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Research report

A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder

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ABSTRACT

Background: Abnormalities in circadian rhythms are prominent features of bipolar disorder. Disrupted circadian rhythms are associated with an increased risk of relapse in bipolar disorder. Normalizing the circadian rhythm pattern of bipolar patients may improve their sleep and lead to fewer mood exacerbations. This study evaluated adjunctive ramelteon for the treatment of insomnia and mood stability in euthymic bipolar patients.

Methods: Participants with euthymic bipolar disorder and sleep disturbances were randomized to receive adjunctive ramelteon or placebo in addition to their regular psychiatric medications for up to 24 weeks or until they experienced a relapse (defined as a depressed or manic event).

Results: 83 participants were randomized to receive ramelteon ($n=42$) or placebo ($n=41$). Forty participants relapsed (48.2%). Cox regression analyses indicated that participants who received ramelteon (odds ratio 0.48, $p=.024$) were less likely to relapse. Kaplan Meier curves also indicated longer median survival times in the ramelteon group (Mdn=188 days) versus the placebo group (Mdn=84 days) $X2(1)=5.33$, $p=.02$. There were no serious adverse events in this study.

Limitations: This was a small study with only 83 participants. The one-week window of confirmed stability is shorter than time intervals used in other studies.

Conclusions: The present study shows that ramelteon was effective in maintaining stability for individuals with bipolar disorder. Patients treated with ramelteon were approximately half as likely to relapse as patients treated with placebo throughout the 24-week treatment period.

1. Introduction

Abnormalities in circadian rhythms are prominent features of bipolar I disorder. It has been suggested in the literature that disrupted 24-h sleep–wake circadian rhythms are associated with an increased risk of relapse in bipolar disorder (Harvey, 2008; McClung, 2007). Sleep disturbance is often a prodrome to manic and depressive episodes in patients with bipolar disorder (Jackson et al., 2003). Bipolar patients have shorter and more variable circadian activity patterns even when not acutely ill (Jones et al., 2005).

The literature suggests that lithium may affect melatonin in the retinal-hypothalamic-pineal pathway. Insects treated with lithium were shown to have lengthened circadian patterns. When administered to *Drosophila,* lithium and valproate (to a lesser extent) lengthened the period of circadian rhythms. Lithium's effect was in part due to its action upon glycogen synthase kinase-3B, a clock gene in *Drosophila* (Dokucu et al., 2005). This suggests that successful treatments for bipolar disorder affect circadian rhythms, and the shifting, resetting and stabilization of these rhythms may be influential in the efficacy of these treatments.

A growing body of evidence supports a relevant role for melatonergic modulators as therapeutics for mood disorders. These findings suggest that modulation of the melatonin receptors may provide a specific and effective way of treating bipolar disorder. Agomelatine, a potent agonist of melatonin MT1 and MT2 receptors with 5-HT2C antagonist properties, has shown some efficacy in the treatment of depressed bipolar disorder patients co-medicated with lithium or valproate (Calabrese et al., 2007).

Patients with euthymic bipolar disorder, although free of significant mood symptoms, often have continued sleep disturbances (Harvey, 2008). It is proposed that normalizing the

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circadian rhythm pattern of bipolar patients will improve their sleep and, consequently, also lead to fewer mood exacerbations. Ramelteon, the first of a new class of sleep-promoting agents, has a unique high selectivity for the melatonin receptors (MT1 and MT2) located within the suprachiasmatic nuclei (SCN), which are primarily responsible for generating the 24-h sleep–wake circadian rhythm. Specifically, ramelteon (a) increases the activity of the M1 receptors which inhibits arousal signals coming from the SCN that maintain wakefulness; and (b) stimulates M2 receptors which synchronize the circadian clock to the day-night cycle (Dubocovich et al., 2003; Liu et al., 1997). Ramelteon offers a pharmacologically exact mechanism to resynchronize the SCN. Also, ramelteon is not habit-forming as are many sedative/hypnotic sleep-promoting agents. Thus, it may be a better option for patients with bipolar disorder due to the high comorbidity of substance use disorders in patients with bipolar disorder (Merikangas et al., 2007).

In a small double-blind study, McElroy et al. (2011) studied adjunctive ramelteon in an eight-week trial of outpatients with bipolar I disorder, mild-to-moderate manic symptoms, and sleep disturbance. Their findings indicated that ramelteon was not superior to placebo in improving insomnia or manic symptoms, but was associated with improvement in a global rating of depressive symptoms. The current study's hypothesis is that administration of ramelteon for bipolar patients will improve sleep and will cause fewer mood exacerbations.

Current treatment strategies for long-term treatment and maintenance of bipolar disorder include lithium, valproate, lamotrigine, olanzapine, quetiapine, aripiprazole, risperidone, and ziprasidone (Sachs et al., 2011). However, effective maintenance therapy of bipolar disorder and the management of residual symptoms continue to represent a significant clinical challenge. Finding effective treatment for bipolar disorder to maintain a long-term response may lead to a complex medication regimen with numerous significant side effects. Establishing that adjunctive ramelteon is helpful in improving the sleep of patients with bipolar disorder and increasing mood stability may increase the number of treatment options for bipolar patients.

The current study is a single-site, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy of adjunctive ramelteon in the treatment of insomnia and mood stability in patients with euthymic bipolar disorder for up 24 weeks of maintenance treatment. The primary objective of this study was to evaluate the effect of ramelteon compared to placebo on the quality of sleep in patients with bipolar disorder during long-term treatment, as assessed by the change from randomization in the Pittsburgh Sleep Quality Index (PSQI) global score. A secondary objective of this study was to evaluate the efficacy of ramelteon compared to placebo in increasing time from randomization to a depressed or manic event in patients with bipolar disorder. Other outcome measures included the mean change from baseline in manic symptoms (via the Young Mania Rating Scale, YMRS) (McIntyre et al., 2004; Young et al., 1978, 2000), depressive symptoms (via the Montgomery Asberg Depression Rating Scale, MADRS) (Montgomery and Åsberg, 1979), and severity of illness (via the Clinical Global Impression for Bipolar Disorder, CGI-BP).

2. Methods

2.1. Participants

Participants were recruited via referral of patients under psychiatric care in outpatient settings of the Department of Psychiatry of Lehigh Valley Health Network from October 2007 to August 2009. Men and women aged 18 to 65 were eligible for participation if they had a documented history of bipolar I disorder as defined by the *DSM-IV-TR* (American Psychiatric Association, 2000), verified by the Mini-International Neuropsychiatric Interview (MINI), and were currently experiencing sleep difficulties, requiring a score of five or greater on the Pittsburgh Sleep Quality Index at screening (Buysse et al., 1989a).

Participants were excluded from the study if they had diagnoses of primary insomnia disorders, severe chronic obstructive pulmonary disease, active substance abuse, any other disease state or psychiatric condition that might affect study results (e.g., current psychotic symptoms or severe personality disorder), and lastly, if they were currently taking the prescription medication fluvoxamine/Luvox. Participants were also excluded if they had a known history of intolerance or hypersensitivity to ramelteon or to any other component in the tablet. Female participants of childbearing potential were required to have a negative urine pregnancy test prior to enrollment and be willing to use a reliable method of birth control during the study. Additionally, participants were excluded from the study if they were experiencing clinically significant suicidality. Patients who met the confirmation of stability criteria (MADRS score ≤ 12 and YMRS ≤ 12) at the screening and again at the baseline visit were randomized to receive ramelteon or placebo in double-blind fashion.

2.2. Measures

At screening, baseline, and monthly follow-up visits, investigators evaluated mood by MADRS and YMRS scores, as well as CGI-BP scores. In addition, participants completed the Pittsburgh Sleep Quality Index (PSQI).

The MADRS threshold value for classifying patients in remission (MADRS ≤ 12) has been chosen to detect patients who have resolution of depressive symptoms. This cut-off measure has been widely used in other studies (Hyman Rapaport et al., 2004; Kasper et al., 2005; Gorwood et al., 2007; Marcus et al., 2011; Carlson et al., 2012).

The standard threshold value for classifying patients in remission (YMRS ≤ 12) was used to detect patients who have resolution of their manic symptoms. This threshold value was established by Young et al. (1978), and has been commonly used in more recent publications (Tohen et al., 2000; Chengappa et al., 2003; Ketter et al., 2007; Kora et al., 2008; Marcus et al., 2011; Carlson et al., 2012).

The CGI-BP is a three-part, physician-administered scale that assesses global illness severity and can be used to measure change; only the overall bipolar rating was used in the outcome analyses. In addition, participants completed the PSQI, a self-rated scale to measure quality of sleep, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction (Buysse et al., 1989a). The 18 items (14 multiple choice and four requiring specific time estimates) were used to calculate seven component scores, each scored from 0 (no difficulty) to 3 (severe difficulty). The seven component scores were then used to derive a global sleep quality index score, which ranges from 0–21 with higher scores representing more significant sleep disturbance. Reliability and validity data have been obtained with the scale (Buysse et al., 1989a, 1989b; Gentilli et al., 1995).

2.3. Procedures

Study protocols and amendments were approved by the Institutional Review Boards of Lehigh Valley Health Network. The study was conducted in accordance with the International Conference on Harmonisation's Guideline for Good Clinical