[Drug] Treatment Of Patients With Chronic Insomnia Characterised By Nocturnal Awakenings: Results from the double-blind treatment period

Abstract

Objectives: To determine the safety and efficacy of [Drug] in the improvement of sleep maintenance insomnia, in adults diagnosed with primary insomnia according to DSM-IV-TR criteria.

Methods: A randomised, placebo-controlled, double-blind phase III trial was performed across 14 countries. Patients were treated with oral [Drug] 5mg or placebo in a 3:1 ratio once daily for 12 weeks. Patients answered an 11-item sleep questionnaire about sleep initiation, the number of awakenings, duration of awakening, sleep duration, sleep quality, ability to concentrate, and morning sleepiness each morning via a telephone interactive voice response system (IVRS). At study visits on days 1, 14, 28, 42, 63, and 84 patients were evaluated according to the Functional Outcomes of Sleep Questionnaire (FOSQ), the Insomnia Severity Index (ISI), the Work Limitation Questionnaire (WLQ), and Hospital Anxiety and Depression Scale (HADS).

Results: [Drug] 5mg per day significantly ($p<0.0001$) decreased patient-reported wake time after sleep onset, improving sleep maintenance by 13:31 min: sec compared to placebo at 12 weeks. Improvement of concentration/memory did not reach statistical significance level at 5%. Total FOSQ score was increased by [Drug] treatment as well as a slight improvement in HADS. Improvement in WLQ measures relating to productivity loss, time management, mental interpersonal, and output scales was found in the [Drug] treatment group. No difference was measured in sleep onset latency.

Conclusion: [Drug] improved patient-reported wake time after sleep onset without residual next-day impairments. This study suggests [Drug] is a promising new sleep maintenance targeted insomnia treatment, filling a crucial gap in current medicine.

Introduction

Approximately 10-15% of adults are estimated to suffer from chronic insomnia (Rosenberg, 2006), 25% of which are diagnosed with primary insomnia (Roth, 2003). Insomnia symptoms differ among patients; many report difficulty falling asleep (sleep-onset insomnia) (Park, 2009), difficulty maintaining sleep, or lack of restorative sleep (Ohayon, 2002). DSM-IV criteria for primary insomnia states a patient must be experiencing poor quality sleep, difficulty initiating or maintaining sleep for one month or more, causing significant impairment on daily functions, and must not be caused by other sleep disorders, mental disorders, general medical conditions, or substance abuse (Eddy, 1999). Comorbid insomnia is related to general medical conditions, mental disorders, or substance abuse (Rosenberg, 2006 and Thorphy, 2009). Rosenberg describes three categories of insomnia: sleep onset insomnia, sleep maintenance insomnia, and terminal (awakening early) insomnia (Rosenberg, 2006).

Sleep disorders in children can cause learning disabilities, and hinder everyday functioning in adults (Ohayon, 2002). Severe insomnia patients have more physical problems than patients with depression and more loss of function in mental health and emotional effects and pain than patients with congestive heart failure (Katz, 2002). Insomniacs are also 2.5-4.5 times more accident-prone and have overall decreased quality of life (Roth, 2007).

Nocturnal awakening is the most common symptom of insomnia. Ohayon (2008) found 35.5% of the population reported awakenings >3 times a week, 23.0% reported waking every. 90% of patients reporting nocturnal awakenings had been experiencing these for >6 months. Common effects of nocturnal awakenings, even microarousals include daytime sleepiness, cognitive difficulties, low mood, irritability, decreased performance quality, and fatigue (Ohayon, 2008 and Bonnet, 1987). Nocturnal awakenings increase the chances of developing major depressive disorder and bipolar disorder (Ohayon, 2008). Reduced ability to respond to glucose challenges due to a shift in autonomic balance has been associated with nocturnal awakenings due to disruption in slow-wave sleep (SWS) (Dijk, 2009).

SWS is characterised by low frequency (<2Hz) and high amplitude (>75μV) brainwaves occurring during NREM (non-rapid eye movement) stages 3 and 4 (Dijk, 2009). SWS is dominant in brain areas that are highly active during wakefulness and those associated with higher brain function; substantial amounts are required for restorative sleep (Akerstedt, 1997 and Dijk, 2009). SWS disruption results in more daytime sleepiness and impaired function (Dijk, 2009). When compared to good sleepers, patients with primary insomnia show a decrease in SWS (Pigeon, 2006). It is suggested that SWS may contribute to sleep maintenance (Dijk 2009).

Current FDA-approved insomnia medications target sleep onset insomnia by decreasing sleep onset latency (SOL) but are not effective in sleep maintenance (Rosenberg, 2006). Some benzodiazepines improve sleep maintenance as well as SOL (Morin, 2009); however, due to the risk of abuse, next-day sedation, and rebound insomnia, they are only for short-term use (Rosenberg, 2006). Other benzodiazepines have a shorter half-life reducing the risk of next-day sedation but concerns of withdrawal symptoms and rebound insomnia remain. The shorter half-life benzodiazepines do not improve sleep maintenance (Rosenberg, 2006 and Morin, 2009). Non-benzodiazepines such as zolpidem and zaleplon reduce SOL but do not show sustained improvement of sleep maintenance (Rosenberg, 2006 and Morin, 2009). Eszopiclone improves SOL and sleep maintenance, and is approved for long-term use (Morin, 2009 and Monti, 2007). However, withdrawal symptoms are a concern (Monti, 2007). Benzodiazepine receptor agonists (benzodiazepines, zolpidem, zaleplon and eszopiclone) are thought to suppress slow wave sleep (Saletu, 1994 and Wisor, 2006). Ramelteon improves SOL but does not reduce nocturnal awakenings (Morin, 2009).

Pharmacological enhancement of SWS has become the focus of new hypnotic development. A new medication will need to enhance SWS, thereby improving sleep maintenance, while also addressing concerns with current hypnotics: next-day sedation, dependence and tolerance symptoms, and safety for long-term treatment (Rosenberg, 2006). Cytoplasmic 5-HT2A receptors are linked to the

promotion of wakeful state (Cornea-Herbert, 1999) and 5-HT2A receptor antagonists have been shown to increase SWS (Sharpley, 1990, Sharpley, 1994 and Sanger, 2007).

Trazodone, an FDA-approved antidepressant, has a high affinity for 5-HT2A receptors and is effective for the treatment of sleep maintenance insomnia (Stahl, 2009). Hindmarch (2008) and Estivill (2008) found [Drug] to increase SWS, reducing nocturnal awakenings. These studies also discovered that [Drug] is well tolerated, without rebound insomnia or next-day effects. The exact mechanism of the 5-HT2A receptor antagonists' effect on sleep is unknown (Landolt, 2009).

The primary aim of this study was to determine the efficacy of [Drug] in the improvement of sleep maintenance by recording patient-reported wake time after sleep onset (pr-WASO) for 12 weeks. Further, other efficacy variables measured include concentration/memory, hobby/work, anxiety and depression, patient-reported number of nocturnal awakenings (pr-NAW), patient-reported total sleep time (pr-TST), patient-reported sleep onset latency (pr-SOL), and quality of sleep.

Discussion

This study determined that 5mg of [Drug] significantly decreased pr-WASO, increasing sleep maintenance at 12 weeks compared to placebo. These results are support previous studies by Hindmarch (2008) and Estivill (2008); both found [Drug] enhances SWS and decreases nocturnal awakenings. These effects are not dose-dependent (Hindmarch, 2008). Zolpidem, zaleplon, and ramelteon do not decrease nocturnal awakening or WASO (Morin, 2009 and Rosenberg, 2006). Benzodiazepines improve sleep maintenance; however, due to the side effects of benzodiazepines, this finding has positive clinical implications (Stewart, 2005 and Morin, 2009).

In this study, [Drug] did not significantly improve concentration/memory from baseline at 12 weeks. As this was a hierarchical step-down procedure, no conclusions could be made as to its efficacy against hobby/work. The lack of significant improvement could be due to the low degree of impairment at baseline for both groups. Further research in this area is needed. As benzodiazepines

have been shown to have a negative impact on patients' memory (Morin, 2009), evidence of concentration/memory improvement would provide yet more benefit to [Drug] use in patients with sleep-maintenance insomnia over benzodiazepines.

Additionally, this study indicated [Drug] decreased pr-NAW and increased pr-TST sleep quality and refreshing quality of sleep, compared to placebo at both 6 and 12 weeks. Decreased NAW and increased TST in [Drug]-treated patients was also observed by Estivill (2008). Thus, [Drug] provides benefit as a sleep maintenance targeted hypnotic, but also decreasing NAW and increasing TST. Zolpidem, zaleplon, and ramelteon increase TST; whereas only benzodiazepines and Eszopiclone are effective against both (Rosenberg, 2006 and Morin, 2009).

Improvements in general productivity, activity level, and social outcome were found at 12 weeks. These results confirm the findings of (Estivill, 2008 and Hindmarch, 2008): [Drug] has no negative effects on attentional or psychomotor functioning, regardless of the time of day it is taken (Hindmarch 2008). Zaleplon, zolpidem, and ramelteon also do not have a negative effect on these functions, but there is little research into whether they improve these abilities (Morin, 2009). This is an advantage over benzodiazepines as they are known to have next-day effects such as impaired cognition and psychomotor functioning (Stewart, 2005 and Morin, 2009).

Pr-SOL did not improve at 6 or 12 weeks, consistent with previous findings from Hindmarch (2008). Ideally, a new hypnotic would increase sleep continuity, while also decreasing SOL. However, as current insomnia medications improve SOL (Morin, 2009 and Rosenberg, 2006), there is still a demand for hypnotics such as [Drug] for sleep maintenance insomnia.

The percentage of patients who experienced at least one TEAE and those who discontinued the study due to AEs was greater in the [Drug] group than the placebo group (55.5% and 4.2% versus 50.5% and 2.4%, respectively). However, the number of serious TEAEs was low and comparable between groups. Common side effects experienced by [Drug]-treated patients include dizziness, diarrhea, somnolence, dry mouth, constipation, diverticulitis, and upper abdominal pain. TEAEs were more

common in elderly [Drug]-treated patients than non-elderly. No evidence of next-day residual effects, rebound insomnia, or withdrawal effects were found, consistent with previous [Drug] studies (Estivill, 2008 and Hindmarch, 2008).

[Drug] would provide an effective, sleep maintenance targeted treatment by decreasing nocturnal awakenings and WASO and enhancing SWS, without the negative side effects of benzodiazepines (Estivill, 2008 Hindmarch 2008), Rosenberg, 2006 and Morin, 2009). As there is no evidence for [Drug]-mediated improvement of SOL, it would not be a suitable treatment for patients with sleep onset.

A key strength of this study was the exclusion of patients with secondary insomnia or other disorders that affect sleep. This provided confidence in the efficacy of [Drug] in the treatment of insomnia. The 1145 patients that received treatment in the study were from 14 different countries, producing a comprehensive evaluation of efficacy, removing cultural bias.

The data in the study was collected via an automated questionnaire (subjective data), rather than physiological parameters (objective data). This limited the study as patients could only report nocturnal awakenings and other variables they remembered. The secondary endpoints (concentration/memory) and (work/hobby) did not significantly improve with [Drug] treatment. As this could be explained by the low degree of impairment in daily functioning at baseline, this hypothesis should be further explored, potentially comparing primary insomnia patients against good sleepers.

This study has demonstrated the efficacy of [Drug] in the treatment of sleep maintenance for adults with primary insomnia. No evidence was found of improvement of concentration/memory, hobby/work, or sleep onset latency. Next-day sedation effects were not reported by the subjects. This study provides evidence for a safe new sleep maintenance targeted insomnia treatment, filling a crucial gap in the current medicine.

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