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Original Article

Efficacy and safety of almorexant in adult chronic insomnia: a randomized placebo-controlled trial with an active reference

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ABSTRACT

Background and objectives: The orally active dual OX_1R and OX_2R antagonist, almorexant, targets the orexin system for the treatment of primary insomnia. This clinical trial assessed the effect of almorexant on sleep maintenance and other sleep endpoints, and its safety and tolerability in adults.
Patients and methods: Prospective, randomized, double-blind, placebo-controlled, active referenced trial in male and female adults aged 18–64 years with chronic, primary insomnia. Patients were randomized 1:1:1:1 to receive placebo, almorexant 100 mg, almorexant 200 mg, or zolpidem 10 mg (active reference) for 16 days. Primary efficacy assessments were objective (polysomnography-measured) and subjective (patient-recorded) wake time after sleep onset (WASO). Further sleep variables were also evaluated.
Results: From 709 randomized patients, 707 (mean age 45.4 years; 61.7% female) received treatment and 663 (93.8%) completed the study. A significant decrease versus placebo in median objective WASO was observed with almorexant 200 mg at the start and end of randomized treatment (−26.8 min and −19.5 min, respectively; both $p < 0.0001$); subjective WASO also decreased over the two-week treatment period ($p = 0.0006$). Objective and subjective total sleep time (TST) were increased with almorexant 200 mg ($p < 0.0001$). Almorexant 200 mg significantly reduced objective and subjective latency to persistent sleep and latency to sleep onset at initiation of therapy, and provided longer duration of sleep stages with no suppression of slow-wave sleep. No impaired next-day performance, rebound insomnia, or withdrawal effects were observed. Adverse events were similar with almorexant and placebo.
Conclusion: Almorexant reduced time to sleep onset and maintained sleep without residual effects on next-day performance or safety concerns. This study provides further support for the role of the endogenous orexin system in insomnia disorder.
ClinicalTrials.gov registration: NCT00608985.

1. Introduction

Insomnia is a very common condition with symptoms that have been estimated to occur in 33–50% of adults [1,2]. Many people have only transient difficulties falling or staying asleep that resolve in a few days or weeks, but 10–20% of insomnia patients go on to suffer from chronic insomnia [2]. This condition severely impairs quality of life and reduces ability to perform daily activities, which

Abbreviations: AEs, adverse events; BMI, body mass index; CI, confidence intervals; CNS, central nervous system; dWRT, delayed Word Recall Test; DSST, Digit Symbol Substitution Test; DORA, dual OX_1R and OX_2R antagonist; ECG, electrocardiogram; iWRT, immediate Word Recall Test; LSEQ, Leeds Sleep Evaluation Questionnaire; LPS, latency to persistent sleep; LSO, latency to sleep onset; MTT, Mirror-Tracing Task; OX_1R/OX_2R, orexin 1 receptor/orexin 2 receptor; POMS, Profile of Mood States Brief Form; PSG, polysomnography; REM, rapid eye movement; RTT, Reaction Time Test; SD, standard deviation; SWS, slow-wave sleep; TST, total sleep time; VAS, visual analogue scale; WASO, wake time after sleep onset.

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leads to greater use of healthcare resources and a substantial economic burden [3–5]. Chronic insomnia is most often associated with long-term physical and psychiatric comorbidities such as arthritis, cardiovascular disease and depression [2,6], but occurs without such comorbidities in 20–25% of patients [5]. Substantial evidence indicates that non-comorbid insomnia is linked with physiological hyperarousal originating in the central nervous system (CNS), and manifesting as abnormal hormone secretion, increased high-frequency electroencephalogram activation, raised whole-body and brain metabolic activation, elevated heart rate, and sympathetic nervous system activation [7,8].

Cognitive behavioral therapy (CBT) [9] or sedative-hypnotic medications are recommended for the treatment of chronic insomnia [10,11]. Short-term treatments with benzodiazepine or a γ-aminobutyric non-benzodiazepine hypnotic are often applied in chronic insomnia [11,12]. However these pharmacological approaches can affect sleep architecture (eg, reduced slow-wave sleep [SWS] and rapid eye movement [REM] sleep), and have been associated with adverse effects such as rebound insomnia and daytime sleepiness [13–15]. Additionally, while several hypnotic medications primarily target sleep maintenance insomnia they do not adequately address sleep maintenance.

Hence, there is a need for new, effective insomnia treatments with improved efficacy and side-effect profiles. Accumulated knowledge of the orexins (orexin A and orexin B excitatory neuropeptides) has helped to outline their important role in the maintenance of wakefulness, and the regulation of arousal [16–19]. As opposed to effects on the sleep side of the sleep–wake cycle (eg, as seen with benzodiazepines), agents affecting the orexin system may modulate CNS hyperarousal and unwanted wakefulness in insomnia [20]. The potential for the orexin system to participate in brain mechanisms underlying insomnia led to the development of orexin receptor antagonists, which target the transmembrane receptors OX_1R and/or OX_2R, for the treatment of insomnia [19–21]. To date, one dual OX_1R and OX_2R antagonist (DORA), suvorexant, has already been approved by the US Federal Drug Administration for the treatment of insomnia [22,23].

The selective, competitive, orally active DORA, almorexant (Actelion Pharmaceuticals Ltd, Switzerland), has demonstrated a favorable safety/tolerability profile and relevant pharmacodynamic effects on sleep measures in healthy adult and elderly subjects [24–28]. In a double-blind, randomized, two-way crossover proof-of-concept/dose-finding study with almorexant 50–400 mg in 161 adults with insomnia, almorexant provided dose-related improvements in mean objective sleep efficiency, wake time after sleep onset (WASO) and latency to persistent sleep (LPS) versus placebo [26]. Dose-dependent decreases in latency to REM sleep and, at higher doses, a decreased latency to sleep stages S1–S4 were also observed [29]. In a subsequent dose-finding trial in elderly patients, almorexant provided dose-related decreases in mean WASO as well as LPS, and increased total sleep time (TST) at doses ranging from 25 to 200 mg [30].

This short-term randomized, double-blind, placebo-controlled, active reference (zolpidem) trial assessed the effect of almorexant on sleep maintenance and other sleep endpoints in a larger population of adults with chronic insomnia. The safety and tolerability of almorexant were also evaluated during 16 days of treatment.

2. Methods

2.1. Patient population

Adults aged 18–64 years with chronic insomnia (as defined by DSM-IV-TR criteria; APA 2000) and a body mass index (BMI) ≥18.5 and <32 were included in the study. Eligible patients were required to have a self-report history of ≥30 min latency to sleep onset (sLSO), ≥30 min subjective wake time after sleep onset (sWASO), a subjective TST (sTST) <6.5 h on at least three of seven consecutive nights, and a usual bedtime between 20:00 and 01:00 h. Objective mean LPS ≥20 min (with no night <15 min), mean WASO ≥20 min (with no night <15 min), and mean TST <420 min over two screening polysomnography (PSG) nights were also required.

Reasons for exclusion from the study included: a history of any sleep or axis-I psychiatric disorder other than insomnia (DSM-IV-TR [31]) within the past six months, an apnea/hypopnea index score ≥10/hour, or an apnea/hypopnea event associated with oxygen saturation <80% on the first PSG screening night. Patients with a periodic limb movement arousal index ≥10/hour on the first PSG screening night, or usual daytime napping ≥1 h per day and ≥3 days per week, were also excluded.

2.2. Study design and treatment

This was a prospective, multicenter, double-blind, randomized, placebo-controlled, active reference (zolpidem), parallel-group trial with a screening period of 14–28 days, followed by a 16-day double-blind treatment period, and a 28-day safety follow-up. After an initial screening visit, patients completed a daily sleep diary at home for seven consecutive days to assess subjective sleep characteristics, including sleep induction/maintenance, habitual napping and bedtimes. Two consecutive PSG nights were performed at screening (Visit 2, during single-blind placebo treatment) and during the double-blind treatment period on Days 1 and 2 (Visit 3) and Days 15 and 16 (Visit 4). A single PSG night was also performed during the withdrawal period on Day 17 (Visit 5, single-blind follow-up placebo treatment) following the treatment period (Supplementary Fig. S1).

Patients meeting study entry criteria were randomized 1:1:1:1 to one of four study oral treatments (placebo, almorexant 100 mg, almorexant 200 mg, or zolpidem 10 mg). Medication was taken each evening, 30 ± 5 min prior to PSG start at sleep clinic visits, or at bedtime (when at home) over the 16-day double-blind treatment period. To maintain blinding, almorexant and its matching placebo were indistinguishable and identically packaged. So too were the reference drug (zolpidem) and its matching placebo.

The protocol and any material provided to enrolled patients were reviewed and approved by the appropriate independent ethics committees or institutional review boards before the study was started. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines on Good Clinical Practice and applicable laws and regulations. Written informed consent was obtained from each patient prior to participation.

2.3. Assessments and efficacy endpoints

Polysomnography was applied using standard methods [32] to objectively assess sleep parameters. Data from each overnight PSG recording was scored centrally at Clinilabs Inc., New York, NY, USA. Patient self-administered daily sleep diaries comprised morning and evening questionnaires assessing subjective sleep parameters (sleep induction and maintenance, TST, habitual napping, bedtime) and time of treatment on a 50-mm visual analogue scale (VAS). The VAS collected information on sleep quality, depth of sleep, morning sleepiness, daytime alertness, and daytime ability to function.

The primary efficacy endpoint was defined for comparison of almorexant 200 mg with placebo. It was a composite endpoint that included three components: 1) change from baseline in mean objective WASO obtained on Days 1 and 2, 2), change from baseline in mean objective WASO obtained on Days 15 and 16; and 3) change