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Original Article

A 2-week efficacy and safety study of gaboxadol and zolpidem using electronic diaries in primary insomnia outpatients

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ABSTRACT

Objectives: To evaluate the efficacy and safety profile of gaboxadol, a selective extrasynaptic $GABA_A$ agonist (SEGA) previously in development for the treatment of insomnia.
Methods: This was a randomised, double-blind, placebo-controlled, parallel-group, 2-week, Phase III study of gaboxadol 5, 10 and 15 mg in outpatients meeting the DSM-IV criteria of primary insomnia ($N = 742$). Zolpidem 10 mg was used as active reference.
Results: At weeks 1 and 2, significant improvement in total sleep time (sTST) compared to placebo was seen for all doses of gaboxadol (all $p < 0.05$). In addition, gaboxadol 10 and 15 mg decreased the number of awakenings (sNAW) ($p < 0.05$) while only gaboxadol 15 mg improved wakefulness after sleep onset (sWASO) ($p < 0.05$). At week 1, all doses of gaboxadol significantly improved time-to-sleep onset (sTSO) ($p < 0.05$). At week 2, a sustained effect on sTSO was observed for gaboxadol 15 mg. Zolpidem also showed effect on all of these variables. Gaboxadol and zolpidem improved sleep quality, freshness after sleep, daytime function and energy at both weeks. Transient rebound insomnia was observed following discontinuation of treatment with zolpidem, but not gaboxadol.
Conclusions: Gaboxadol 15 mg treatment for 2 weeks significantly improved sleep onset and maintenance variables as well as sleep quality and daytime function, as did zolpidem. Gaboxadol 5 and 10 mg also showed benefits on most efficacy variables. Gaboxadol was generally safe and well tolerated, with no evidence of withdrawal symptoms or rebound insomnia after discontinuation of short-term treatment. For zolpidem, transient rebound insomnia was observed.
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1. Introduction

Insomnia is a prevalent complaint and is estimated to affect up to one-third of the adult population [1] and may have adverse consequences for the individual and society [2].

Most of the commonly prescribed hypnotics are categorised as benzodiazepine receptor agonists (BzRAs) which modulate the γ-aminobutyric acid (GABA) subtype A receptor – the key mediator of fast inhibitory transmission in the central nervous system [3].

The presence of an α_4, α_6 or δ subunit in the $GABA_A$ receptor complex confers insensitivity towards benzodiazepines [4]. These benzodiazepine-insensitive receptor subtypes are predominantly located outside the synaptic cleft [5,6] (also termed extrasynaptic receptors) where they mediate the tonic inhibitory currents thought to play a key role in the refinement of the neuronal firing pattern [7,8]. Gaboxadol is a novel selective extrasynaptic $GABA_A$ agonist (SEGA); the $\alpha_4\delta$ containing receptor subtype currently seems the most relevant target mediating its hypnotic activity [9].

The aim of the present study was to confirm the acute hypnotic effects of gaboxadol (observed in previous studies in healthy subjects in a model of transient insomnia [10,11] and in primary insomnia patients [12,13]) in patients with primary insomnia, following a longer treatment duration as required by European guidelines [14]. The study included zolpidem (10 mg) as a reference. Zolpidem was previously proven efficacious on sleep onset and maintenance [15,16].

On March 28, 2007 Lundbeck and Merck announced the discontinuation of the development program for gaboxadol in the treatment of insomnia, based on an assessment of the overall clinical profile of the compound.

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2. Methods

2.1. Design

This was a randomised, double-blind, 5-arm study to compare the effects of gaboxadol 5 mg, 10 mg, and 15 mg versus placebo on subjective sleep variables over 2 weeks, and in a randomised run-out over 1 week. Zolpidem 10 mg was included as an active reference. The design also allowed evaluation of impact of the hypnotic treatments on patient-rated sleep quality and overall daytime performance. The study was conducted at 73 centres in Europe and Canada. Patients were enrolled between 29 January 2003 and 1 September 2004.

2.2. Patients

Outpatients aged 18–65 years who met DSM-IV criteria [17] for primary insomnia were enrolled. Patients also had to have a usual bedtime between 20:00 and 24:00 h and had to meet the following criteria: self-reported total sleep time (sTST) <6 h and self-reported time-to-sleep onset (sTSO) $\geqslant$45 min on at least 4 out of 7 nights. These criteria had to be fulfilled the month prior to screening (a retrospective clinical evaluation) and again during the 1-week, single-blind, run-in phase (prospective daily recording of sleep data using an electronic sleep diary). Patients with a history or current abuse or dependence on any substance with abuse potential, any psychotic disorder, or any other current Axis I diagnosis other than primary insomnia were excluded. The following medications were prohibited prior to the screening visit: within 1 week – any psychoactive or hypnotic drug (including herbal remedies), benzodiazepines, any opiate or opiate derivative containing drug, itraconazol or rifampicin; within 2 weeks – sedating antihistamines, antiepileptics, flurazepam, or diazepam; within 5 weeks – fluoxetine. Patients were excluded if they (a) consumed more than 14 units (women) or 21 units (men) of alcohol a week, or (b) consumed more than 5 caffeine-containing beverages a day, or (c) consumed more than the nicotine-equivalent of 15 cigarettes a day.

All patients gave written informed consent after full explanation of the study procedures and prior to any study-related activity. The study was approved by the appropriate ethics committee for each participating centre and was performed in accordance with good clinical practice (GCP) and the Declaration of Helsinki.

2.3. Procedure

Patients attended a screening visit during which their demographic data, medical, psychiatric, and medication history, and symptoms of insomnia were recorded based on a structured interview and a physical examination. The psychiatric examination was performed using the Mini International Neuropsychiatric Interview (MINI) [18] to rule out comorbidities. Only investigators were trained and allowed to perform the MINI and structured interview. Eligible patients underwent a 1-week, single-blind, placebo run-in phase (baseline week). For data collected on a daily basis (patient diaries), the mean scores during the run-in phase served as baseline. For data collected at the patient visits (LSEQ), the randomisation visit at the end of the run-in week served as baseline. Patients who continued to meet the eligibility criteria at the end of the run-in week were randomised to 2 weeks of treatment with one of the following: gaboxadol 5 mg, gaboxadol 10 mg, gaboxadol 15 mg, zolpidem 10 mg, or placebo. The treatment phase was followed by a 1-week, double-blind, run-out phase in which 50% of patients previously assigned to an active treatment were randomised to placebo, while the other 50% remained on their existing treatment. There was a 1-week safety follow-up period after the end of the run-out phase.

The randomisation code was generated by a statistician at H. Lundbeck A/S. Patients were randomised in a 1:1:1:1:1 ratio, using a block size of 10. The randomisation code specified the treatment to be received for both the 2-week treatment phase and the 1-week run-out phase. The treatments were encapsulated to ensure study blinding. Patients were instructed to take one capsule before bedtime every night throughout the study.

2.4. Efficacy assessments

The patients were each given a hand-held computer electronic diary, programmed with a morning and an evening questionnaire. In the morning questionnaire, a number of variables with respect to the previous evening/night were recorded including sTST, self-reported number of nocturnal awakenings (sNAW), self-reported duration of nocturnal awakenings (i.e., wakefulness after sleep onset, sWASO), sTSO, self-reported quality of sleep (sQUAL), and self-reported freshness after sleep (sFRESH). sQUAL and sFRESH were recorded using a 100-point visual analogue scale (VAS), where 0 points referred to the worst conceivable condition and 100 points referred to the best conceivable condition. Most questions were adapted from a morning patient-self-rating scale [19]. The morning questionnaire was completed after the patient had finished the normal morning waking and bathroom routines. In the evening questionnaire, the following daytime performance variables were recorded with similar 100-point VASs: energy (ENERGY) and ability to function (FUNCTION). For some of the above variables, the VAS was reversed to avoid habitual responses from the patients. The evening questionnaire was completed after dinner and before taking study medication and bedtime.

Patients also assessed their sleep at the end of each week using the Leeds Sleep Evaluation Questionnaire (LSEQ) [20]. This questionnaire consists of ten 100-mm VASs pertaining to four aspects of sleep: (1) getting to sleep, (2) quality of sleep, (3) awakening from sleep, (4) behaviour following wakefulness.

The evaluation of the rebound insomnia was based on sTST and sTSO data from the patient diary in the 1-week randomised run-out phase.

2.5. Safety assessments

Adverse events were recorded throughout the study and were rated by the investigator with regard to intensity and likelihood of being drug-related. Vital signs, ECGs, routine laboratory assessments, and physical examinations were performed at regular intervals.

A Withdrawal Symptoms Questionnaire designed for the use of benzodiazepines [21] was included in the evening diary during the run-out phase.

2.6. Data analysis

All efficacy analyses were based on observed cases (OC) for the population of randomised patients who took at least one dose of double-blind treatment and who had at least one post-baseline assessment of an efficacy variable (full analysis set). The primary measures for the analysis were changes from baseline in the weekly means of sTST, sTSO, sNAW, and sQUAL. sTSO was analysed after transformation with the natural logarithm (log_sTSO) to normalise the distribution. Treatment groups were compared using estimates from a repeated measurements model with an unstructured covariance matrix that included week, centre, and treatment as factors and the baseline value of the variable as a covariate.

To adjust for multiplicity, a two stage gate-keeping test strategy was applied. As the first stage of the procedure, sTST and log_sTSO were compared between gaboxadol 15 mg and placebo during

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