

Association Between Z Drugs Use and Risk of Cognitive Impairment in Older Patients With Chronic Insomnia

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Abstract

Background Benzodiazepines (BZDs) and Z drugs are widely used for patients with chronic insomnia. The long term use of BZDs in older patients can cause cognitive impairment and potentially increase the risk of dementia. However, evidence for an association with Z drugs is limited. This study aimed to investigate the association between the risk of cognitive impairment and exposure to Z drugs in older patients with chronic insomnia.

Methods We recorded older patients with chronic insomnia who visited the outpatient department of neurology, Beijing Friendship Hospital, and assessed the global cognitive function (MoCA) and five cognitive domains (CVLT, TMT-B, BNT-30, CDT and DST). Multiple regression analysis was conducted to determine the independent factors of cognition, and evaluate the effect of Z drugs use (zolpidem and zopiclone) on cognition.

Results A total of 88 subjects were identified. BZDs use ($P=0.03$, $B=2.67$, 95% CI 0.36-4.97) and BZDs exposure density ($P=0.01$, $B=1.22$, 95% CI 0.33-2.11) were independent risk factors of cognitive impairment in older patients with chronic insomnia. Neither Z drugs use ($P=0.11$) nor Z drugs exposure density ($P=0.92$) correlated with global cognitive function. Moreover, compared with BZDs users, there were positive associations between Z drugs use and memory ($P=0.00$), attention ($P=0.00$) and verbal function ($P=0.04$). Additionally, education level ($P=0.02$, $OR=0.74$, 95% CI 0.57-0.95), duration of insomnia ($P=0.04$, $OR=1.05$, 95% CI 1.00-1.11) and severity of insomnia ($P=0.03$, $OR=1.27$, 95% CI 1.02-1.57) were also independent factors of global cognitive function.

Conclusion We found no evidence that Z drugs use and Z drugs exposure density were associated with cognitive impairment in older patients with chronic insomnia. However, the use of BZDs and BZDs exposure density were associated with an increased risk of cognitive impairment. Thus, BZDs use should be avoided and Z drugs should be prescribed with extreme caution in the elderly.

1. Background

In recent years, with the increasing competition in modern life and the quickening pace of life, the incidence rate of insomnia is increasing, which seriously affects people's life. About 10–30% of the world's people have insomnia, and about 50% of them suffer from chronic insomnia[1]. It is reported that in healthy subjects, sleep disorders increase levels of amyloid-beta ($a\beta$) in the cerebrospinal fluid (CSF), leading to the progression of neurodegeneration and the emergence of mild cognitive impairment [2–4]. Animal studies have shown that sleep restriction increases the susceptibility to $a\beta$ induced memory impairment in mice, accompanied by the increase of plasma corticosterone and pro-inflammatory cytokines in the brain lead to memory impairment and synaptic damage [5]. Therefore, sleep disorders have become the major risk factors for the development of Alzheimer's disease (AD) [6]. Treatment of sleep disorders may reduce the risk of probable future AD [7].

The treatment of chronic insomnia mainly includes cognitive behavioral therapy, drug therapy, light therapy, complementary and alternative drug therapy. Although cognitive behavioural therapy is the recommended first-line treatment [8], there are many limitations in its implementation. Therefore, Benzodiazepines (BZDs) and their receptor agonist Z drugs are commonly used for insomnia. However, long-term use of BZDs in elderly causes serious side effects, which not only lead to drug dependence and tolerance but also increase the risk of fall and fracture [9]. The effect of BZDs on cognition in the elderly is highly debated. Some studies have reported that long term use increase the risk of cognitive impairment [10–12], others have shown the contrary results [9, 13–16]. Although the association between BZDs and cognitive decline remains uncertain, it was determined that the use of BZDs in elderly should be avoided or limited for the short term.

Z drugs as an agonist of the BZD receptor component of the GABA_A receptor complex are commonly used for insomnia. Z drugs usually include Zolpidem, Zopiclone, Eszopiclone and Zaleplon. There are limited clinical studies on the association between Z drugs and cognitive impairment. Cheng HT et al. [17] reported that the use of a high cumulative dose of zolpidem increases the risk of AD among the elderly living in Taiwan. Shih HI et al. [18] suggested that the effect of zolpidem on cognition in patients with AD remained uncertain. The association between the Z drugs use and the risk of developing cognitive impairment in older patients with chronic insomnia is unknown. The aim of this study was to evaluate the effect of Z drugs on cognition among elderly patients with chronic insomnia.

2. Methods

Subjects

This case-control study was conducted from March 2019 to September 2019. We recruited the patients with chronic insomnia who visited the outpatient department of neurology, Beijing Friendship Hospital affiliated to Capital Medical University. The study was approved by the Ethics Review Committee of Beijing Friendship Hospital Affiliated to Capital Medical University (2019-P2-051-01). Inclusion criteria: 1. Patients with chronic insomnia who meet Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) diagnostic criteria and Pittsburgh Sleep Quality Index (PSQI) score > 7. 2. Age range 50–80 years. 3. The patients have been educated for more than six years and can complete the cognitive function test and other tests specified in the program. 4. Patients signed informed consent. Exclude criteria: 1. Secondary insomnia caused by physical diseases (such as sleep apnea syndrome, restless legs syndrome, periodic physical activity, rapid eye movement sleep disorder, etc.). 2. Patients with schizophrenia, bipolar disorder, delirium and other mental disorders who meet DSM-IV diagnostic criteria. 3. Alcohol and drug dependence or abuse. 4. The patient has serious or unstable organic diseases (including serious heart, liver and kidney diseases, tumours, etc.). 5. Hamilton Depression Scale (HAMD) (17 items) score > 17, Hamilton Anxiety Scale (HAMA) score > 14. 6. Patients with dementia at baseline (such as AD, Parkinson's disease, Lewy body dementia, frontotemporal dementia). 7. The patient had a history of stroke, symptoms and signs of neurological deficit, and responsible lesion. 8. Patients have brain trauma, epilepsy, encephalitis, hydrocephalus, brain tumours and other neurological diseases that

can cause cognitive impairment. 9. Patients had abnormal laboratory indexes: moderate anaemia, fasting blood glucose more than two times of the upper limit of normal, creatinine level more than 1.5 times of the upper limit of normal, liver enzymes (aspartate aminotransferase or alanine aminotransferase levels) more than two times of the upper limit of normal. 10. Jet lag or work shift cause chronic insomnia. 11. Systolic blood pressure > 180 mmHg or < 90 mmHg, or diastolic blood pressure > 120 mmHg or < 60 mmHg. 12. Patients who take drugs to improve cognition, such as donepezil, galanthamine, kabbalatin, memantine, etc., or take drugs that have negative effects on cognition, such as anticholinergic drugs, antipsychotic drugs, antiepileptic drugs, glucocorticoids, etc.

Assessment of cognition and insomnia

The patients were divided into normal cognition group (Montreal Cognitive Assessment ,MOCA score \geq 26) and mild cognitive impairment group (MOCA score < 26). If the education period \leq 12 years, 1 point will be added. California verbal learning test (CVLT), Trail making test-B (TMT-B), Boston naming test-30 (BNT-30), Clock drawing test (CDT) and Digit span test (DST) were used to assess the memory, executive function, verbal function, visuospatial ability and attention. The total score of 5 times of memory recall in CVLT \leq 35 is considered memory impairment. TMT-B score \geq 135.5 seconds, BNT-30 score \leq 22, CDT score \leq 3 and DST score \leq 4 are respectively considered abnormal. We used the PSQI scale to evaluate the severity of insomnia. Age at onset of insomnia (years), duration of insomnia (years), use of sedative-hypnotics and family history of insomnia were also recorded to analyse.

BZDs and Z drugs use

BZDs and BZD-related drugs, called Z drugs, are categorised according to the World Health Organization's Anatomical Therapeutic Chemical classification system. Estazolam, Lorazepam, Diazepam, and Clonazepam were categorised as BZDs. Zolpidem and Zopiclone were as Z drugs. Duration of drugs use (years), frequency of drugs use (times/week), BZDs and Z drugs use, BZDs and Z drugs exposure density (mg/d) were recorded. The first two indexes were obtained from patients; the latter two indexes were calculated from prescription register data since the one year before recruitment. The exposure density of each BZD or Z drug, which corresponded to an average one-day exposure, equals the total doses in milligrams divided by the duration of use in days. Each drug use and exposure density was calculated separately, and the overlapping drugs use were calculated respectively, according to each drug.

Confounders

We recorded known potential confounders for cognitive impairment, including marriage, living alone, economy, education level, insomnia and some comorbidities, such as hypertension, diabetes mellitus, coronary heart disease, dyslipidemia. Depression is an important mental differential diagnosis of cognitive impairment. HAMD-17 items and HAMA scales were used to evaluate depression and anxiety disorder. Daily physical activity was assessed by International Physical Activity Questionnaires (IPAQ) (short format). The collected laboratory indexes include fasting blood glucose (mmol/l), triglyceride

(mmol/l), total cholesterol (mmol/l), Low-density lipoprotein cholesterol (LDL-C, mmol/l), high-density lipoprotein cholesterol (HDL-C, mmol/l), serum uric acid (umol/l) and serum albumin (g/l).

Statistical analysis

All statistical analysis was conducted using SPSS, version 22.0. Continuous variables were expressed as mean \pm SD and categorical variables as numbers and percentages. The independent sample t-test or Mann-Whitney U test was performed to compare continuous variables. The χ^2 test or Fisher exact test was performed for categorical variables. Correlation analysis was used to analyse the associations between cognition and drugs use or other social-demographic, clinical and laboratory variables. Multiple logistic regression analysis or linear regression analysis was conducted to determine the independent factors of cognition. Statistical significance was defined by P-value $<$ 0.05 (two-tailed).

3. Results

3.1 Social-demographic and clinical characteristics of patients

The mean age of the patients with chronic insomnia was 61.18 ± 5.78 years (range, 50–79 years), with 32 (36.36%) men. The average age at onset of insomnia and duration of insomnia were 45.91 ± 15.29 years (range, 16–73 years) and 46.00 ± 15.31 (range, 1–46 years) respectively. Sixty-four (72.73%) patients had taken BZDs or Z-drugs for insomnia. The average duration and frequency of sedative-hypnotics were 8.92 ± 12.39 years and 5.80 ± 2.07 times a week, respectively. BZDs were used by 34.09% ($n = 30$) with 47.73% using Z drugs ($n = 42$). The reported BZDs were Estazolam (21.88%), Lorazepam (12.50%), Diazepam (9.38%), and Clonazepam (3.13%), the Z drugs used include Zolpidem (37.50%) and Zopiclone (25.00%). The average BZDs and Z drugs exposure densities were 0.57 ± 1.04 mg/d and 4.47 ± 4.50 mg/d, respectively. Fifty-six (63.64%) patients used BZD or Z drug alone, while 8 (9.09%) used BZD combined with Z drug. Among the 88 patients, the concomitant illness of hypertension, diabetes mellitus, coronary heart disease, dyslipidemia and gout was 40.91%, 15.91%, 13.64%, 45.45% and 2.27% respectively.

Correlation analysis showed that there were a negative association between PSQI score and MoCA score ($r = -0.22$, $P = 0.04$), a significant positive association between PSQI score and TMT-B seconds ($r = -0.31$, $P = 0.00$). However, no correlation was found between PSQI score and CVLT score, BNT-30 score, CDT score and DST score.

3.2 Correlation between global cognitive function and social-demographic and clinical characteristics

Among the 88 patients, they were divided into normal cognition group ($n = 20$, 22.73%) and mild cognitive impairment group ($n = 68$, 77.27%) according to the MoCA score. Table 1 shows the socio-demographic and clinical characteristics and the comparison between the two groups. Compared to the mild cognitive

impairment group, patients with normal cognition had better economy level ($P = 0.01$), a higher education level ($P = 0.00$), lower PSQI score ($P = 0.01$), less insomnia duration ($P = 0.05$) and less history of diabetes mellitus ($P = 0.03$). However, there is no significant difference in sex, BMI, marriage, living with others, HAMA and HAMD scores, age at onset of insomnia and use of sedative-hypnotics.

Table 1
Patient characteristics in normal cognition and cognitive impairment groups

	Patients with normal cognition (n = 20)	Patients with cognitive impairment (n = 68)	Univariate (P)
Male	6 (30.00%)	26 (38.24%)	0.50
Age (years)	59.20 ± 3.83	61.76 ± 6.14	0.08
Married/cohabitating	20 (100.00%)	58 (85.29%)	0.11
Living with others	20 (100.00%)	60 (88.24%)	0.19
Poor economy	6 (30.00%)	44 (64.71%)	0.01
Education (years)	13.50 ± 2.44	10.56 ± 3.38	0.00
BMI, kg/m ²	24.10 ± 3.96	23.42 ± 2.76	0.48
Smoking,%	6 (30.00%)	12 (17.65%)	0.34
Concomitant illness			
Hypertension,%	8 (40.00%)	28 (41.18%)	0.93
Diabetes mellitus,%	0 (0.00%)	14 (20.59%)	0.03
Coronary heart disease,%	0 (0.00%)	12 (17.65%)	0.06
Dyslipidemia,%	12 (60.00%)	28 (41.18%)	0.14
Gout,%	0 (0.00%)	2 (2.94%)	1.00
Insomnia			
Age at onset (years)	49.70 ± 12.57	45.71 ± 15.91	0.31
Duration of insomnia (years)	9.03 ± 13.08	16.12 ± 15.13	0.05
Use of sedative-hypnotics	14 (70.00%)	50 (73.53%)	0.76
PSQI score	12.20 ± 3.61	14.56 ± 2.31	0.01
Family history of insomnia,%	6 (30.00%)	20 (29.41%)	0.96
Laboratory indexes			
Fasting blood glucose, mmol/l	5.52 ± 0.24	5.29 ± 0.72	0.17
Triglyceride,mmol/l	0.98 ± 0.34	1.14 ± 0.42	0.30
Total cholesterol, mmol/l	4.19 ± 0.93	4.93 ± 1.04	0.06

	Patients with normal cognition (n = 20)	Patients with cognitive impairment (n = 68)	Univariate (P)
LDL-C, mmol/l	2.35 ± 0.55	2.80 ± 0.67	0.07
HDL-C, mmol/l	1.26 ± 0.26	1.45 ± 0.37	0.14
Serum uric acid, μmol/l	277.98 ± 56.33	291.84 ± 41.33	0.49
Serum albumin, g/l	43.32 ± 3.17	41.48 ± 3.23	0.13
HAMD score	10.70 ± 4.08	9.76 ± 4.81	0.43
HAMA score	10.20 ± 5.31	10.41 ± 3.96	0.87
IPAQ score	1784.50 ± 1341.70	2444.06 ± 2215.92	0.20

Correlation analysis showed that global cognitive function was correlated with age ($r = -0.31$, $P = 0.00$), economy level ($r = 0.44$, $P = 0.00$), education level ($r = 0.61$, $P = 0.00$), PSQI score ($r = -0.22$, $P = 0.04$), history of dyslipidemia ($r = -0.22$, $P = 0.04$), triglyceride level ($r = -0.45$, $P = 0.01$), total cholesterol level ($r = -0.54$, $P = 0.00$) and LDL-C level ($r = -0.59$, $P = 0.00$). Further, a multiple logistic regression analysis was performed to define the independent predictors of global cognitive function. Duration of insomnia ($P = 0.04$, odds ratio, 1.05, 95% confidence interval, CI, 1.00-1.11;), education level ($P = 0.02$, odds ratio, 0.74, 95% CI, 0.57–0.95;) and PSQI score ($P = 0.03$, odds ratio, 1.27, 95% CI, 1.02–1.57;) were independently associated with global cognitive function (see Table 2).

Table 2
Multiple logistic regression analysis for factors independently associated with global cognition in insomnia patients

	P Value	Odds ratio	95% CI
Duration of insomnia (years)	0.04	1.05	1.00-1.11
PSQI score	0.03	1.27	1.02–1.57
Education (years)	0.02	0.74	0.57–0.95

3.3 Correlation between sedative-hypnotics and global cognitive function

In the BZDs and Z drugs users, Table 3 shows the comparison between normal cognition group and mild cognitive impairment group. The patients with normal cognition had less BZDs use ($P = 0.01$) and BZDs exposure density ($P = 0.01$), lower PSQI score ($P = 0.00$), higher education level ($P = 0.00$), higher serum albumin level ($P = 0.00$) and lower serum uric acid level ($P = 0.02$). In multiple linear regression analysis, there were three factors that independently predicted global cognitive function, including BZDs use, BZDs

exposure density and education level. The coefficients of these factors were shown in Table 4. The results indicate that patients with normal cognition were likely to have less BZDs use and lower BZDs exposure density. No significant correlations were found between global cognitive function and Z-drugs use, Z-drugs exposure density, duration and frequency of drugs use.

Table 3

Univariate analysis for factors associated with cognition in benzodiazepine and Z-drug use patients

	Patients with normal cognition (n = 14)	Patients with cognitive impairment (n = 50)	Univariate (P)
Duration of drugs use (years)	10.43 ± 15.54	8.50 ± 11.51	0.61
Frequency of drugs use (times/week)	5.64 ± 1.73	5.85 ± 2.17	0.76
Benzodiazepines use	2 (14.29%)	28 (56.00%)	0.01
Benzodiazepines exposure density,mg/d	0.14 ± 0.36	0.69 ± 1.14	0.01
Z-drugs use	12 (85.71%)	30 (60.00%)	0.11
Z-drugs exposure density,mg/d	4.39 ± 2.63	4.49 ± 4.92	0.92
PSQI score	11.71 ± 2.97	14.76 ± 2.48	0.00
Education (years)	14.57 ± 2.07	11.20 ± 3.49	0.00
Serum albumin, g/l	44.80 ± 1.32	41.15 ± 3.42	0.00
Serum uric acid,umol/l	245.77 ± 50.38	297.46 ± 42.96	0.02

Table 4

Multiple linear regression analysis for factors independently associated with cognition in benzodiazepine and Z-drug use patients

	P Value	B value	95% CI
Benzodiazepines use	0.03	2.67	0.36–4.97
Benzodiazepines exposure density,mg/d	0.01	1.22	0.33–2.11
Education (years)	0.00	0.70	0.36–1.04

3.4 Correlation between sedative-hypnotics and memory, executive function, attention, verbal function, visuospatial ability

To better investigate the effect of sedative-hypnotics on cognition, the associations between sedative-hypnotics and five major cognitive domains were analysed. According to the scores of CVLT, the patients were divided into normal memory group (> 35) and impaired memory group (\leq 35). Table 5 shows the factors with statistical differences between the two groups. There were significant correlations between memory and duration of insomnia ($P = 0.00$), duration of sedative-hypnotics use ($P = 0.00$), BZDs use ($P = 0.01$), BZDs exposure density ($P = 0.00$), Z drugs use ($P = 0.00$), male ($P = 0.05$), age ($P = 0.00$) and economy level ($P = 0.00$). In multiple linear regression analysis, Z drugs use ($P = 0.00$, B value, -0.54, 95% CI, -0.89- -0.20;), duration of insomnia ($P = 0.02$, B value, -0.01, 95% CI, -0.02- -0.00;), male ($P = 0.00$, B value, 0.32, 95% CI, 0.11–0.52;), and economy level ($P = 0.00$, B value, 0.40, 95% CI, 0.21–0.59;) were independently associated with memory (Table 5). Patients with better memory were likely to be female, less worried about their finances, had short insomnia duration and prefer to Z drugs.

Table 5

Univariate and multiple analysis for factors associated with memory in benzodiazepine and Z-drug users

	CVLT \leq 35	CVLT > 35	Univariate	Multivariate		
	(n = 40)	(n = 24)	P value	B value	P value	95%CI
Duration of insomnia(years)	19.00 \pm 16.45	9.17 \pm 9.10	0.00	-0.01	0.02	-0.02- -0.00
Duration of drugs use(years)	12.03 \pm 14.61	3.75 \pm 3.76	0.00	-0.01	0.14	-0.02- 0.00
Benzodiazepines use	24(60.00%)	6(25.00%)	0.01	-0.11	0.47	-0.40- 0.19
Benzodiazepinesexposure density, mg/d	0.80 \pm 1.24	0.18 \pm 0.33	0.00	0.12	0.06	-0.01- 0.25
Z-drugs use	20(50.00%)	22(62.86%)	0.00	-0.54	0.00	-0.89- -0.20
Male	20(50.00%)	6(25.00%)	0.05	0.32	0.00	0.11– 0.52
Age(years)	64.00 \pm 6.49	56.92 \pm 3.45	0.00	-0.00	0.64	-0.02- 0.01
Poor economy	28(70.00%)	4(16.67%)	0.00	0.40	0.00	0.21– 0.59

Correlation analysis showed significant positive associations between Z drugs use and DST score ($r = -0.39$, $P = 0.00$), BNT-30 score ($r = -0.26$, $P = 0.04$). However, no correlation was found between Z drugs and TMT-B seconds and CDT score. There was only a significant negative correlation between BZDs use and DST score ($r = -0.37$, $P = 0.00$). The Z drugs exposure density was not associated with the scale of each cognitive domain.

4. Discussion

As far as we know, this is the first study to evaluate the effect of Z drugs on cognitive function in older patients with chronic insomnia. In all patients with chronic insomnia, we found that duration and severity (PSQI) of insomnia, education level were independent factors associated with global cognitive function (MoCA). Patients with long duration of insomnia, high PSQI score and low education level were likely to have a worse global cognitive function. Among the sedative-hypnotics users, we observed the independent associations between BZDs use, BZDs exposure density, education level and global cognitive function. It suggests that patients with normal cognition would have less BZDs use and lower BZDs exposure density. We found that neither Z drugs use nor Z drugs exposure density correlated with global cognitive function. However, Z drugs were independently associated with memory, significantly associated with attention and verbal function. Additionally, we did not detect the associations between Z drugs exposure density and each cognitive domain.

The correlation of Z drugs and cognition in this study is not aligned with that of previous studies. Cheng HT et al. [17] and Lee J et al. [19] reported that use of Zolpidem was associated with an increased risk of Alzheimer's disease among older people, especially a high cumulative dose, while Shih HI et al. [18] found that the effect of Zolpidem on cognition in patients with AD remained uncertain. Our findings of BZDs use were consistent with several previous studies that reported long term use of BZDs increases risk of cognitive decline [10–12], though there were also some studies that reported no association between BZDs use and cognitive impairment [9, 13–16]. For retrospective studies, lacking well-controlling confounders, such as education level, marriage, depression, stroke, diabetes, hypertension, coronary heart disease, physical activity, smoking, medicines affected cognition, especially insomnia, is the possible cause of these inconsistent findings. As known, insomnia increases the risk of developing AD. If we do not adjust the confounder of insomnia, the correlation between sedative-hypnotics and cognitive decline may not be reliable.

The mechanism of how sedative-hypnotics could increase the risk of cognitive decline is still unclear. There is a hypothesis that the cognitive reserve capacity of the elderly is limited after taking BZDs for a long time. Because BZDs and Z drugs are positive regulators of the GABA_A receptor, they will reduce brain activation, decrease synaptic plasticity, and affect the ability of patients to create new memories [20]. Second, it has been reported that the binding of BZDs and $\alpha 5$ GABA_A subunit, which is mainly expressed in the hippocampus, impairs monkeys' memory of context information. However, Zolpidem does not impair the performance of visual cue based tasks due to the affinity for $\alpha 1$ GABA_A rather than $\alpha 5$ GABA_A [21]. Those results suggest that $\alpha 5$ GABA_A receptor plays a special role in BZDs related cognitive impairment. It is speculated that BZDs increase the risk of cognitive impairment through $\alpha 5$ GABA_A in the hippocampus, while Z drugs, which bind for $\alpha 1$ GABA_A has a lower risk. However, another study showed that the activation of $\alpha 1$ GABA_A receptor might influence the spatial learning ability of rodents [22]. Our study found no association between Z drugs and cognitive impairment, can be partly explained by its

affinity for $\alpha 1\text{GABA}_A$ subunit rather than $\alpha 5\text{GABA}_A$. The molecular mechanism of cognitive impairment caused by BZDs and Z drugs needs further prospective study to confirm.

In this study, the use of BZDs and Z drugs in patients aged 50–75 years old with chronic insomnia was up to 72.73%. The high prevalence of drugs may vary due to doctors and patients' ignorance of the risk of drug-induced falls, fractures and cognitive decline, as well as the lack of attention to behavioural cognitive therapy. Besides, the exclusion of patients without sedative-hypnotics who have not visited the outpatient department may partly contribute to the high prevalence of drugs. Due to age-related pharmacokinetic and pharmacodynamics changes, the elderly are more sensitive to the effects of BZDs on the central nervous system [23]. Therefore, the use of BZDs in this population may lead to daytime sedation and decreased alertness [24]. Our study found that BZDs are an independent factor of cognitive impairment in patients with chronic insomnia. These evidence indicate that the use of BZDs, especially long-term use, is not encouraged in the elderly.

This study had several strengths. First, at each time of patient visit, doctors used a standardized cognitive test to collect data to ensure the reliability of data. Second, this study excluded patients with schizophrenia, major depression, stroke, brain trauma, epilepsy, brain tumour, alcohol dependence, and patients taking medicines that affect cognition, and recorded the patients' education and economic level, marriage, smoking, physical activity, concomitant illness, laboratory examination and sleep assessment, so that well-controlled the confounders of cognition. Thus, the reliability of the conclusion is guaranteed. Finally, this study assessed the cognitive status of patients in detail, including global cognitive function and five cognitive domains function, to better evaluate the effect of BZDs and Z drugs on cognition.

This study also had some limitations. Insomnia is considered to be a prodromal symptom of dementia. The use of BZDs may not be a cause of dementia, but insomnia as a clinical manifestation of the early stage of dementia. Our study can not completely exclude the possibility of reverse causation. Our study is a single centre study with small sample size. A large sample prospective study is needed to confirm the findings of our study in the future.

5. Conclusion

We found that BZDs use and BZDs exposure density were independent risk factors of cognitive impairment in older patients with chronic insomnia, but no correlation was found between Z drugs use and cognitive impairment. Moreover, compared with BZDs users, our study showed positive associations between Z drugs use and memory, attention and verbal function. Additionally, education level, duration and severity of insomnia were also independent factors of global cognitive function. Our findings suggest that the cognitive status should be extensively evaluated and monitored in older patients with sedative-hypnotics, the prescription of BZDs should be avoided or limited in the short term, Z drugs should be prescribed with extreme caution in elderly.

Abbreviations

Benzodiazepines

BZDs, Montreal Cognitive Assessment:MoCA, California Verbal Learning Test:CVLT, Trail Making Test-B:TMT-B, Boston Naming Test-30:BNT-30, Clock Drawing Test:CDT, Digit Span Test:DST, Cerebrospinal Fluid:CSF, Alzheimer's Disease:AD, Diagnostic and Statistical Manual of Mental Disorders, 5th edition:DSM-V, Pittsburgh Sleep Quality Index:PSQI, Hamilton Depression Scale:HAMD, Hamilton Anxiety Scale:HAMA, International Physical Activity Questionnaires:IPAQ, Low-density Lipoprotein Cholesterol:LDL-C, High-density Lipoprotein Cholesterol:HDL-C.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Committee of Beijing Friendship Hospital Affiliated to Capital Medical University (2019-P2-051-01). Written informed consent was obtained from all participants. If the participants were diagnosed with cognitive decline, informed consent was signed by their legal guardians.

Consent for publication

The author confirmed that its publication has been approved by all co-authors.

Competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

YL and ZW participated in data collection. GF participated in data analysis and prepared manuscript, revised manuscript and tables; ZYB oversaw data analysis, manuscript revision and financial support. All authors have read and approved the manuscript.

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Availability of data and material

The data used during the current study are available from the corresponding author on reasonable request.

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