学位論文

「Effects of zolpidem/triazolam on cognitive performance 12 hours after acute administration」

（超短時間型睡眠薬 triazolam と zolpidem 急性投与による認知機能への影響は服用 12 時間後まで持続していた）

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

Abstract

Objective

Most previous studies have concluded that decreased cognitive function and performance due to ultra-short acting hypnotics do not persist after 6-9 hours post-administration. This study examined the effects of ultra-short acting hypnotics on cognitive function and performance 12 hours after administration, i.e., a time considered sufficient for the effects of hypnotics to disappear.

Methods

Thirteen healthy young male volunteers (mean age, 23.4 ± 3.2 years) participated in this study. Participants attended three sessions of polysomnography (PSG) recording preceded by oral administration of placebo for the first session, and 5 mg zolpidem or 0.25 mg triazolam for the second and third sessions, in a double-blinded, randomized manner at intervals of at least 5 days. A cognitive test battery was administered following each session, consisting of a psychomotor vigilance task (PVT), which reflects alertness and sleepiness, digit symbol substitution test (DSST), which reflects attention and working memory function, and assessment of subjective sleepiness and mental condition using a visual analog scale (VAS).

Results and Conclusions

The administration of hypnotics significantly increased total sleep time, sleep efficiency, and sleep stages 2 and 4, and significantly decreased wake after sleep onset and sleep stage 1. PVT parameters were not affected by the administration of hypnotics, but DSST score was significantly lower, and "subjective alertness," "vigor," and "sadness" significantly deteriorated, after administration. In conclusion, while objective sleepiness disappeared 12 hours after the administration of ultra-short acting hypnotics, their effects to decrease cognitive function persisted even after 12 hours post-administration.

Keywords: polysomnography, digit symbol substitution test, zolpidem, triazolam, ultra-short acting hypnotics, healthy young male

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1. Introduction

Hypnotics are among the most commonly prescribed medications in developed and emerging countries. According to questionnaire-based studies, 16-21% of the general population have subjective symptoms of insomnia more than three times a week, and 9-15% meet the International Classification of Sleep Disorders – Second Edition (ICSD-2) diagnostic criteria for insomnia (i.e., insomnia symptoms with daytime consequences) [1]. The prevalence of insomnia has been repeatedly reported to increase with advancing age [2,3].

In Japan, the prescription rate of hypnotics for three months in the general population, which corresponds to the proportion of adults receiving at least one prescription of hypnotics at least every three months, was reported to be 4.7% in 2009 [4]. In six European Union countries (eg, Belgium, France, Germany, Italy, the Netherlands and Spain) and Thailand, prescription rates of anxiolytics and hypnotics at least every 12 months were 7.3-9.8% [5, 6]. A survey on sleep medication administration at a hospital revealed that benzodiazepine-based agents (BZDs) are more frequently prescribed than other types of hypnotics, with roughly 90% or more of patients on sleeping pills using BZDs [4]. BZDs improve subjective and objective total sleep time, sleep latency, and wake after sleep onset.

While hypnotics are widely used in developed and emerging countries, their negative effects on social and industrial safety have been reported. For instance, a number of epidemiologic studies have reported that taking hypnotics, especially BZDs, significantly increases falls in elderly individuals, as well as traffic accidents [7-9]. Therefore, the use of hypnotics for treating insomnia requires careful attention to patient daytime activities as well as nighttime insomnia symptoms so as not to induce daytime dysfunction or accidents. From this perspective, shorter half-life hypnotics, such as short acting and ultra-short acting BZDs with a half-life of 6-12 hours and <6 hours, respectively, are commonly used in many countries.

However, various effects of these hypnotics have been reported. Based on previous studies showing that ultra-short acting hypnotics do not affect driving ability 9 hours after administration [10-12], guidelines of the US Department of Transportation state that it is generally safe to drive vehicles 5 hours after taking zaleplon, and 9 hours after taking zolpidem, at recommended doses. However, recent studies have reported that 9-10 hours may not be sufficient to eliminate the negative effects of hypnotics on driving ability. Mets et al. carried out on-the-road highway driving performance tests 8.5 hours after administration of ramelteon (8 mg) or zopiclone (7.5 mg) in healthy adults, and found that lane keeping ability and cognitive function were significantly deteriorated [13]. Another study using a driving simulator with simultaneous eye movement analyses revealed that driving performance and ocular saccades were deteriorated even 10 hours after administration of zopiclone (7.5 mg) and flunitrazepam (1 mg) [14].

These findings suggest that decreased cognitive function and performance may not be fully recovered ≥9 hours after administration of ultra-short acting hypnotics. Moreover, since none of the

above-mentioned studies performed polysomnography (PSG), quantitative or qualitative sleep changes due to hypnotics are unknown, and whether or how nighttime sleep changes affect daytime cognitive performance remains unaddressed. From the pharmacokinetic perspective, however, approximately 25% of administered drugs remain in blood vessels 9-10 hours after administration, so the impairing effects of ultra-short acting hypnotics on many functions of the human brain, including cognitive function, may persist after ≥9 hours.

This study aimed to examine the effects of ultra-short acting hypnotics by assessing performance on a psychomotor vigilance task (PVT), which reflects alertness and sleepiness, and the digit symbol substitution test (DSST), which reflects attention and working memory function, 12 hours after administration, i.e., a time considered sufficient for the effects of hypnotics to disappear. Simultaneously, PSG was recorded to examine the relationship between changes in objective nighttime sleep variables and daytime performance tests. We used triazolam and zolpidem, commonly used ultra-short acting BZD and non-BZD hypnotics, respectively, at ordinary doses for adults in Japan (i.e., 0.25 mg and 5 mg, respectively).

2. Methods

2-1. Participants

Participants were healthy young male volunteers aged 18-40 years who were recruited through advertisements in local newspapers, the university website, and recruitment posters on the university campus. Female subjects were not recruited because the experimental setting of this study made it difficult for females to participate, given the need to judge pregnancy at the time of drug administration and considerable changes in sleep indices due to the menstrual cycle. Exclusion criteria were as follows: any medication or nutraceutical use (including St John's Wort) [15] within seven days prior to drug administration; blood donations of ≥400 mL within three months or ≥200 mL within one month prior to study initiation; and the use of sleep medication within three months. Participants were asked to keep their regular sleep-wake habits during the study period.

2-2. Study Design

The study protocol was approved by the intramural ethics committee of Kitasato University. The study design and PSG procedure [16] are shown in Figure 1. After providing written informed consent, participants were screened according to the standard procedure of Kitasato Clinical Trial Center, which included medical interviews and examinations. Those with morbidities and/or a history of sleep disorders or psychiatric disorders, abnormal findings in clinical chemistry, hematology, and urinalysis tests (e.g., liver and kidney dysfunction), positive markers of infectious diseases (e.g., human immunodeficiency virus, hepatitis B virus, hepatitis C virus), abnormal electrocardiographic (ECG) findings including a QT interval longer than 450 msec, and body mass index <18 or >30 kg/m^2 were

excluded.

Participants underwent three sessions of PSG recording from 2300h to 0700h, preceded by oral administration of placebo, 5 mg zolpidem, or 0.25 mg triazolam at 2230h, and followed by a cognitive test battery performed from 1100h to 1200h on the following day. A pharmacist prepared identical opaque capsules containing each medication (placebo, triazolam, or zolpidem) to ensure that neither participants nor researchers attending PSG sessions were able to identify the content. The cognitive test battery consisted of the PVT, reflecting sleepiness, and the DSST, reflecting working memory and cognitive integration. PSG sessions were conducted at intervals of at least 5 days. In the first session, all participants were administered placebo, and PSG was recorded in order to exclude participants with sleep apnea syndrome (apnea hypopnea index $\geq$10, or 3% oxygen desaturation index $\geq$10) and periodic limb movement disorder (periodic limb movement index $\geq$20). Participants and researchers in charge of PSG sessions, except for a physician standing by in case of emergency, were explained that placebo, triazolam, and zolpidem were to be administered randomly during the three experiment sessions. Zolpidem and triazolam were administered in a double-blinded, randomized manner during the second and third sessions.

2-3. Measurements

2-3-1. PSG

Electrodes were placed according to the standard manual of American Association of Sleep Medicine (AASM) version 2.1, and EEG recordings, vertical and horizontal electrooculography, ECG, and electromyography of submental muscles were performed. In addition, an air-flow sensor and respiratory movement sensor for breast and abdomen were placed. ECG of bilateral anterior tibial muscles was performed for placebo PSG. Overnight PSG recordings were performed in a sound-attenuated bedroom with infrared video-controlled supervision. PSG recordings obtained from 2300h to 0700h were scored by trained polysomnologists according to the Rechtschaffen and Kales manual for sleep staging, and according to the AASM version 2.1 for apnea, hypopnea, and limb movements. PSG measurements included total sleep time (TST), sleep latency, sleep efficiency, wake after sleep onset (WASO), REM latency, sleep stages 1, 2, 3, and 4, REM, and slow wave sleep (SWS; sum of sleep stages 3 and 4).

2-3-2. Cognitive tests (PVT and DSST)

2-3-2-1. PVT

The PVT is a simple reaction time (RT) test used internationally to assess drowsiness [17-19]. In this monotonous test lasting 20 minutes, three different figures were randomly and irregularly displayed on a computer screen at inter-stimulus intervals ranging from 2 to 10 sec, which is designed to induce drowsiness. Participants were instructed to click the right mouse-button as quickly as

possible when the designated target figure appeared. Test results include correct answer RT (msec), incorrect answer RT (msec), correct answer rate, lapses (RT >500 msec), and false start. In this study, a PVT test program developed by NoruPro Light Systems, Inc. was used.

2-3-2-2. DSST

The DSST is a pencil and paper test of psychomotor performance [20], in which the participant is given a key grid of numbers and matching symbols and a test section with numbers and empty boxes. Participants were asked to fill empty boxes with matching numbers as quickly and correctly as possible within 90 seconds. The number of correct number–symbol matches was used as the DSST score. The DSST is easy to administer and sensitive to individual differences related to cognitive performance. To avoid the learning effect, we prepared three different versions of DSST that used different symbols. Participants were presented different DSST versions randomly during each experiment session.

2-3-3. VAS

The VAS is used widely to measure subjective items. For example, in studies that measure subjective pain, participants are asked to indicate pain intensity along a 100-mm horizontal line, and this rating is measured from the left edge [21, 22]. In this study, the VAS was used to measure 12 items relating to subjective sleep and mental conditions. The details of the 12 items are shown in Table 3.

2-4. Statistical analysis

Data were analyzed by repeated measures analysis of variance (repeated measures ANOVA) and correlation analysis. ANOVA was used to assess differences among administered drugs (placebo, 5 mg zolpidem, and 0.25 mg triazolam). ANOVA-dependent variables were sleep indices (TST, SWS, REM stage, non-REM stages 1, 2, 3, and 4, sleep latency, REM latency, and WASO), cognitive indices (PVT parameters and DSST score), and subjective measures (VAS). When a significant main effect was observed, post-hoc tests were performed. Correlation analysis was used to assess the presence of interactions between sleep indices, cognitive indices and subjective measures. To examine correlations between cognitive indices and other variables, Spearman's rank correlation tests were performed. $P < 0.05$ was considered statistically significant for all analyses.

3. Results

Fifteen healthy young male volunteers provided written informed consent to participate in this study. Of these, two were excluded, including one who withdrew his consent after placebo PSG recording, and another who showed disordered sleep breathing during placebo PSG. Ultimately, 13

participants (mean age, 23.4 ± 3.2 years) were included in this study.

3-1. Sleep variables

Table 1 shows sleep variables under each condition. TST was 429 ± 33.8 min after placebo administration, 457 ± 9.5 min after triazolam administration, and 456 ± 10.8 after zolpidem administration. Sleep efficiency was 89.5 ± 7.1% after placebo administration, 95.1 ± 1.8% after triazolam administration, and 94.9 ± 2.2% after zolpidem administration. Sleep stage 2 was 246.7 ± 32.6 min after placebo administration, 288.8 ± 32.7 min after triazolam administration, and 275.8 ± 34.1 min after zolpidem administration. Sleep stage 4 was 17.4 ± 20.0 min after placebo administration, 23.3 ± 28.0 min after triazolam administration, and 28.8 ± 35.5 min after zolpidem administration. WASO was 50.1 ± 33.8 min after placebo administration, 22.7 ± 9.5 min after triazolam administration, and 24.0 ± 10.8 min after zolpidem administration. Sleep stage 1 was 45.6 ± 21.6 min after placebo administration, 29.6 ± 12.3 min after triazolam administration, and 31.0 ± 17.1 min after zolpidem administration.

Significant main effects of triazolam and zolpidem were observed in TST, sleep efficiency, WASO, and sleep stages 1, 2 and 4, but not in SWS, sleep latency, REM latency, sleep stage 3, and REM. Post-hoc tests revealed that administration of both hypnotics significantly increased TST, sleep efficiency, sleep stages 2 and 4, and significantly decreased WASO and sleep stage 1. However, no significant differences were observed in these variables between triazolam and zolpidem, which differ in chemical structure.

3-2. Cognitive tests

As shown in Table 2, no significant main effect was observed in PVT. On the other hand, post-hoc tests revealed a significant main effect on DSST score, which was significantly lower in those administered hypnotics (41.5 ± 5.2, triazolam; 42.2 ± 4.2, zolpidem) compared to placebo (44.8 ± 5.7).

As shown in Table 3, significant main effects of hypnotics were observed in "subjective alertness," "vigor," and "sadness." Post-hoc tests revealed that hypnotic administration significantly decreased "subjective alertness" and "vigor," and significantly increased "sadness."

3-3. Correlation between items

PVT parameters and DSST score were not significantly correlated with VAS items. DSST score was positively correlated with sleep stage 1 and time in bed.

4. Discussion

The two ultra-short acting hypnotics used in this study, i.e., triazolam and zolpidem, showed sleep enhancing effects. TST, sleep efficiency, and sleep stages 2 and 4 were significantly increased by these

hypnotics, while WASO and sleep stage 1 were significantly decreased. DSST score was significantly lower in those administered ultra-short acting hypnotics, even after 12 hours post-administration, and "subjective alertness," "vigor," and "sadness" were significantly deteriorated, although no significant effects were observed in PVT. No differences were observed between triazolam and zolpidem in all analyses. These results suggest that administration of ultra-short acting hypnotics decreases cognitive performance in midday, i.e., 12 hours after administration, with dissociating effects. Moreover, some subjective measures were also deteriorated, even after 12 hours.

Previous studies mainly investigated the effects of hypnotics on cognitive function and performance on the following day, with some reporting that driving ability is not affected by ultra-short acting hypnotics 9 hours after administration [10-12]. However, recent studies have suggested that 9-10 hours may not be sufficient to eliminate the negative effects of hypnotics on driving ability. One study carried out on-the-road highway driving performance tests 8.5 hours after administration of ramelteon (8 mg) or zopiclone (7.5 mg) in healthy adults, and found that lane keeping ability and cognitive function were significantly deteriorated [13]. Another study using a driving simulator with simultaneous eye movement analyses revealed that driving performance and ocular saccades were deteriorated even 10 hours after administration of zopiclone (7.5 mg) or flunitrazepam (1 mg) [14].

Administration of hypnotics has been reported to decrease cognitive function, as reflected by PVT and DSST, as well as word learning performance. The effects of hypnotics to decrease cognitive function have been found to persist from 30 min up to 10 hours post-administration [23-24]. However, the residual effects of hypnotics after more than 12 hours have not been investigated in detail. Therefore, evaluating the residual effects of hypnotics for longer hours is warranted.

The present study is the first to reveal the persisting effects of ultra-short acting hypnotics on cognitive performance, even 12 hours after administration. This finding may have a social impact, as most physicians regard sleepiness as the indicator of residual effects of hypnotics. Therefore, physicians may either reduce the doses of hypnotics or consider changing prescriptions when patients complain about daytime sleepiness. Our results indicate that even if patients are unaware of the residual effects (i.e., sleepiness), their cognitive functions may be significantly deteriorated even in midday and may cause problems, such as falls, traffic accidents, and industrial accidents.

In Japan, there is no regulation on driving after taking hypnotics, although the Ministry of Health, Labour and Welfare issued a notice in 2014 stating that occupational long-haul drivers must not drive continuously for more than 13 hours and that they must rest for more than 8 hours continuously [25]. Drivers taking hypnotics or physicians prescribing hypnotics are legally responsible when traffic accidents occur. The Ministry of Land, Infrastructure and Transport of Japan prohibits commercial aviation flight crews from taking hypnotics under any circumstances, except for ultra-short acting hypnotics, within 36 hours before flight [26]. The US Department of Transportation states that it is

generally safe to drive vehicles 5 hours after taking zaleplon, and 9 hours after taking zolpidem, at recommended doses [10-12]. According to driving regulations related to use of hypnotics in other developed countries and the European Union, 12 hours after administration of ultra-short acting hypnotics is considered sufficient to prevent traffic accidents [7]. Our study suggests that these regulations should be reconsidered, as complex and integrated functions may not be fully recovered for safe driving within the time frames specified in existing regulations or recommendations by governments or traffic regulators in developed countries.

With respect to objective sleep variables measured by PSG, hypnotics increased sleep efficiency and sleep stages 2 and 4, and decreased WASO and sleep stage 1, suggesting that while sleep quality improved, SWS was not affected. The effect of BZDs to decrease SWS has been reported, although non-BZD agents have no such effect [27-30]. In the present study, SWS was not affected by triazolam or zolpidem. This discrepancy may be explained by the fact that triazolam and zolpidem were administered acutely in our study, whereas in previous studies, hypnotics were administered repeatedly or chronically.

Based on VAS scores, administration of hypnotics significantly deteriorated "subjective alertness," "vigor," and "sadness" even after more than 12 hours elapsed since the administration, possibly because our participants were aware of the residual effects of hypnotics. Though it is unclear which kind of cognitive functions or physiological process were represented by these subjective scores, these residual effects might have not been detected by PVT but by DSST and VAS.

This study has several limitations. First, we investigated the acute effects of ultra-short acting hypnotics on nighttime sleep and daytime cognitive function in healthy young males. Therefore, chronic effects of hypnotics may differ, as well as the effects of hypnotics on those with insomnia or older people. Future studies should investigate the complex and integrated cognitive functions in older people and patients with insomnia who are taking hypnotics chronically. Second, driving performance was not examined in this study. While it is ideal to conduct experiments in real traffic settings to investigate the effects of hypnotics on driving performance, such experimental settings are dangerous and difficult to design. Conversely, the DSST reflects attention and working memory, which are important functions required for driving. Third, first night effects, i.e., adaptation to the laboratory environment, were not fully controlled in this study. It may be possible that sleep enhancements after hypnotic administrations were caused by adaptation to the laboratory environment. If adaptation was the main reason for sleep enhancement after hypnotic administration, cognitive functions might have been recovered after sufficient hours which is contrary to the results. Therefore, first night effects might not have significantly affected our results and deterioration of DSST 12 hours after administrations might be evoked by hypnotics.

In conclusion, decreased cognitive function as measured by DSST persisted even 12 hours after administration of ultra-short acting hypnotics, while sleepiness as measured by PVT disappeared.

Although the present study did not examine the effects of chronic administration and had a limited sample size (i.e., did not include elderly people or those with insomnia), our findings highlight the need to reexamine existing guidelines and regulations on the administration of hypnotics to drivers and pilots.

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6. Results List（業績目録）

（Ⅰ）主学術論文（英文原著）

◎１．Matsunaga Y, Tagaya H, Fukase Y, Hakamata Y, Murayama N, Kumagai Y, Kuroyama M. : Effects of zolpidem/triazolam on cognitive performance 12 hours after acute administration. Sleep Med,52:213-218,2018.

（Ⅱ）原　著（主学術論文を除く）

○１．松永祐輔、下田隆大、渡邉孝明、原田愛永、寄川兼汰、深瀬裕子、村山憲男、吉田煦、田ヶ谷浩邦、松永篤彦：血液透析患者の日常生活活動における困難感と抑うつ症状について．総合病院精神医学、30:341-348,2018.

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（Ⅲ）著　書

なし

（Ⅳ）総説・講座

○１．田ヶ谷浩邦、村山憲男、深瀬裕子、松永祐輔：睡眠薬は認知証の危険因子か？. 老年精神医学雑誌、28:347-352,2017.

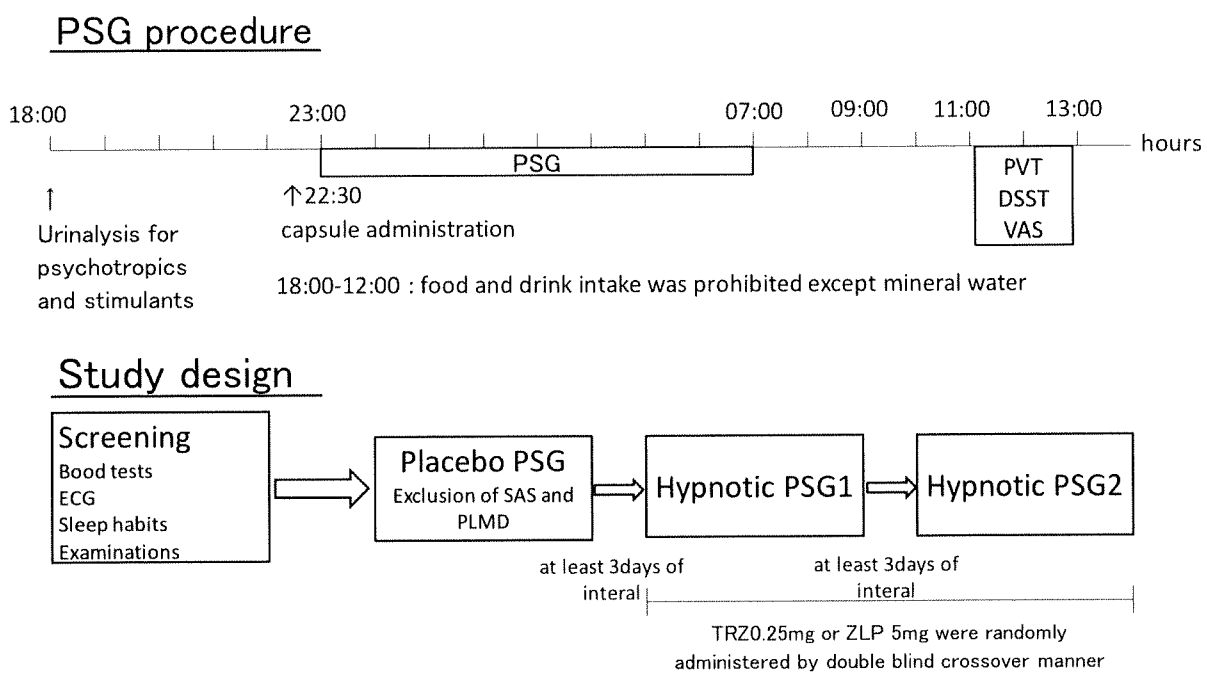
○２．田ヶ谷浩邦、村山憲男、深瀬裕子、松永祐輔：睡眠障害のメカニズム. MEDICAL REHABILITATION、203:7-12,2016.

（Ⅴ）症例・臨床治験・その他

なし

7. Figure and Tables

Figure 1. Study design and Polysomnography procedure



Note. PSG = Polysomnography, PVT = psychomotor vigilance task, DSST = digit symbol subtraction test, VAS = visual analog scale, SAS = sleep apnea syndrome, PLMD = periodic limb movement disorder, TRZ = triazolam, ZLP = zolpidem.

Table 1. Result of Polysomnography

	Placebo	BZD (triazolam)	non-BZD (zolpidem)	
	(Mean ± SD)	*(Mean ± SD)*	*(Mean ± SD)*	*p-value*
total sleep time [TST] (min)	429.9 ± 33.8	457.3 ± 9.5	456.0 ± 10.8	*
Slow-wave sleep [SWS] (min)	48.1 ± 28.7	53.6 ± 33.1	58.5 ± 36.1	n.s
Sleep latency (min)	5.8 ± 2.9	6.2 ± 3.0	5.5 ± 5.3	n.s
Sleep efficiency (%)	89.5 ± 7.1	95.1 ± 1.8	94.9 ± 2.2	*
wake after sleep onset [WASO] (min)	50.1 ± 33.8	22.7 ± 9.5	24.0 ± 10.8	*
REM latency (min)	109.3 ± 48.8	115.2 ± 50.0	100 ± 50.0	n.s
non-REM stage 1 (min)	45.6 ± 21.6	29.6 ± 12.3	31.0 ± 17.1	*
Stage 2 (min)	246.7 ± 32.6	288.8 ± 32.7	275.8 ± 34.1	*
Stage 3 (min)	30.7±19.9	30.2 ± 22.0	29.7 ± 17.6	n.s
Stage 4 (min)	17.4 ± 20.0	23.3 ± 28.0	28.8 ± 35.5	*
Stage REM (min)	89.5 ± 18.7	85.4 ± 18.8	90.5 ± 17.8	n.s

Note. BZD = benzodiazepine, * = $p < 0.05$, n.s = not significant, , REM = Rapid eye movement.

Table 2. Result of Cognitive test

	Placebo	BZD (triazolam)	non-BZD (zolpidem)	
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*p-value*
PVT correct answer RT (msec)	371.6 ± 47.9	343.2 ± 108.2	372.5 ± 35.2	n.s
incorrect answer RT (msec)	180.7 ± 215.3	174.5 ± 178.7	230.5 ± 171.8	n.s
correct answer rate (%)	92.9 ± 20.7	96.8 ± 8.2	98.9 ± 1.4	n.s
Lapses (RT>500msec)	0.2 ± 0.4	0.5 ± 1.1	0.4 ± 1.1	n.s
false start	3.6 ± 11.0	0.3 ± 0.6	0.5 ± 1.1	n.s
DSST score	44.8 ± 5.7	41.5 ± 5.2	42.2 ± 4.2	*

Note. BZD = benzodiazepine, PVT = Psychomotor vigilance test, RT = reaction time, Lapses = more than 500 msec of reaction time, DSST = digit symbol Substitution test, * = $p < 0.05$, n.s = not significant.

Table 3. Result of visual analog scale

	Placebo	BZD (triazolam)	non-BZD (zolpidem)	
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*p-value*
1. subjective alertness (mm)	60.3 ± 22.9	55.4 ± 20.3	40.1 ± 17.1	*
2. mood (mm)	60.5 ± 17.9	58.8 ± 12.9	47.2 ± 22.1	n.s
3. vigor (mm)	63.5 ± 20.1	58.3 ± 14.1	50.3 ± 15.2	*
4. tension (mm)	31.7 ± 22.2	38.6 ± 18.8	36.8 ± 12.3	n.s
5. irritability (mm)	12.6 ± 15.9	21.5 ± 20.9	27.8 ± 24.3	n.s
6. happiness (mm)	38.3 ± 18.6	45.6 ± 17.6	42.6 ± 17.6	n.s
7. motivation (mm)	56.7 ± 17.3	57.4 ± 15.2	50.2 ± 12.1	n.s
8. subjective time passage (mm)	43.2 ± 15.3	44.2 ± 16.8	45.4 ± 18.2	n.s
9. clearness (mm)	50.6 ± 19.4	46.5 ± 13.4	40.1 ± 15.6	n.s
10. positiveness (mm)	66.8 ±14.9	66.8 ± 21.4	68.1 ± 17.2	n.s
11. sadness (mm)	8.8 ± 14.5	17.1 ± 19.7	25.4 ± 21.7	*
12. tiredness (mm)	32.2 ± 22.2	30.8 ± 21.3	43.6 ± 19.5	n.s

Note. BZD = benzodiazepine, * = $p<0.05$.