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Original Article

Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a randomized, 6-week sleep laboratory trial

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ABSTRACT

Objective: Esmirtazapine (Org 50081), a medication that binds with high affinity to serotonin 5-HT_{2A} and histamine-1 receptors, was evaluated as a potential treatment for insomnia.
Methods: Adults with primary insomnia were treated with esmirtazapine (3.0 or 4.5 mg) or placebo in this 6-week, double-blind, randomized, polysomnography (PSG) study. The end points included wake time after sleep onset (WASO) (primary), latency to persistent sleep, and total sleep time. Patient-reported parameters were also evaluated, including sleep quality and satisfaction with sleep duration. Residual daytime effects and rebound insomnia (sleep parameters during the single-blind placebo run-out week after treatment ended) were also assessed.
Results: Overall, 419 patients were randomized and 366 (87%) completed treatment. The median decrease in PSG WASO (double-blind average) was 20.5 min for placebo, and 52.0 min and 53.6 min for the 3.0- and 4.5-mg esmirtazapine groups, respectively ($P < 0.0001$ vs. placebo for both doses). Changes in the other PSG parameters and in all patient-reported parameters were also statistically significant with both doses versus placebo. Overall, 35–42% of esmirtazapine-treated patients had adverse events (AEs) versus 29% in the placebo group. AEs were mild or moderate in most esmirtazapine-treated patients. Furthermore, the incidence of AEs leading to discontinuation was low (<8%).
Conclusions: Six weeks of treatment with esmirtazapine was associated with consistent improvements in objective and patient-reported parameters of sleep onset, maintenance, and duration. It was generally well tolerated, and residual daytime effects were minimal and no rebound insomnia was observed.

1. Introduction

The neurobiology of the sleep–wake cycle involves the interaction between numerous neurotransmitters and hormones to generate wakefulness or sleep [1]. γ–Aminobutyric acid (GABA) is the main inhibitory transmitter in the brain and is the system targeted by benzodiazepine receptor agonists (BzRAs) [2], the current standard of care for insomnia in the USA. Histamine, on the other hand, plays a key role in promoting wakefulness [1], and several antihistamines (eg, hydroxyzine, doxepin, and diphenhydramine) are approved in the USA to treat disturbed sleep. Like histamine, serotonin (5-HT) also promotes arousal, and in addition it suppresses rapid eye movement (REM) sleep. It has been shown that agonists of certain 5-HT receptor subtypes, for example, 5-HT_2, increase wakefulness, while antagonists promote sleep [3–5].

Mirtazapine is an antidepressant agent used at doses of 15–45 mg. It is a racemic mixture of R(−) and S(+) enantiomers, and it acts as an antagonist at α_2-adrenoceptors, increasing both noradrenergic and serotonergic neurotransmission [6,7]. In addition to its

Abbreviations: 5-HT, serotonin; AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; BWSQ, Benzodiazepine Withdrawal Symptoms Questionnaire; BzRA, benzodiazepine receptor agonist; DSST, digit symbol substitution test; ECG, electrocardiogram; GABA, γ–Aminobutyric acid; H_1, histamine-1; IGR, Investigator's Global Rating; ISI, insomnia severity index; ITT, intent to treat; LOCF, last observation carried forward; LPS, latency to persistent sleep; OC, observed cases; PSG, polysomnography; REM, rapid eye movement; SAE, serious adverse event; SD, standard deviation; SL, sleep latency; sTST, subjective TST; SWS, slow-wave sleep; TST, total sleep time; VAS, visual analog scale; WASO, wake time after sleep onset.

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Clinicaltrials.gov trial registration ID NCT00506389

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antidepressant effects, mirtazapine also has sleep-promoting properties, both in preclinical models [8] and in healthy volunteers [9], and in patients with depression [10]; these effects are thought to result from high-affinity binding at 5-HT_2 and histamine-1 (H_1) receptors (affinity at H_1 is approximately six times greater than that at 5-HT_2) [11]. Esmirtazapine maleate (Org 50081), which was in development for the treatment of insomnia, is the maleic acid salt of the S(+) enantiomer of mirtazapine. As esmirtazapine has a shorter half-life (10 h) than racemic mirtazapine and the R(−) enantiomer (18 h for both), it is anticipated that esmirtazapine will have a smaller risk for residual sedative effects the next day. Two previous double-blind, randomized, placebo-controlled studies have shown that short-term treatment with 1.5, 3.0, and 4.5 mg of esmirtazapine significantly improved objective and patient-reported measures of sleep duration, onset, and maintenance, with higher doses (3.0 and 4.5 mg) being more effective than the lower dose (1.5 mg) [12,13]. However, these studies were of short duration (up to two weeks), and given that insomnia is a chronic condition, longer-term studies are required. The aim of the current trial was, therefore, to evaluate the efficacy and safety of 3.0 and 4.5 mg of esmirtazapine over a longer period (six weeks) in patients with chronic primary insomnia.

2. Materials and methods

2.1. Study design and patients

This was a 6-week, double-blind, randomized, placebo-controlled, parallel-group study conducted between June 2007 and April 2008 in 43 outpatient research clinics in the USA and Canada (protocol number 176002; clinicaltrials.gov ID NCT00506389). The study consisted of a screening period (10–14 days), a 6-week double-blind treatment period, and a 1-week discontinuation period (Supplemental Fig. 1). There were two polysomnography (PSG) nights at baseline, three during the double-blind phase (on Nights 1, 15, and 36), and two during the discontinuation period (on the first two nights of the week). During the screening and discontinuation periods, patients were treated with single-blind placebo.

Eligible patients were aged 18–65 years and were diagnosed with primary insomnia, that is, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, at least 1 month before study entry. They also had to fulfill the following PSG criteria on two screening/baseline PSG nights: average total sleep time (TST) < 6.5 h (and ≥3 and <7 h on both nights), wake time after sleep onset (WASO) ≥ 45 min (and ≥30 min on both nights), and latency to persistent sleep (LPS) ≥ 15 min (and ≥10 min on both nights). The

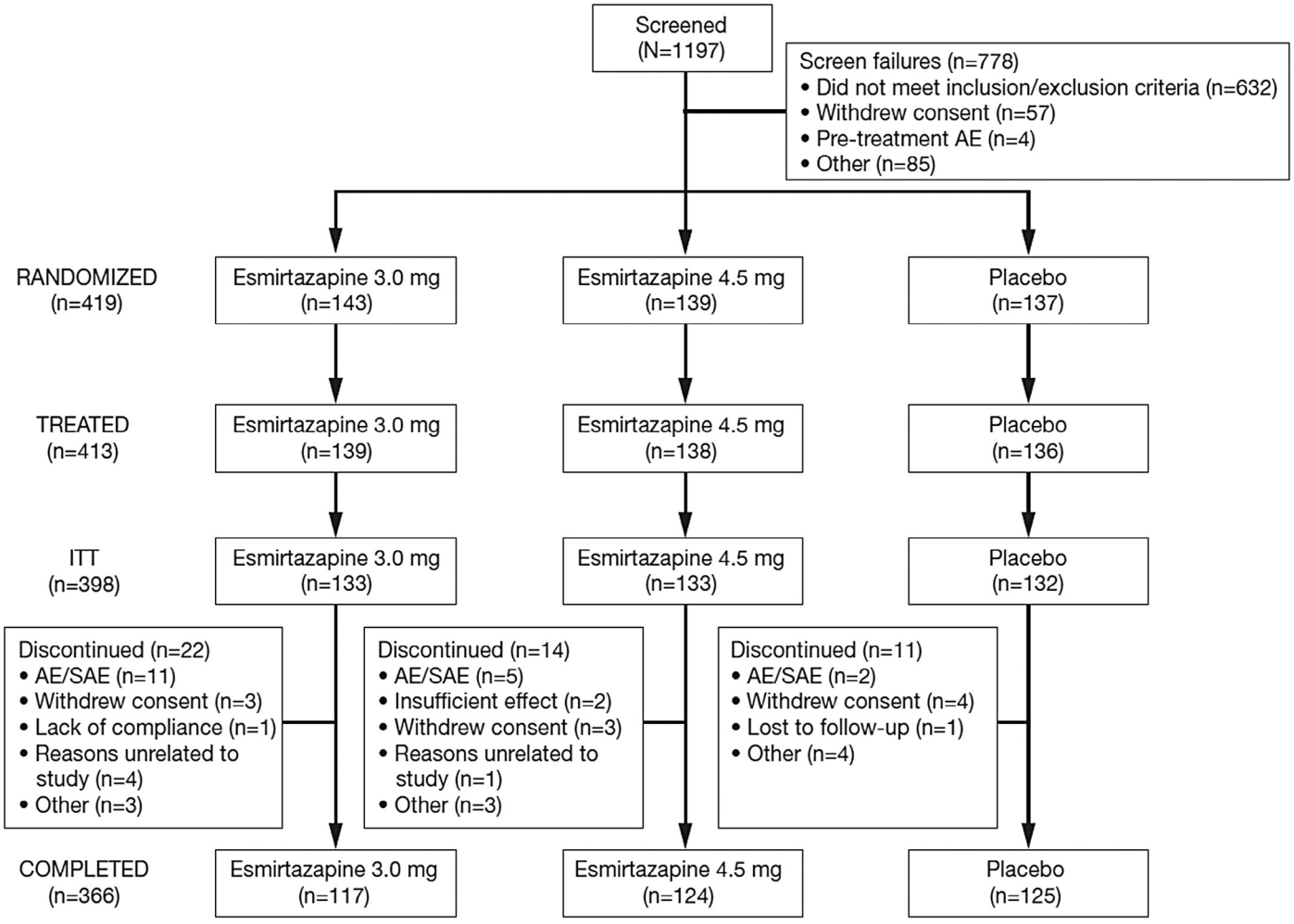

Fig. 1. Patient disposition in non-elderly patients with primary insomnia. AE, adverse event; ITT, intent-to-treat population; SAE, serious adverse event.