.0
female	26 (63.4)	26 (61.9)	52 (62.7)			
male	15 (36.6)	16 (38.1)	31 (37.3)			
Race:				1.33	2	0.51
African Am	1 (2.4)*	2 (4.8)*	3 (3.6)*			
white-euro	40 (97.6)	39 (92.9)	79 (95.2)			
white-S. Am	0 (.0)**	1 (2.4)**	1 (1.2)*			
Minority status:				1.00	1	0.62
non-minority	40 (97.6)	39 (92.9)	79 (95.2)			
minority	1 (2.4)*	3 (7.1)*	4 (4.8)*			
Ethnicity:				.99	1	1.0
not hispanic	41 (100)	41 (97.6)	82 (98.8)			
hispanic	0 (0)**	1 (2.4)**	1 (1.2)*			
Diagnosis BP	41 (100)	42 (100)	83 (100)	-	-	-
Most recent episode:				1.67	3	0.64
unknown	1 (2.4)**	0 (0)**	1 (1.2)*			
manic	7 (17.1)	10 (23.8)	17 (20.5)			
depressed	17 (41.5)	15 (35.7)	32 (38.6)			
mixed	16 (39.0)	17 (40.5)	33 (39.8)			
	M (SD)	M (SD)		t	df	p
Age (years)	45.2 (10.8)	46.6 (11.0)		-.57	81	0.57

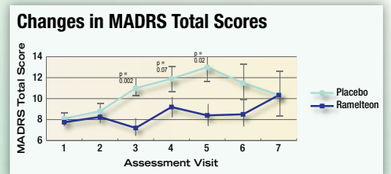
Am = American

* expected count less than 5; and ** expected count less than 1, both of which render the test statistic suspect occur for an entire row (however, it is clear from the small numbers that it is impossible to draw conclusions about group differences)

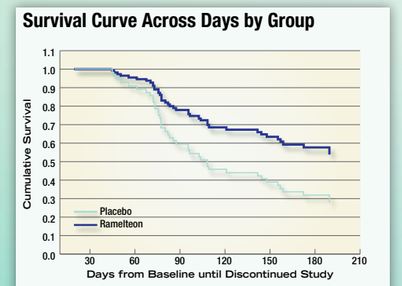
Changes in PSQI Total Scores



Changes in MADRS Total Scores



Survival Curve Across Days by Group

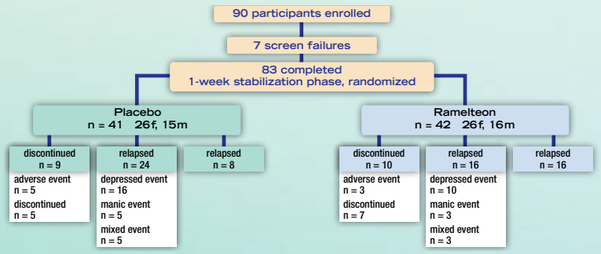


Odds of relapse (p=0.024)
Ramelteon to placebo 0.5

Median Survival (p=0.02)
Placebo –84 days
Ramelteon –188 days

Medication Distribution

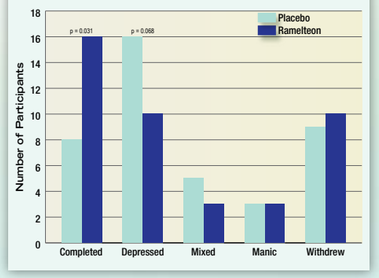
	Placebo n=41	Ramelteon n=42	x2	df	p
	n (%)	n (%)			
Lithium	8 (19.5)	7 (16.7)	0.11	1	0.74
Lamotrigine	16 (39.0)	17 (40.5)	0.02	1	0.89
Valproate	4 (9.8)	6 (14.3)	0.4	1	0.53
Carbamazepine/Oxycarbamazepine	4 (9.8)	3 (7.1)	0.18	1	0.67
Atypical mood stabilizers	4 (9.8)	3 (7.1)	0.18	1	0.67
Seroquel or Zyprexa	13 (31.7)	8 (19.2)	1.76	1	0.19
Other Atypical Antipsychotics	12 (29.3)	11 (26.2)	0.1	1	0.75
Antipsychotics	2 (4.9)	1 (2.4)	0.37	1	0.54
Antidepressants	29 (70.7)	28 (66.7)	0.16	1	0.69
Stimulants	6 (14.6)	7 (16.7)	0.07	1	0.8
Anxiolytics/sedatives/hypnotics	22 (53.7)	24 (57.1)	0.1	1	0.75
Total mood stabilizers	31 (75.6)	30 (71.4)	0.19	1	0.67
Total Atypical antipsychotics	23 (56.1)	19 (45.2)	0.98	1	0.32
Total on evidence-based bipolar depression medications	26 (63.4)	25 (59.6)	0.13	1	0.72



Conclusions

This is the first study to examine the potential of ramelteon at treating sleep and mood in patients with bipolar disorder. The present study shows that ramelteon was very effective in maintaining stability for individuals with bipolar disorder. Patients treated with ramelteon were approximately 50% more likely to remain stable throughout the trial. In other words, ramelteon treated participants were about twice as likely not to become depressed or manic during the 6 month treatment period.

Final Study Outcome



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This poster contains information that has not been approved by the U.S. Food and Drug Administration

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