

A method to assess the dissipation of the effects of residual hypnotics: Eszopiclone versus Zopiclone.

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Conflicts of Interest and Source of funding: Julia Boyle has received research support from GlaxoSmithKline, Merck&Co Inc and Pfizer Ltd.

John A. Groeger has received research support from GlaxoSmithKline, H Lundbeck A/S, Merck & Co Inc and has served as consultant for Glaxo-Smith Kline, H Lundbeck A/S, Merck&Co Inc.

Derk-Jan Dijk has received research support from GlaxoSmithKline, H Lundbeck A/S,

Merck&Co Inc, Philips Lighting, Organon, Takeda, Wellcome Trust and has served as consultant

for Actelion, Cephalon, Glaxo-Smith Kline, Lilly, H Lundbeck A/S, Merck&Co Inc., Metronaps, Ono Pharmaceuticals, Pfizer Inc, Philips Lighting, Sanofi Aventis, Takeda.

James Cooper, Carol Rockett, Paul Gandhi, Sion Jones and Jenny Scott, are employees of GlaxoSmithKline.

Walter Paska was an employee of GSK at the time of study conduct.

For the remaining authors none were declared.

Scientists and biostatisticians at GlaxoSmithKline, which sponsored the study, described in this manuscript, collaborated with study investigators in study design, data analysis, interpretation of the results, preparation of the manuscript, and the decision to submit the manuscript for publication. Statistical analyses were conducted at GlaxoSmithKline.

Running title: Eszopiclone next-day impairment profile.

Funding: The study was funded by GlaxoSmithKline.

Abstract

Next-day residual effects of single evening doses of 3 mg eszopiclone, 7.5 mg zopiclone and placebo were assessed in a randomised, double-blind, placebo-controlled, 3-way crossover study, that used a mild sleep restriction protocol (sleep duration 7 hours). During each period, 91 healthy volunteers spent 2 consecutive nights in the laboratory with time in bed restricted to 7 hours. Volunteers completed the Continuous Tracking Test, Critical Flicker Fusion task, Digit Symbol Substitution Test, N-back tasks, and Linear Analogue Rating Scales every half-hour from 7.5 to 11.5 hours post-dose commencing 15 min after awakening. Night-time dosing of both eszopiclone (3 mg) and racemic zopiclone (7.5 mg) was associated with next-day performance impairment and these residual effects dissipated over time. Eszopiclone did not differ from zopiclone on the primary endpoint, mean CTT tracking error averaged from 7.5-9.5 hours post-dose, however a pre-specified post hoc parametric analysis of reciprocal-transformed data favoured eszopiclone over racemic zopiclone ($P=0.026$).

Key words: insomnia, hypnotic, eszopiclone, zopiclone, sleep, sleep inertia

Introduction

The adverse personal and economic consequences of insomnia, which affects an estimated 1 in 5 adults worldwide ¹, are well established ². There is consistent evidence that insomnia is often coexistent with psychiatric disorders such as depression and anxiety ³, as well as emerging evidence that a bidirectional relationship may exist ⁴.

Insomnia is treated primarily with hypnotics that, while generally well tolerated, can be associated with side effects potentially as detrimental as insomnia itself. In particular, residual sedation (the “hangover” effect), which constitutes prolongation of the drugs’ hypnotic effect, results in daytime sleepiness, impairment of psychomotor and cognitive functioning ⁵ and increased risk of injury and accidents ⁶.

The two compounds under investigation, zopiclone and eszopiclone, are non-benzodiazepine hypnotics prescribed in the treatment of both transient and short-term insomnia and often for its chronic variant. Zopiclone, a cyclopyrrolone class racemic mixture of two stereoisomers of which only one is active, was introduced in the second half of the eighties and has been proven to be an effective hypnotic, it has however been shown to impair next-day functioning ⁷.

The single-isomer hypnotic eszopiclone [(S)-zopiclone] is a short-acting non-benzodiazepine insomnia medication. As the active isomer of racemic zopiclone, eszopiclone is effective at less than half the dose of racemic zopiclone ⁸. In addition, exposure to eszopiclone 3.5 mg, a similar concentration of the (S)-isomer contained in 7.5 mg zopiclone, has an earlier time to peak concentration (T_{max} 1.0 hr compared with racemic zopiclone 1.5 hr), and significantly less exposure to active metabolites, which may explain the difference of the two compounds on their residual effect profile ⁹.

The pharmacokinetic profile of eszopiclone, therefore could potentially reduce residual-effects, and in randomised, double-blind, placebo-controlled studies in healthy volunteers and patients with primary insomnia, cognitive function and psychomotor function were not impaired the morning after 3 mg eszopiclone compared with placebo ¹⁰. However, whilst a proportion of patient studies have reported improved subjective ratings of daytime alertness, there was evidence that, subjective daytime alertness and ability to function was reduced at the 3mg dose ¹¹.

Eszopiclone has been compared with placebo in studies of next-day residual effects. However, it has not been previously compared with racemic zopiclone in a head-to-head study evaluating next-day psychomotor and cognitive effects. The study reported herein was conducted to compare the effects of a single bedtime dose of eszopiclone (3 mg) on next-day psychomotor and cognitive function with those of zopiclone (7.5 mg) and placebo in healthy volunteers. Unlike previous studies of residual effects, which assessed for impairment after at least 8 hours of sleep¹⁰, the present study used a sleep-restriction protocol that limited sleep duration to 7 hours in order to approximate real-life circumstances ¹². The dissipation of residual effects after the sleep episode was assessed with high temporal resolution (at half hourly intervals) from 15 minutes to 255 minutes after wake time to include the period characterized by sleep inertia during which residual effects are expected to be most evident ¹³.

Materials and Methods

Participants

Medical and psychiatric history; physical examination and serum chemistry, hematology, and urinalysis results determined the inclusion of 25 to 40-years old participants of both sexes who had provided informed written consent. Exclusion criteria included pregnancy, lactation,

ineffective contraception; signs and symptoms of a sleep disorder or irregularity; weight <50 kg or BMI <18 or >30; history of substance abuse or dependence; smoking >5 cigarettes/day; consuming >300 mg xanthinated products or more than 3 to 4 units (men) or 2 to 3 units (women) of alcohol (UK government guidelines; daily units); use of prescription or OTC psychotropic medications (excluding the occasional use of some cold, flu, or allergy remedies containing antihistamines and opiates) in the 3 months before screening; and any other medication within 2 weeks before screening. A wrist-mounted actigraphy device (Actiwatch AW, CamNtech Ltd, Cambridge UK) aided assessment of ongoing eligibility throughout screening, treatment sessions, and washout periods. Further, alcohol breath tests and urine tests for drugs of abuse were administered throughout the study to ensure compliance.

Procedures

This was a randomised, double-blind, double-dummy, placebo-controlled, 3-way crossover study (GlaxoSmithKline protocol ESZ111503) , comparing a single bedtime dose of 3 mg of eszopiclone with 7.5 mg of zopiclone and placebo relative to next-day psychomotor and cognitive function in healthy adults. The protocol was approved by an independent ethics committee (Brent Medical Ethics Committee, Harrow, UK). The study was conducted at a single UK site in accordance with "good clinical practice" (GCP); the European Union clinical trials directive, 2004; and the guiding principles of the Declaration of Helsinki. The study was registered with clinicaltrials.gov, identifier: NCT00699608.

The 7- to - 28 day screening period included a clinical visit and 1-night polysomnography (PSG) recording. Upon satisfactory eligibility criteria participants returned to the clinic after a further 2 to 21 days and were randomised in balanced order to 3 crossover treatment sessions during which they received 3 mg eszopiclone, 7.5 mg zopiclone, or placebo (1 randomised treatment in each

crossover session). Each treatment session comprised two consecutive days of admission to the study clinic for completion of multiple next-day assessments of psychomotor and cognitive function following dosing at 10:45 PM with single-blind placebo on Night 1 and double-blind study medication on Night 2. Next-day assessments were completed on Day 2 (baseline) and Day 3 (post-treatment), respectively. Lights-out was at 11:00 PM, and sleep time was restricted to 7 hours (11:00 PM to 6:00 AM) in order to approximate real-life circumstances and to assess the time course of residual effects. A safety follow-up visit was scheduled 7 ± 1 days after the last treatment session.

Measures

Cognitive and psychomotor measures included: Continuous Tracking Test (CTT)¹⁴, Critical Flicker Fusion (CFF)¹⁵, DSST¹⁶, N-backs (1-back and 3-back)¹⁷, and Linear Analogue Rating Scales (LARS)¹⁸. Testing commenced at 06:15, 15 minutes after awakening (7.5 hours post-dose). The primary comparison of interest was the difference between eszopiclone 3 mg and zopiclone 7.5 mg on the CTT mean tracking error averaged over 5 assessments: 7.5, 8, 8.5, 9, and 9.5 hours postdose. Secondary endpoints were assessed in the morning at 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, and 11.5 hours after double-blind dosing, including CTT mean tracking error and mean reaction time; CFF mean threshold frequency, DSST total of attempted substitutions and total of correct substitutions; N-back percentage of correct responses and reaction time; and LARS subjective estimates of sedation, mood and coordination.

Data Analysis

Data on psychomotor and cognitive test performance were analyzed for all participants who received at least 1 dose of double-blind study medication (Intention-to-treat, ITT population). Analyses of covariance (ANCOVA) techniques were used to analyse the primary and secondary

endpoints. The model for the primary endpoint included fixed-effect terms of participants' baseline, adjusted period-specific baseline, age, gender, treatment, and period. Subject was included as a random effect. The individual time points were analysed using a repeated-measures model with interactions of time-point*treatment, time-point*subject level baseline, and time-point*period-specific baseline, in addition to the core covariates used in the primary model. Point estimates for the mean differences with corresponding 95% confidence intervals (CIs) were calculated. The associated *P*-values were provided for eszopiclone 3mg versus zopiclone 7.5mg as well as each treatment versus placebo. No adjustment for multiplicity was done.

Error diagnostics from residuals were examined to ensure the assumptions of the model were valid. Assumptions of normality and homogeneity of variance underlying the ANCOVA model were violated, i.e. non-normal residuals and non-constant variance. Therefore transformations of the primary endpoint and nonparametric methods were applied to assess the robustness of the analysis. The ANCOVA model assumptions were violated for the N-back percentage of correct responses; therefore, a *a priori* rank transformation was applied to the data.

To aid interpretation of the clinical relevance of the findings, a *post hoc* evaluation of standardised differences for the reciprocal-transformed and rank-transformed primary endpoint was performed. *Post hoc* evaluations of standardised differences were also completed for the secondary endpoints. Standardised differences were calculated for three 1-hourly assessment phases corresponding to early morning (7.5 to 8.5 hours postdose), mid-morning (9 to 10 hours postdose), and late morning (10.5 to 11.5 hours postdose).

Tolerability

Tolerability was considered as the percentage of participants with adverse events (AE) or serious adverse events (SAE) during the double-blind treatment period, i.e. the time of receiving double-

blind study medication on Night 2 until midnight of the next day, which was Day 3. This followed the European Medicine Authority definition for AE and SAE¹⁹ Adverse-event data were summarised with descriptive statistics for the ITT population. Other safety measures included vital signs, clinical laboratory assessments, and physical examinations at the screening and follow-up visits as well as regular pregnancy testing.

Results

Sample

Ninety-one participants were randomised to treatment and received at least 1 dose of double-blind study medication. Four of the 91 participants prematurely withdrew from the study because of non-study commitments, 1 for the protocol violation of a positive alcohol-breath test, and 1 because of AEs. Participants were White (69%); Black (15%), Asian (15%). Mean age was 29.8 years (SD=3.9), and 51% were female. Mean BMI was 23.9 (SD=2.9).

Primary Endpoint

Primary Analysis

Eszopiclone (3 mg) did not differ significantly from zopiclone (3.75 mg eszopiclone) on the primary endpoint, i.e. CTT mean tracking error; average of the first 5 assessments on Day 3, [eszopiclone (3 mg) versus zopiclone (7.5 mg) – 0.99 pixels, 95% CI – 2.74 to 0.76, $P=0.267$].

Both active treatments significantly differed from placebo (eszopiclone versus placebo: 2.20 pixels, 95% CI 0.45 to 3.96, $P=0.014$; zopiclone versus placebo: 3.19 pixels, 95% CI 1.46 to 4.93, $P<0.001$) (Figure 1).

Post Hoc Analyses of the Primary Endpoint

Parametric ANCOVA analysis of the reciprocal-transformed endpoint yielded a statistically significant difference favoring eszopiclone (3 mg) over zopiclone (3.75 mg eszopiclone; $P=0.026$) as well as statistically significant differences between each active treatment and

placebo ($P < 0.001$). A nonparametric rank-transformed analysis yielded results consistent with the parametric reciprocal-transformed analysis, but the difference between eszopiclone and zopiclone did not reach statistical significance at the 5% level ($P = 0.061$). In the *post hoc* analysis of standardised differences for the reciprocal-transformed and rank-transformed primary endpoint, small but potentially clinically relevant differences of 0.30 and 0.24, respectively, were observed in favour of eszopiclone over zopiclone.

Secondary Endpoints

The secondary endpoints (Figure 1] were broadly consistent with those for the primary endpoint. Numerical trends favoring eszopiclone over zopiclone were generally observed, but in the majority of cases fell short of statistical significance. The N-back test differentiated eszopiclone from zopiclone most clearly and consistently (Figure 2). Trends toward improvement in performance as time since waking increased were observed for the DSST number attempted and number correct, and LARS sedation (Figure 3).

Post hoc analyses of standardised differences on the secondary endpoints, revealed small but potentially clinically relevant standardised differences (≥ 0.20) favouring eszopiclone (3mg) over zopiclone (3.75mg eszopiclone) for 7 of the 14 endpoints during the early phase of the morning (CTT mean tracking error, CTT reaction time, 1-back and 3-back percentage of correct responses, 3-back reaction time, LARS sedation, and LARS coordination); 1 of 14 endpoints during the middle phase (1-back percentage of correct responses), and 3 of 14 endpoints during the late phase of the morning (CTT mean tracking error, 3-back percentage of correct responses, and LARS sedation, Figure 3).

Adverse Events

The proportion of participants with at least 1 AE was 50% with eszopiclone, 49% with zopiclone, and 13% with placebo. The most common AEs were dysgeusia and somnolence (Table 1). No SAEs were reported. One participant prematurely withdrew from the study because of AE. This participant, a 25-year-old female, reported feelings of fear and hallucinations, both events began 26 minutes after a dose of eszopiclone in the second crossover period. The fear event lasted for 39 minutes, and the hallucination event lasted for 6 minutes. Both events were of moderate severity. The investigator deemed these adverse events to be drug related.

Discussion

Next-day residual impairment constitutes a significant problem with many hypnotics. In experimental studies in healthy volunteers, hypnotics cause sedation and impair psychomotor function, attention, and memory the day after bedtime use⁶ and in epidemiologic studies, hypnotics are associated with increased risk of traffic accidents²⁰. One of the outcomes of the development of eszopiclone was the assertion that the compound improved upon the next-day residual-effect profiles of other insomnia medications including its racemate parent zopiclone. To assess the veracity of this claim this randomised, double-blind, placebo-controlled head-to-head study compared eszopiclone (3 mg) with zopiclone (3.75 mg eszopiclone) in a protocol designed to quantify the time course of residual effects after mild sleep restriction in healthy volunteers, i.e. 7 hours of time in bed for 2 consecutive nights.

Compared with placebo, both eszopiclone (3 mg) and zopiclone (3.75 mg eszopiclone) were associated with next-day residual effects that were most severe shortly after awakening, dissipated over time but remained significant for several hours after awakening. Some differentiation between the compounds was observed, in particular for tasks that had a high demand on executive resources (3-back) rather than the less demanding tasks of sensori-motor

performance. Interestingly there were indications of smaller residual effects with eszopiclone (3 mg) compared with zopiclone (3.75 mg eszopiclone) across a range of tests including the CTT, DSST, the N-back (1- and 3-back), and the LARS (sedation and coordination scores).

The difference between eszopiclone (3 mg) and zopiclone (7.5 mg) was not statistically significant on the primary endpoint. Transformation of the primary endpoint and ranked analysis in accordance with *a priori* stipulations, demonstrated differences between eszopiclone and zopiclone that were either statistically significant or approached statistical significance in favour of eszopiclone, however both compounds differed significantly from placebo. Previous studies in patients with primary and coexistent insomnia have shown that eszopiclone was consistently associated with improvements in daytime functioning, subjective alertness and health-related quality of life^{21,7}. Also a study with healthy participants and primary insomnia patients using a comprehensive battery of psychometric tests and car driving ability did not demonstrate residual impairment, however testing for residual impairment did not begin earlier than 9.75 hr post-dose¹³. The mild sleep restriction protocol used in this study proved an effective tool for demonstrating residual impairment. Time constraints limited the number of cognitive assessments that could be made and did not allow inclusion of vigilance type tests, such as the psychomotor vigilance task.

This study is, to the authors' knowledge, the first well-controlled study attempting to characterise thoroughly the time course of residual effects of insomnia medications using a sleep-restriction protocol approximating real-life circumstances and assessing the time course of residual effects. Previous studies assessing next-day effects of eszopiclone allowed at least 8 hours of sleep^{9,13}. Whether a similar residual effect profile would be observed if a sleep period of 8 hrs was allowed in a study with primary insomnia patients, is unclear as healthy volunteers are typically more

sensitive to residual effects. In addition, subtle deficits in cognitive performance have been observed in insomnia patients, particularly attention based tasks with high cognitive load ²¹ and therefore a complex interaction between performance enhancement and residual impairment may occur in patient populations.

The AE profile of eszopiclone in this study is consistent with previous findings in healthy volunteers and patients with primary insomnia ⁹. The incidence of specific AE was similar between eszopiclone and zopiclone. No new safety or tolerability findings were noted.

In summary, previous research has shown that eszopiclone is an effective hypnotic medication on short or long-term administration with no evidence of tolerance. This study is the first to examine the time course of the residual effect profile of eszopiclone, zopiclone and placebo following a sleep restriction protocol. The study showed that both eszopiclone (3 mg) and zopiclone (3.75 mg eszopiclone) compared with placebo caused statistically and clinically relevant next-day residual effects that continued for several hours after awakening. The data indicated these effects were typically smaller in magnitude for eszopiclone, and did not persist to the same extent, although these may have been a function of the smaller dose of eszopiclone. As with many hypnotics, however, patients should be cautious when driving a vehicle, or operating machinery the day after ingestion.

Figure 1. CTT Mean Tracking Error:

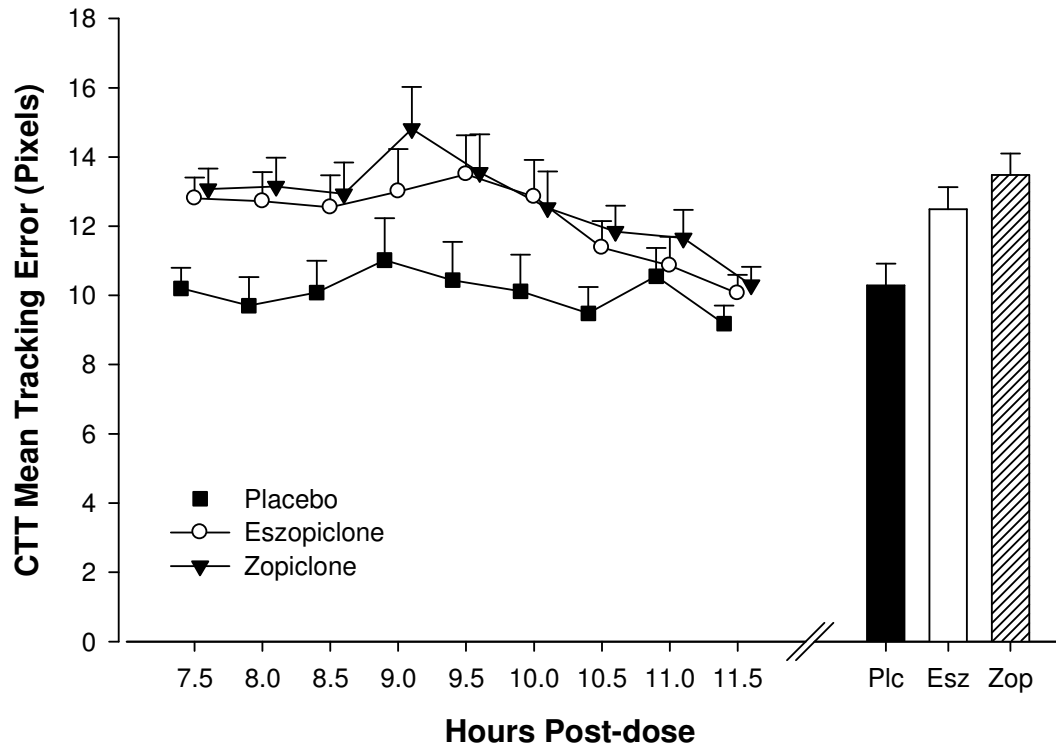


Figure 2. 1-Back and 3-Back Memory Tests: Percentage of Correct Responses.

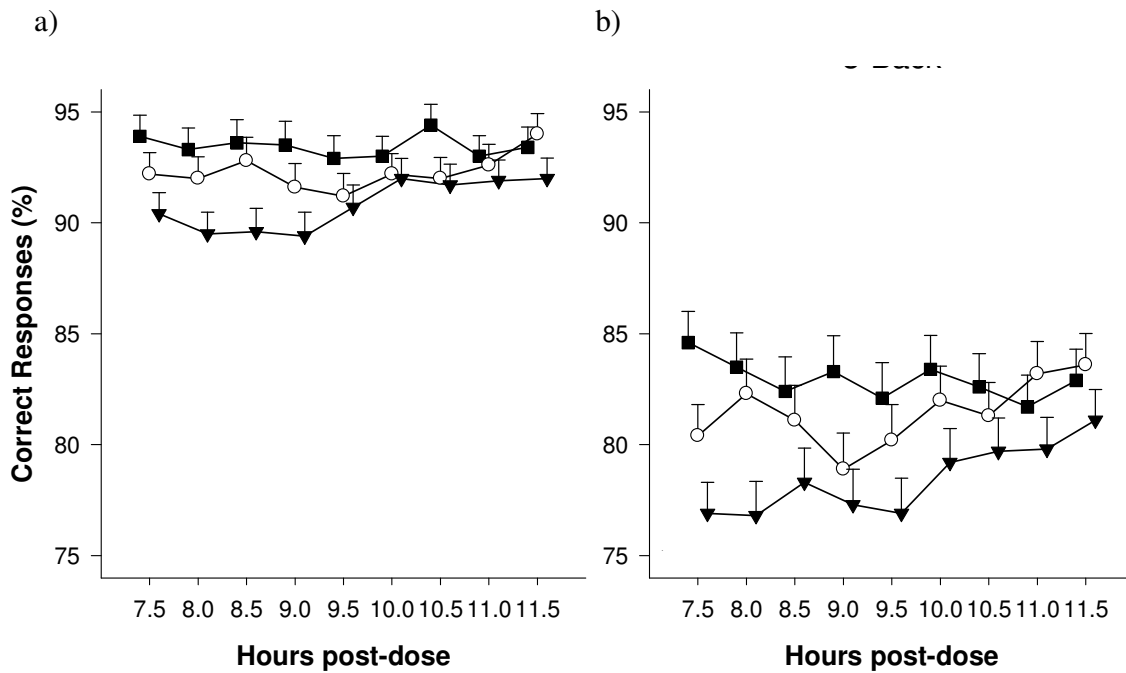


Figure 3. Post Hoc Analysis of Standardised Differences.

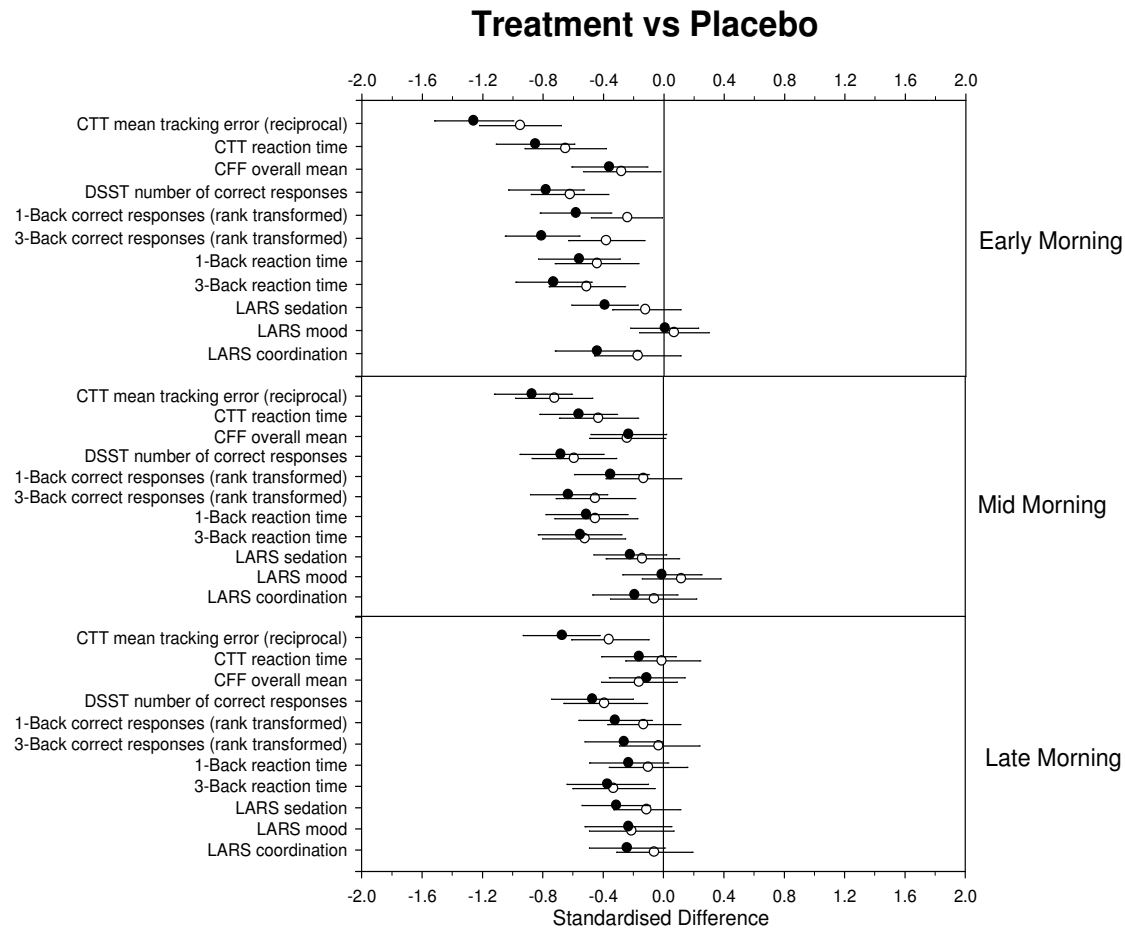


Table 1. Adverse Events Reported During Double-Blind Treatment (Night 2 Through Midnight on Day 3). Adverse events reported in $\geq 2\%$ of participants with any treatment in the ITT population are listed.

	Eszopiclone (n=88)	Racemic Zopiclone (n=90)	Placebo (n=89)
	N (%)		
Dysgeusia	27 (31)	30 (33)	0 (0)
Somnolence	11 (13)	7 (8)	1 (1)
Fatigue	6 (7)	6 (7)	4 (4)
Nausea	4 (5)	4 (4)	3 (3)
Dizziness	4 (5)	5 (6)	0 (0)
Headache	2 (2)	2 (2)	2 (2)
Disturbance in attention	2 (2)	3 (3)	0 (0)
Hallucination	2 (2)	0 (0)	0 (0)
Nightmare	2 (2)	0 (0)	0 (0)
Rash	2 (2)	0 (0)	0 (0)

Figure Legends

Figure 1. Adjusted means (SEM) for CTT mean tracking error in pixels (untransformed data). Data for the placebo and zopiclone condition were displaced along the x-axis to avoid data points being obscured. Values plotted at the mean time point are the primary endpoint and reflect the mean of the first 5 time points post dose.

Figure 2. Adjusted means (SEM) for N-back percentage correct at each time point on Day 3 on the 1-back task (panel A) and the 3-back task (panel B) (untransformed data). Placebo (■), eszopiclone 3 mg (○) and zopiclone 7.5 mg (▼).

Figure 3. Early-morning, middle-morning, and late-morning standardised differences (95% CIs) between eszopiclone (○) and placebo, and racemic zopiclone (●) and placebo for secondary endpoints. A standardised difference <0 reflects impairment of waking performance following treatment compared with placebo. The more negative the standardized difference the greater the impairment. A standardized difference of 0.2 – 0.5 reflects a small size effect, 0.5 – 0.8 a medium effect and >0.8 a large effect size. Significance cannot be determined from whether or not 0 is included within the CI.

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