



# Effect of Long-Term Benzodiazepines for Chronic Insomnia on Cognitive Function and Waking Electroencephalography: A Case-Control Study

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**Objective** The relationship between benzodiazepine use and cognitive decline in insomnia patients has been reported, but still conflicting. Thus, we tried to determine whether long-term exposure of benzodiazepine might be associated with changes of cognition and electroencephalography (EEG) findings in patients with chronic insomnia.

**Methods** Insomniacs using benzodiazepines (n=29), drug-free insomniacs (n=27), and age- and sex-matched controls (n=28) were recruited. Neurocognitive function tested with Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery, quantitative EEG in awake state, and information of benzodiazepine usage were obtained.

**Results** Drug-free insomniacs reported more severe symptoms than insomniacs using benzodiazepine (p<0.001). Insomniacs using benzodiazepine showed a decrease of executive function in Trail Making Test A than drug-free insomniacs and controls (0.73±0.66 vs. 1.27±0.38 vs. 1.09±0.47, p<0.001) and in categorical fluency than drug-free insomniacs (-0.01±0.99 vs. 1.26±0.97, p=0.002). However, such decrease of executive function was not proportional to daily dose or cumulative dose of benzodiazepine. The EEG was not significantly different between insomniacs using benzodiazepine and drug-free insomniacs, while EEG of insomniacs showed low relative theta power in frontal and parietal regions but high relative beta power in frontal region than that of controls.

**Conclusion** Benzodiazepine users with chronic insomnia showed an impairment of executive function compared to drug-free insomniacs and controls although they showed relatively decreased severity of insomnia symptoms. Chronic insomniacs showed a hyper-arousal manifestation in front-parietal region of brain regardless of benzodiazepine exposure. **Psychiatry Investig 2022;19(4):259-267**

**Keywords** Insomnia; Benzodiazepines; Cognition; Executive function; Electroencephalography.

## INTRODUCTION

Insomnia is highly prevalent in the general population, with prevalence ranging from 10% to 48%. It is likely to become chronic if insomnia is not dealt with appropriately or immediately.<sup>1</sup> Individuals with chronic insomnia can be affected by adverse health outcomes such as cognitive decline including

dementia, cardiovascular diseases,<sup>2</sup> metabolic disease,<sup>3</sup> depression,<sup>4</sup> and suicidal risk.<sup>5</sup> As sleep has a crucial function in memory restoration,<sup>6,7</sup> adequate treatment of insomnia could delay or be protective for cognitive decline in the future.

Up to now, therapeutic options for insomnia are limited to medication and cognitive behavioral therapy (CBT). Although CBT is the first recommendation for chronic insomnia,<sup>8</sup> CBT requires some time and cost for face-to-face encountering with therapists as well as willingness of patients to participate in the treatment. If CBT for insomnia is not sufficiently effective or is unavailable, pharmacological intervention can be offered. In clinical practice, patients who have suffered from insomnia severely usually report considerable anxiety or worry<sup>9</sup> and they are likely to prefer medications.<sup>10</sup> The most widely used medications for insomnia are benzodiazepines and benzodiaze-

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pine-receptor agonists. However, long-term use of benzodiazepines is known to be associated with an elevated risk of dependency, development of tolerance, and rebound insomnia on discontinuation and a risk of cognitive impairment such as visuospatial ability, speed of processing, and verbal learning.<sup>11</sup> Thus, pharmacological guidelines for insomnia from American Academy of Sleep Medicine,<sup>8</sup> European Sleep Research Society,<sup>12</sup> and American College of Physicians<sup>13</sup> have provided a recommendation that prescriptions should be limited to four to five weeks or less. Nevertheless, the proportion of patients receiving long-term prescription of benzodiazepine is not negligible.<sup>14,15</sup> Long-term users can be predicted by early age of insomnia onset, more frequent benzodiazepine use, and higher state-anxiety.<sup>16</sup> A relationship between cognitive decline including dementia and long-term use of benzodiazepine has been reported.<sup>17</sup> However, it remains controversial due to heterogeneity of studies and unknown mechanism. Chronic insomniacs usually worry about their cognitive decline associated with long-time use of benzodiazepines. Complicating issues exist regarding whether insomnia disorder itself is associated with cognitive deficits<sup>18</sup> or benzodiazepine used for treatment of insomnia might change the cognitive function.<sup>11,17</sup>

As insomnia becomes chronic, the hyper-arousal phenomenon which represents arousal signs in somatic, cognitive, and central nervous system (CNS) in body is usually observed. The CNS arousal can be measured by the electroencephalography (EEG), and quantitative EEG is an easy to apply and cost-effective method to estimate temporal resolution of functional brain activities by quantifying, as well as has advantages over EEG in the dimensional approach to symptomatology of psychiatric disorders compared to normal value.<sup>19,20</sup> It has been reported that the EEG of patient with insomnia showed increased activities of beta or gamma frequency, and/or decreased activity of theta frequency during sleep period or before sleep onset.<sup>21-24</sup> However, daytime EEG of chronic insomniacs have not been investigated yet although cognitive decline can be usually experienced mostly during the daytime. The aim of this study was to explore whether long-term exposure of benzodiazepine might be associated with cognitive decline in chronic insomnia compared to drug-free insomniacs and healthy controls. In addition to neuropsychological performance, daytime EEG was performed to understand effects of benzodiazepine on brain activity comprehensively.

## METHODS

### Participants

As a case-control study, we recruited aged 55 years or older with insomnia disorder who were taking medications from

the sleep clinic at Seoul National University Bundang Hospital (SNUBH). We collected information related to previous history of medication and insomnia symptom through face-to-face interview by a psychiatrist. Insomnia disorder was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition by physicians specialized in sleep disorders. Chronic insomniacs were defined as those who have sleep disturbance and associated daytime symptoms that present for at least three months.<sup>25</sup> Drug-free insomnia patients and age- and sex-matched healthy controls were enrolled by advertisement at local newspapers and subway stations. Those whose duration of insomnia disorder was more than one year were included in the study. None of these participants showed other sleep disorders, major psychiatric disorders, dementia, substance use disorders, neurological disorders, or any history of brain injury. This study was approved by the Institutional Review Board of SNUBH (B-1509/316-002). All participants were informed of the purpose and procedures of the study. They gave written consent before entering this study.

### Measurements

#### Sleep and mood-related questionnaires

For evaluating insomnia severity and daytime sleepiness of participants, insomnia severity index (ISI)<sup>26</sup> and Epworth sleepiness scale (ESS)<sup>27</sup> were used. Additionally, Beck Depression Inventory (BDI)-II<sup>28</sup> was used because depressive symptoms could affect cognitive function. Subjects with BDI-II  $\geq 20$  were excluded from final analysis.

#### Neurocognitive function test

We used the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Neuropsychological Assessment Battery (CERAD-K-N) to evaluate cognitive function of all subjects.<sup>29</sup> The CERAD-K-N consisted of nine neuropsychological tests, including 1) general cognitive function: the Mini-Mental State Examination (MMSE), 2) memory function: the Word List Recall Test, the Word List Recognition Test, the Constructional Recall Test, and 3) executive function: the Categorical Fluency Test, the Constructional Praxis Test, and the Trail Making Test A (TMT-A), and Frontal Assessment Battery. Clock Drawing Test for visuospatial abilities and Digit Span Test for attention were additionally administered to subjects. Scores of CERAD-K-N were used as Z-scores after adjusting for subjects' age and education. In case of participants who had abnormal cognitive function, cognitive disorder specialists in the Division of Geriatric Psychiatry clinically evaluated for confirmative diagnosis of mild cognitive impairment (MCI) based on standard criteria

for MCI<sup>30</sup> by means of a face-to-face standardized diagnostic interview.

### Quantitative electroencephalography

EEG at waking state was performed at fixed times around 9 AM or 4 PM and it was set at a time period during which alertness was maintained, neither right after mealtime nor being too sleepy. Test was recorded in a sitting position for 15 min. For the first 7 min, subjects kept their eyes closed. For the next minute, subjects opened their eyes. For the last 7 min, subjects kept their eyes closed. All subjects were observed by an examiner to check and prevent drowsiness. EEG electrodes were placed according to the international 10–20 system at FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, and O2, with an average reference. Recording of EEG started when electrical impedance of all electrodes was below 5 k $\Omega$ . EEG signals were sampled at 1,000 Hz and digitalized. The high pass filter was set to be 100 Hz with the low pass filter set to be 0.3 Hz. An artifact-free 120-s EEG recording with eyes closed (24 epochs of 5-s EEG segments) was selected by visual analysis. Artifacts comprised muscle activity, small body movements, eyelid movements, and micro-sleep. Spectral analysis for EEG data was done by the fast Fourier transform. Absolute power values of five bands at each electrode were computed: delta (1.0–4.0 Hz), theta (4.0–8.0 Hz), alpha (8.0–12.0 Hz), beta (12.0–25.0 Hz), and high beta (25.0–30.0 Hz). Relative power values were computed as the percentage of absolute power and grouped into five cerebral regions: frontal, central, parietal, temporal, and occipital areas.

### Benzodiazepine exposure

As an independent variable, information of benzodiazepine exposure before the index date was collected through a medical chart review of SNUBH, retrospectively. Starting age of benzodiazepine use and duration of exposure over the follow-up in SNUBH were obtained. We also calculated total duration of exposure by including duration of previous exposure before coming to SNUBH depending on the participants' report. Long-term benzodiazepine users were defined as receiving BDZs for more than 180 days within one year period.<sup>31,32</sup> Defined daily dose (DDD) was defined as the assumed average maintenance dose per day for a drug used for its main indication in adults according to World Health Organization (zolpidem, 10 mg; zolpidem CR, 12.5 mg; alprazolam, 1 mg; clonazepam, 8 mg; lorazepam, 2.5 mg; diazepam, 10 mg; clonazepam, 20 mg; triazolam, 0.25 mg).<sup>33</sup> It is widely used as a dose standard unit per day for drug utilization studies.<sup>32</sup> We calculated DDD as the total amount of benzodiazepine exposure before the index date as follows: First, the total milligrams for each benzodiazepine prescription were calculated by multi-

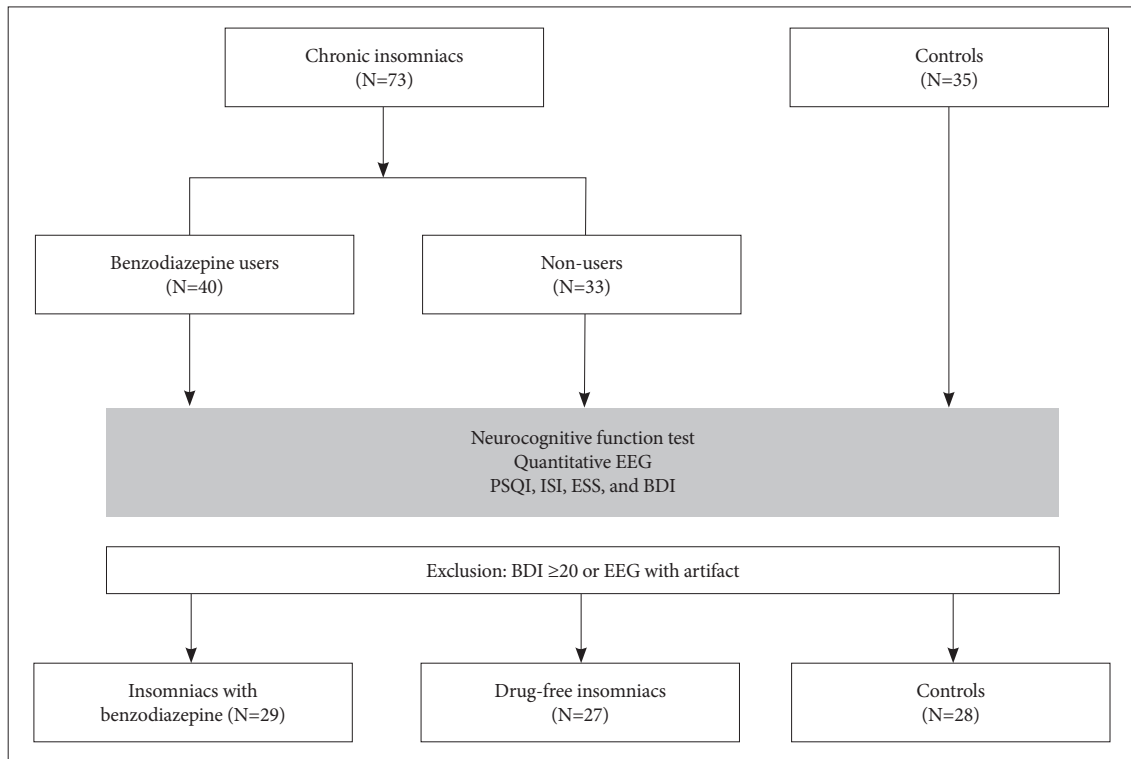
plying the number of pills. Second, this sum was divided by assigned DDD for each benzodiazepine. Third, it was divided by the total duration (days) from initial exposure to the index date. An individual's cumulative dose of benzodiazepine was calculated by summing up DDD amounts of all benzodiazepine prescriptions during the follow-up period in SNUBH.

### Statistical analysis

Results are reported as means $\pm$ standard deviations (SDs). The Kolmogorov-Smirnov test was used to confirm normality of all data. Comparisons of demographic characteristic, sleep variables, and mood variables among three groups were performed using the  $\chi^2$  test or analysis of variance with post hoc. Results (Z-scores) of neuropsychological tests were compared by multivariable analysis of covariance (ANCOVA) after adjusting for confounders including ESS, BDI, and exposure of other psychotropics. For estimating statistical power strictly, Bonferroni's correction for multiple comparisons was performed to compare Z-scores. Group-band interaction and between group-differences in relative EEG power were assessed by two-way ANCOVA for each cortical region, with group as an independent factor and five frequency bands as repeated measures. Confounding factors of EEG such as age, sex, ESS, and BDI were adjusted. In addition, we performed subgroup analysis only for insomnia with benzodiazepine group. Spearman correlations were computed to examine the relationship between benzodiazepine exposure and the change of cognition or EEG. All significance tests were two sided and p-value was set at <0.05. SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all analyses.

## RESULTS

Figure 1 shows a flow of the present study. Forty patients with insomnia disorder who were taking benzodiazepine, 33 benzodiazepine-free patients with insomnia disorder, and 35 age and sex-matched controls were enrolled at baseline. After excluding 24 subjects whose BDI  $\geq$ 20 or EEG with artifact, a total of 84 participants were included in the final analyses: insomniacs using benzodiazepine (n=29), drug-free insomniacs (n=27), and age- and sex-matched control (n=28). Ages (mean $\pm$ SD) of the participants were 68.03 $\pm$ 8.38, 64.89 $\pm$ 6.94, and 64.56 $\pm$ 6.48 years in insomniacs using benzodiazepine, drug-free insomniacs, and controls, respectively. Insomnia severity was significantly different among three groups (ISI scores of drug-free insomniacs [18.11 $\pm$ 5.13] vs. insomniacs using benzodiazepine [11.66 $\pm$ 7.13] vs. control [4.89 $\pm$ 4.98],  $p$ <0.001). Drug-free insomniacs reported more severe symptoms than insomniacs using benzodiazepine ( $p$ <0.001). Sex ratio, daytime somnolence, and mild cognitive disorder were not



**Figure 1.** Flow chart of this study. EEG, electroencephalography; PSQI, Pittsburgh Sleep Quality Index; ISI, insomnia severity index; ESS, Epworth sleepiness scale; BDI, Beck Depression Inventory.

**Table 1.** Comparison of demographic characteristics, sleep variables, and mood variables among insomniacs using benzodiazepine group, drug-free insomniacs, and controls

	Insomniacs using benzodiazepine (a) N=29	Drug-free insomniacs (b) N=27	Controls (c) N=28	F	p	Post hoc
Age (yr)	68.03±8.38	64.89±6.94	64.56±6.48	1.972	0.146	
Sex (female)	19 (65.5)	23 (85.2)	20 (71.4)	2.921	0.232	
Epworth sleepiness scale	5.52±3.59	6.74±3.43	7.89±4.92	2.466	0.091	
Insomnia severity index	11.66±7.13	18.11±5.13	4.89±4.98	27.718	<0.001	b>a>c
Beck Depression Inventory	9.34±4.88	9.07±4.9	5.96±5.03	4.068	0.021	a>c
Mild cognitive impairment diagnosis	4 (13.8)	2 (7.4)	2 (7.1)	0.938	0.626	
Starting age of benzodiazepine use (yr)	61.9±8.6	-	-	-	-	
Duration of benzodiazepine exposure (yr)	11.8 (0.54–30.24)	-	-	-	-	
Defined daily dose*	0.72±0.52	-	-	-	-	

Variables are presented as mean±standard deviation, N (%), or median (minimum-maximum). \*when defined maximal dose is 1

significantly different among the three groups. In insomniacs using benzodiazepine, mean age at onset of benzodiazepine use was 61.9±8.6 years and duration of benzodiazepine exposure was 11.8 (median) years (range, 0.54–30.24 years). The DDD was 0.72±0.52 mg (reference is 1) in insomniacs using benzodiazepine (Table 1).

When we compared Z-scores of neurocognitive function among the three groups (Table 2), insomniacs using benzodiazepine showed a decreased executive function than drug-

free insomniacs and controls in alteration of Trail Making Test A (insomniacs using benzodiazepine [0.73±0.66] vs. drug-free insomniacs [1.27±0.38] vs. control [1.09±0.47], p<0.001) and categorical fluency (insomniacs using benzodiazepine [-0.01±0.99] vs. drug-free insomniacs [1.26±0.97] vs. control [0.77±1.08], p=0.002) than drug-free insomniacs after adjusting for score of BDI, ESS, and exposure to other medications. Although we also conducted subgroup analysis with only subjects prescribed benzodiazepines for more than 5 years to ex-

**Table 2.** Z-scores of neurocognitive performances in chronic insomniacs compared among insomniacs using benzodiazepine group, drug-free insomniacs, and controls

	Insomniacs using benzodiazepine (a) N=29	Drug-free insomniacs (b) N=27	Controls (c) N=28	F	p	Post hoc
Global cognition						
Mini-Mental State Examination	-0.18±1.01	0.45±0.75	0.24±1.00	2.73	0.072	
Attention/concentration						
Digit span backward	0.16±1.30	0.61±1.25	0.51±1.13	2.68	0.075	
Memory						
Word list recognition	-0.14±0.89	0.07±0.7	0.12±0.68	0.18	0.833	
Word list recall	-0.07±0.92	0.29±1.04	0.47±1.02	0.82	0.447	
Recall of constructional praxis	0.08±1.03	0.28±0.81	0.35±1.06	1.67	0.195	
Executive function						
Trail making test digit symbol test A	0.73±0.66	1.27±0.38	1.09±0.47	10.2	<0.001	a<b, a<c
Categorical fluency	-0.01±0.99	1.26±0.97	0.77±1.08	4.32	0.002	a<b
Frontal assessment battery	0.28±0.70	0.56±0.69	0.25±0.80	2.34	0.104	
Constructional praxis	0.20±0.65	0.36±0.43	0.25±0.69	0.23	0.796	
Visuospatial abilities						
Clock drawing	0.08±0.85	0.28±0.50	0.33±0.52	1.60	0.209	

Data are presented as mean±standard deviation. Multivariable analysis of covariance after adjusting for confounders (including Epworth sleepiness scale and Beck Depression Inventory, and exposure of other psychotropics) and Bonferroni's correction for multiple comparisons ( $p<0.005=0.05/10$ ) were conducted

**Table 3.** A correlation between characteristics of benzodiazepine use and neurocognitive function in insomniacs using benzodiazepine

	Age at onset of use	Duration of exposure	DDD	Cumulative dose
MMSE	-0.148	-0.454*	0.271	-0.183
Digit span backward	-0.412*	0.245	-0.016	0.065
Trail Making Test A	-0.468*	0.221	-0.238	-0.113
Categorical fluency	-0.168	-0.175	-0.086	-0.315
Frontal assessment battery	0.227	-0.444*	0.276	-0.265

\* $p<0.05$ . Spearman's correlation was conducted. MMSE, Mini-Mental State Examination; DDD, daily defined dose

clude a reverse causation in which cognitive decline usually preceded insomnia symptoms as a prodrome, overall results were not changed.

Especially in insomniacs using benzodiazepine, we tried to examine effects of characteristics in benzodiazepine usage on cognitive function (Table 3). Start the use of benzodiazepines at an older age was associated with a decrease of executive function (Trail Making Test A:  $\rho=-0.468$ ) and a decrease of attention/concentration (digit span backward:  $\rho=-0.412$ ) with a large effect size. Longer duration of benzodiazepine exposure was associated with decreases of executive function (frontal assessment battery:  $\rho=-0.444$ ) and global cognition (MMSE:  $\rho=-0.454$ ). However, DDD and cumulative dose of benzodiazepine were not associated with any cognitive function.

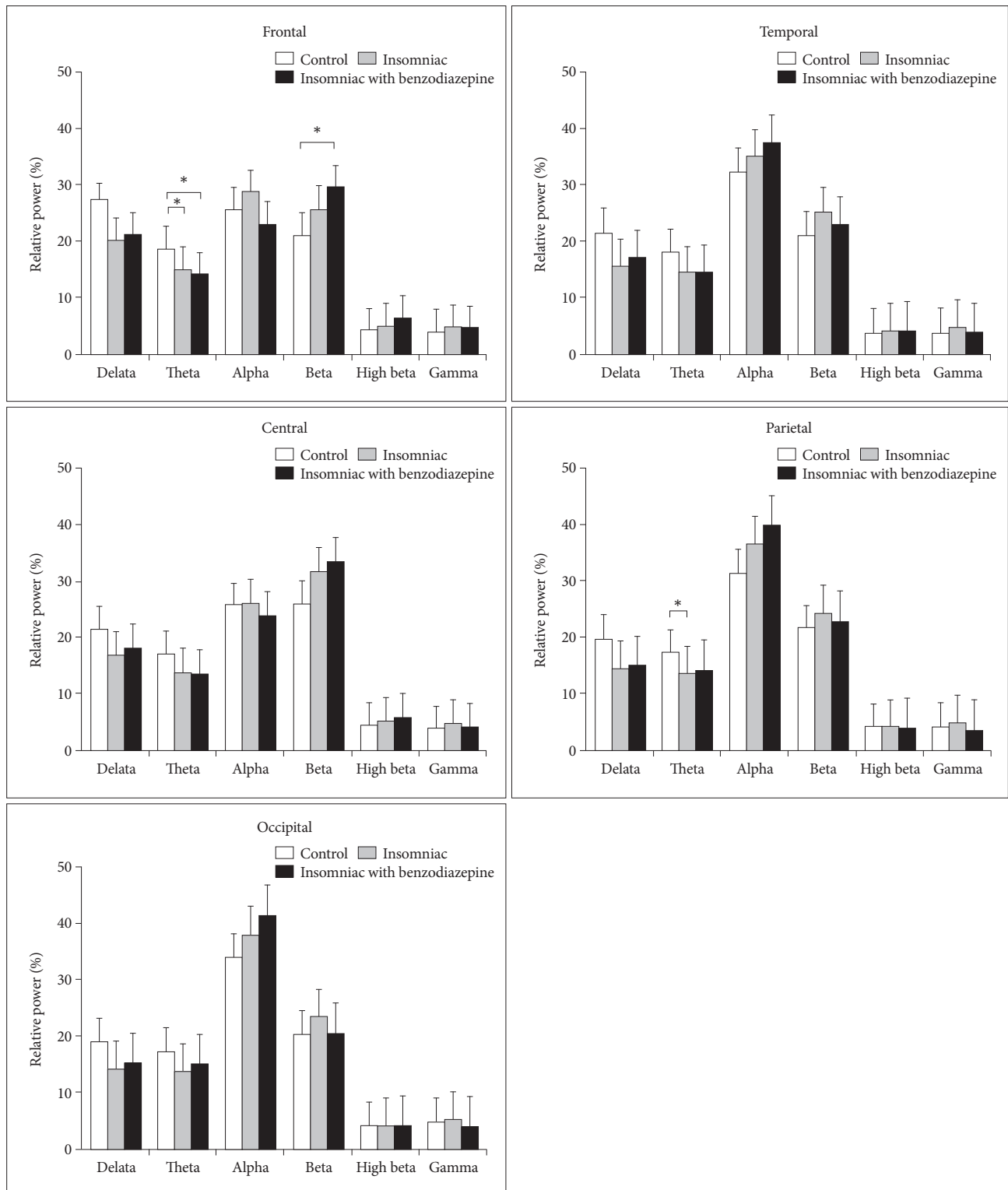
When we compared quantitative EEG in three groups af-

ter adjusting for age, sex, and scores of BDI and ESS (Figure 2), significant group-band interaction ( $F=3.099$ ,  $p=0.01$ ) in frontal area and between-group difference ( $F=3.608$ ,  $p=0.032$ ) in parietal area were found. In post-hoc analyses, a significant difference between insomniacs using benzodiazepine and drug-free insomniacs was not found. Instead, insomniacs using benzodiazepine showed low relative theta power (insomniacs with using benzodiazepine=14.1% vs. control=18.5%,  $p=0.014$ ) and high relative beta power (insomniacs with using benzodiazepine=29.3% vs. control=21%,  $p=0.045$ ) in frontal region than controls. Drug-free insomniacs showed low relative theta power in frontal region (insomniacs=14.8% vs. control=18.5%,  $p=0.021$ ) and parietal region (insomniacs=13.4% vs. control=17.2%,  $p=0.039$ ) than controls.

## DISCUSSION

Benzodiazepine users with chronic insomnia showed im-

paired executive function without memory decline compared to drug-free insomniacs and controls, although they showed relatively decreased severity of insomnia symptoms. The EEG



**Figure 2.** Comparison of relative electroencephalography spectral power among insomnia with benzodiazepine group, insomnia without benzodiazepine group, and controls. \* $p < 0.05$ .

of chronic insomniacs seemed to show a hyper-arousal manifestation regardless of benzodiazepine exposure compared to controls, which had low relative theta and high relative beta power in fronto-parietal regions.

The main outcome of this study was the significant relationship between a long-term use of benzodiazepines and a decline of executive function. Our result seems to be in line with previous findings regarding cognitive function which is affected by long-term benzodiazepine use (e.g., decreased visuospatial ability, speed of processing, verbal learning, and prospective/retrospective memory).<sup>11,17</sup> In previous systemic reviews, long-term cognitive impacts of benzodiazepine in all-aged adults were associated with impairments in processing speed, divided attention, visuoconstruction, working memory, recent memory, and expressive language.<sup>34</sup> Another systemic review on the elderly population has reported that the process speed (examined by digital symbol test) is significantly impaired, while global cognition (examined by MMSE), memory (examined by auditory verbal test), and executive function (examined by Stroop color and word test) are not significant or show high heterogeneity throughout selected studies in benzodiazepine users than in controls.<sup>35</sup> These relatively different interpretations or inconsistency can be caused by different types of cognitive measurement when selecting tests by investigators in different studies. For example, Mura et al.<sup>36</sup> have used TMT-A and -B tests for evaluating processing speed while others selected a digit symbol test<sup>37</sup> or a block design for the same purpose.<sup>38</sup> Also, one cognitive test does not always reflect one cognitive function, but involves or needs several cognitive functions at the same time. For example, the categorical verbal fluency test which consists of the production of words in a limited amount of time starting within a semantic category needs processing speed as fast as possible. It requires retrieval of the content of semantic memory, in which concepts and words are hierarchically organized by the executive function.<sup>39</sup> Executive function is defined as a supervisory capacity in the overall hierarchy of brain processing and encompasses skills necessary for purposeful, goal-directed behaviors.<sup>40</sup> It is often associated with prefrontal cortical areas. It characteristically includes processes such as goal formation, planning, initiation, preservation and alteration of goal-directed behavior, problem solving, response inhibition, and cognitive flexibility.<sup>41</sup> Therefore, low scores of TMT-A and categorical fluency of subjects in this study might indicate that long-term use of benzodiazepine is associated with a decline of executive function as a superordinate concept of cognition.

However, the decrease of executive function was not proportional to daily dose or cumulative dose of benzodiazepine in this study. Rather, it was associated with duration of benzodiazepine exposure and age at starting medication. Long-

duration of benzodiazepine exposure also means long-duration of suffering from insomnia without remission. Indeed, a remission rate of chronic insomnia was less than a half in spite of receiving benzodiazepine treatment and sleep disturbance remained and became chronic.<sup>42</sup> Sleep disturbance for long period could cause cognitive problems including memory and frontal lobe function.<sup>18</sup> An activation of the glymphatic system during sleep is associated with a brain clearance system that removes potentially toxic biomolecules such as beta-amyloid protein.<sup>43</sup> Brain damage caused by decreased peripheral brain-derived neurotrophic factor<sup>44,45</sup> has been suggested as a mechanism of cognitive decline or pathogenesis of neurodegenerative diseases. If the duration of suffering insomnia in drug-free insomniacs is much shorter than that of insomniacs using benzodiazepine, the gap of cognitive function between them would become relatively big. Speculation of a relative short duration in drug-free insomniacs not enough to change one's cognitive function might be an explanation about the no-difference in cognitive function between drug-free insomniacs and controls.

In addition, decreased executive function was associated with starting benzodiazepine use at an old age. Sleep disturbances including frequent early awakening and decreased sleep quality commonly happen in elderly people and a prevalence of insomnia symptoms generally increases with age.<sup>1</sup> Their poor sleep parameters such as lower sleep efficiency, greater wake after sleep onset, and circadian fragmentation of sleep are potentially correlated with worsening executive function.<sup>46</sup> Elderly people are more susceptible to cognitive impairment caused by benzodiazepine than younger people due to their decreased overall brain capacity and increased pre-dementic lesions in the brain.<sup>47</sup> Benzodiazepine drugs may have more adverse effects in elderly than in adults because of decreasing drug metabolism and changing pharmacokinetics with advancing years.<sup>48</sup> For these reasons, FDA recommends to start zolpidem in the elderly at half the dose used for adults. When starting to take benzodiazepine at a late age, it might be important to note the decrease of cognitive function in the future.

We found no significant difference in EEG between insomnia patients who took benzodiazepine for a long time and those who did not take drugs. Both groups showed a hyperarousal pattern of EEG compared to the control group. Attenuation of theta and enhancement of beta power can be electrophysiological correlates of sleep state misperception in insomnia such as tendency of patients to overestimate sleep latency or underestimate total sleep time relative to polysomnographic measures.<sup>49,50</sup> Beta and gamma activities are increased after total sleep deprivation but decreased in the morning after sleep as a restoring effect of sleep. Less theta power in

insomniacs suggests a decrease in homeostatic sleep propensity.<sup>22</sup> Regarding the long-term effect of benzodiazepines on EEG of brain, benzodiazepine such as lorazepam generally increases beta band but decreases alpha band.<sup>51</sup> More relative beta activity and less relative delta/theta activity compared to controls have been found in benzodiazepine abusers during night time polysomnography.<sup>52,53</sup> Taken together, the hyperarousal phenomenon of the fronto-parietal area in this study might be induced by both long-term of non-restoring sleep (decreasing theta/increasing beta) and long-term of use of benzodiazepine (increasing beta).

This study has several limitations. First, it is difficult to generalize our results due to a relatively small sample size. Second, the information about total duration of insomnia among drug-free insomniacs was not collected. As total duration of insomnia could affect cognitive decline, we could not control the effect of insomnia duration on cognitive function. In addition, previous history of benzodiazepine use before starting medication at SNUBH was not included in analyses. However, it might be negligible because previous exposure of benzodiazepine was relatively short. Third, no information of objective or actual sleep time per night in all insomnia patients could limit the interpretation. The absolute sleep time may be more important to influence the decline of memory than subjective dissatisfaction of sleep.<sup>45,54</sup> Fourth, there might be a selection bias among study participants. For example, people who remained under the benzodiazepine treatment were only those who tolerated the treatment well while people who complained any side effects of benzodiazepine might have drop-outed the follow-up. To examine and compare effect of benzodiazepines on cognitive function independently of insomnia which also affects cognition, future studies are needed to investigate and try to match several conditions such as age, severity of insomnia, duration of insomnia, and objective sleep time of study participants. The strength of this study was that the effort to adjust various variables such as depression, daytime sleepiness, and drug use history and reduce possibility of reverse causation might have contributed to increased validity of this study.

We found that executive functions of patients with insomnia after a long-term use of benzodiazepine were decreased. Long duration of insomnia and long-term use of benzodiazepine seemed to be causes of the decreased executive function. What we did not know before this study was that patients having insomnia symptoms could maintain the CNS arousal during the daytime regardless of taking benzodiazepine as long as the patient has insomnia. Novel treatment of insomnia such as cognitive behavioral therapy for insomnia, biofeedback, repetitive transcranial magnetic stimulation, light therapy, and exercise could be alternative options in addition to pharmacological intervention.<sup>55</sup> Nevertheless, benzodiazepine could

still be one of effective and fast methods to treat severe insomnia. Thus, clinicians should take into consideration advantages and disadvantages of using benzodiazepines for insomnia treatment. When using benzodiazepines, shortening the prescription period of benzodiazepine considering patients' age may help minimize one's executive dysfunction.

### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

### Conflicts of Interest

Hong Jun Jeon, a contributing editor of the *Psychiatry Investigation*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

### Author Contributions

Conceptualization: Hong Jun Jeon, In-Young Yoon. Data curation: Young Rong Bang. Formal analysis: Young Rong Bang. Investigation: all authors. Methodology: Hong Jun Jeon, In-Young Yoon. Writing—original draft: Young Rong Bang. Writing—review & editing: Young Rong Bang, In-Young Yoon.

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### REFERENCES

- Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
- Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation* 2011;124:2073-2081.
- Troxel WM, Buysse DJ, Matthews KA, Kip KE, Strollo PJ, Hall M, et al. Sleep symptoms predict the development of the metabolic syndrome. *Sleep* 2010;33:1633-1640.
- Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2001;135:10-19.
- Bjørngaard JH, Bjerkeset O, Romundstad P, Gunnell D. Sleeping problems and suicide in 75,000 Norwegian adults: a 20 year follow-up of the HUNT I study. *Sleep* 2011;34:1155-1159.
- Paller KA, Creery JD, Schechtman E. Memory and sleep: how sleep cognition can change the waking mind for the better. *Annu Rev Psychol* 2021;72:123-150.
- Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults. *Lancet Neurol* 2014;13:1017-1028.
- Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2017;13:307-349.
- Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* 2007;3:S7-S10.
- Davies J, Rae TC, Montagu L. Long-term benzodiazepine and Z-drugs use in England: a survey of general practice [corrected]. *Br J Gen Pract* 2017;67:e609-e613.



11. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs* 2004;18:37-48.
12. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* 2017;26:675-700.
13. Hauk L. Treatment of chronic insomnia in adults: ACP guideline. *Am Fam Physician* 2017;95:669-670.
14. Ohayon MM, Caulet M. Psychotropic medication and insomnia complaints in two epidemiological studies. *Can J Psychiatry* 1996;41:457-464.
15. Neutel CI. The epidemiology of long-term benzodiazepine use. *Int Rev Psychiatry* 2005;17:189-197.
16. Morin CM, Bélanger L, Bernier F. Correlates of benzodiazepine use in individuals with insomnia. *Sleep Med* 2004;5:457-462.
17. Stewart SA. The effects of benzodiazepines on cognition. *J Clin Psychiatry* 2005;66 Suppl 2:9-13.
18. Noh HJ, Joo EY, Kim ST, Yoon SM, Koo DL, Kim D, et al. The relationship between hippocampal volume and cognition in patients with chronic primary insomnia. *J Clin Neurol* 2012;8:130-138.
19. Coutin-Churchman P, Añez Y, Uzcátegui M, Alvarez L, Vergara F, Mendez L, et al. Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting. *Clin Neurophysiol* 2003;114:2294-2306.
20. Kesebir S, Yosmaoğlu A. QEEG in affective disorder: about to be a biomarker, endophenotype and predictor of treatment response. *Heliyon* 2018;4:e00741.
21. Perlis ML, Merica H, Smith MT, Giles DE. Beta EEG activity and insomnia. *Sleep Med Rev* 2001;5:363-374.
22. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep* 2001;24:110-117.
23. Wolynczyk-Gmaj D, Szelenberger W. Waking EEG in primary insomnia. *Acta Neurobiol Exp (Wars)* 2011;71:387-392.
24. Hamida ST, Penzel T, Ahmed B. EEG time and frequency domain analyses of primary insomnia. *Annu Int Conf IEEE Eng Med Biol Soc* 2015;2015:6206-6209.
25. American Academy of Sleep Medicine. International classification of sleep disorders (3rd ed). Darien: American Academy of Sleep Medicine; 2014. p. 21-22.
26. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601-608.
27. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.
28. Beck AT, Steer RA, Brown GK. Beck depression inventory (2nd ed). San Antonio: The Psychological Corporation; 1996.
29. Lee DY, Lee KU, Lee JH, Kim KW, Jhoo JH, Kim SY, et al. A normative study of the CERAD neuropsychological assessment battery in the Korean elderly. *J Int Neuropsychol Soc* 2004;10:72-81.
30. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256:183-194.
31. Wu CS, Wang SC, Chang IS, Lin KM. The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data. *Am J Geriatr Psychiatry* 2009;17:614-620.
32. Wu CS, Ting TT, Wang SC, Chang IS, Lin KM. Effect of benzodiazepine discontinuation on dementia risk. *Am J Geriatr Psychiatry* 2011;19:151-159.
33. World Health Organization. WHO collaborating centre for drug statistics methodology: guidelines for ATC classification and DDD assignment. Geneva: World Health Organization; 2009.
34. Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol* 2018;33:901-911.
35. Liu L, Jia L, Jian P, Zhou Y, Zhou J, Wu F, et al. The Effects of benzodiazepine use and abuse on cognition in the elders: a systematic review and meta-analysis of comparative studies. *Front Psychiatry* 2020;11:00755.
36. Mura T, Proust-Lima C, Akbaraly T, Amieva H, Tzourio C, Chevassus H, et al. Chronic use of benzodiazepines and latent cognitive decline in the elderly: results from the three-city study. *Eur Neuropsychopharmacol* 2013;23:212-223.
37. Del Ser T, Zea MA, Valentí M, Olazarán J, López-Álvarez J, Rebollo-Vázquez A, et al. Effects of commonly prescribed drugs on cognition and mild cognitive impairment in healthy elderly people. *J Psychopharmacol* 2019;33:965-974.
38. Helmes E, Østbye T. Associations between benzodiazepine use and neuropsychological test scores in older adults. *Can J Aging* 2015;34:207-214.
39. Quaranta D, Piccininni C, Caprara A, Malandrino A, Gainotti G, Marra C. Semantic relations in a categorical verbal fluency test: an exploratory investigation in mild cognitive impairment. *Front Psychol* 2019;10:2797.
40. Budson AE, Kowall NW. The handbook of Alzheimer's disease and other dementias. Hoboken: Wiley-Blackwell; 2014.
41. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol* 2010;9:1200-1213.
42. Pillai V, Roth T, Roehrs T, Moss K, Peterson EL, Drake CL. Effectiveness of benzodiazepine receptor agonists in the treatment of insomnia: an examination of response and remission rates. *Sleep* 2017;40:zsw044.
43. Mendelsohn AR, Larrick JW. Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. *Rejuvenation Res* 2013;16:518-523.
44. Johann AF, Hertenstein E, Kyle SD, Baglioni C, Feige B, Nissen C, et al. Insomnia with objective short sleep duration is associated with longer duration of insomnia in the Freiburg Insomnia Cohort compared to insomnia with normal sleep duration, but not with hypertension. *PLoS One* 2017;12:e0180339.
45. Fan TT, Chen WH, Shi L, Lin X, Tabarak S, Chen SJ, et al. Objective sleep duration is associated with cognitive deficits in primary insomnia: BDNF may play a role. *Sleep* 2019;42:zsy192.
46. Holanda FWN Júnior, de Almondes KM. Sleep and executive functions in older adults: a systematic review. *Dement Neuropsychol* 2016;10:185-197.
47. Pariente A, de Gage SB, Moore N, Bégaud B. The benzodiazepine-dementia disorders link: current state of knowledge. *CNS Drugs* 2016;30:1-7.
48. Dingemans J, Häussler J, Hering W, Ihmsen H, Albrecht S, Zell M, et al. Pharmacokinetic-pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects. *Br J Anaesth* 1997;79:567-574.
49. Carskadon MA, Dement WC, Mitler MM, Guilleminault C, Zarcone VP, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiatry* 1976;133:1382-1388.
50. Baker FC, Maloney S, Driver HS. A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women. *J Psychosom Res* 1999;47:335-341.
51. Michail E, Chouvarda I, Maglaveras N. Benzodiazepine administration effect on EEG fractal dimension: results and causalities. *Annu Int Conf IEEE Eng Med Biol Soc* 2010;2010:2350-2353.
52. Mazza M, Losurdo A, Testani E, Marano G, Di Nicola M, Dittoni S, et al. Polysomnographic findings in a cohort of chronic insomnia patients with benzodiazepine abuse. *J Clin Sleep Med* 2014;10:35-42.
53. Bastien CH, LeBlanc M, Carrier J, Morin CM. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep* 2003;26:313-317.
54. Fernandez-Mendoza J, He F, Puzino K, Amatrudo G, Calhoun S, Liao D, et al. Insomnia with objective short sleep duration is associated with cognitive impairment: a first look at cardiometabolic contributors to brain health. *Sleep* 2021;44:zsa150.
55. Perlis ML. Response to "do increases in beta EEG activity uniquely reflect insomnia?" (C. H. Bastein and M. H. Bonnet). *Sleep Med Rev* 2001;5:379-383.