Original Article

A Retrospective Study of Chart Review for the Use of Benzodiazepines and Related Drugs among Patients with Dementia

*Shin-Chiao Tien, M.D.[1], Jiahn-Jyh Chen, M.D.[1], Hung-Yu Chan, M.D., Ph.D.[1,2]**

[1]*Department of Geriatric Psychiatry, Taoyuan Psychiatric Center, Taoyuan,* [2]*Department of Psychiatry, National Taiwan University Hospital and School of Medicine, National Taiwan University, Taipei, Taiwan*

Abstract

Objective: Benzodiazepines and related drugs (BZDRs) increase the risk of undesirable health outcomes in the elderly and should be prescribed judiciously. In this study, we intended to evaluate the prevalence of BZDRs among patients with dementia and to identify the risks associated with BZDR use. **Methods:** This study was conducted at a public psychiatric hospital in northern Taiwan. Patients with Taiwan National Health Insurance catastrophic illness certificate of dementia were recruited. We reviewed their medical records for a two-year period since the issued date of patients' certificates. **Results:** The prevalence of BZDRs among the patients with dementia was up to 49% (151/308). The most popular BZDRs in this study were estazolam (16.2%), followed by zopiclone (11.4%) and zolpidem (7.5%). The most common adverse events (AEs) related to BZDRs were delirium (6.0%), followed by somnolence (4.6%) and fall (2.0%). Patients with physical comorbidities had significantly higher risk of BZDR-related AEs compared to those without physical comorbidities (adjusted odds ratio = 2.097, 95% confidence interval = 1.225–3.589, $p < 0.05$). **Conclusion:** In this study, we identified that BZDRs were highly prevalent in patients with dementia and physical comorbidities, that BZDRs were associated with higher risk of AEs, and that delirium, somnolence, and fall were common AEs during the period of BZDR treatment. Clinicians should be aware of the AEs of BZDRs and prescribe BZDRs carefully for older-demented patients.

Key words: behavioral and psychological symptoms of dementia, comorbidity, delirium, prevalence
***Taiwanese Journal of Psychiatry* (Taipei) 2020; 34: 78-83**

Introduction

The pharmacological properties of benzodiazepines (BZDs) enhance or activate brain endogeneous γ-aminobutyric acid (GABA), resulting in becoming the main effect of inhibitory neurotransmitter in the central nervous system [1]. The properties of BZDs lead to apply for a wide range of clinical indications, for instance, behavioral and psychological symptoms of dementia (BPSDs). Non-BZD hypnotics such as zolpidem and its derivatives (the Z-drugs) belong to the imidazopyridine family. Z-drugs act as an agonist of the BZD omega-1 receptor component of the $GABA_A$ receptor complex and are commonly used in patients with insomnia, including elderly patients [2].

BZDs and non-BZD sedative hypnotics are known collectively as benzodiazepines and related drugs (BZDRs). In other words, BZDRs include benzodiazepines with clear three (A, B, and C) ring BZD structures and related drugs (i.e., BDZ receptor agonists or Z-drugs) without clear three ring BZD structures. Although both structures are different, they act similarly on BZD-$GABA_A$-chloride ionophore receptor complex, resulting in activating chloride ion channels [3].

The prevalence of patients with dementia suffering BPSD is even up to 97% during the course of dementia [4]. BPSDs are prominent manifestations of the illness, including delusions, hallucinations, wandering, screaming, and insomnia [5, 6]. The treatment of BPSD requires both pharmacologic and

Received: Feb. 21, 2020 revised: Mar. 26, 2020 accepted: Mar. 28, 2020
date published: Jun. 26, 2020

Access this article online

Quick Response Code:

Website: www.e-tjp.org

DOI: 10.4103/TPSY.TPSY_20_20

[1]*Corresponding author. No. 71, Longshou Street, Taoyuan 33058, Taoyuan, Taiwan.
E-mail: Hung-Yu Chan <jan30@seed.net.tw>

How to cite this article: Tien SC, Chen JJ, Chan HY. A retrospective study of chart review for the use of benzodiazepines and related drugs among patients with dementia. Taiwan J Psychiatry 2020;34:78-83.

psychological interventions. Some particular BPSDs, such as restlessness, agitations, and insomnia, can be treated by benzodiazepines and related drugs (BZDRs) if psychological interventions have not been adequate [7]. But the current observational studies revealed that BZDRs are linked to daytime somnolence, dizziness, declined cognitive functions, increased risk of falling, fractures, and mortality among the geriatric populations [8]. No randomized control trials exist on BZDR for BPSD [9]. The relevance of BZDRs prescription to treat BPSD is still debated [10]. In the clinical real life, BZDRs are commonly used in patients with dementia for varieties of indications [11, 12]. Furthermore, that the long-term use of BZDRs is popular despite most guidelines suggest that BZDRs can be used less than 2 to 4 weeks [13-15].

Polypharmacy is common among the population of the elderly due to the need to treat the various disease states. But polypharmacy of BZDR use is accompanied by adverse health consequences, including cognitive impairment, increased risk of fall, decreased functional states, and increased risk of BZDR dependence [15, 16]. Therefore, several international guidelines have suggested a conservative practice for BZDR prescriptions [17-19].

The populations of previous studies in relationship between BZDRs and dementia are mostly in community-dwelling patients [20]. Our study adopted the population from a specialized psychiatric center in Taiwan. The primary goal of the present study was to assess the prevalence of BZDR use and adverse events (AEs) in patients with dementia. The secondary goal was to explore the specific factors associated with BZDR use and polypharmacy of BZDRs.

Methods

Study design and setting

This study is a chart review study and dataset was obtained from Taoyuan Psychiatric Center (TPC) which is a specialized psychiatric center located in northern Taiwan. TPC has outpatient clinics and inpatient services for the temporary or permanent care of residents. The hospital has acute geriatric psychiatric ward with 30 beds, which admits patients who are at least 60 years old with acute psychiatric problems. Geriatric outpatient visits are at least 15,000 times annually. Chart records of all patients we recruited were between January 2005 and December 2013 for eligibility. Patients who were no less than 65 years old and were diagnosed with dementia, based on *the International Classification of Diseases* (ICD)*, Ninth Revision, Clinical Modification* code 290, and whom were issued Taiwan National Health Insurance catastrophic illness certificates, were eligible for the study. Dementia is classified as a catastrophic illness in Taiwan and patients who were diagnosed with dementia by a qualified psychiatrist or neurologist can be issued the certificate after secondary formally reviewed by Taiwan National Health Insurance for free service for medical expenses. We reviewed the medical chart records of all patients for two years with the day of issued catastrophic illness certificates of dementia as the index date.

The institutional review board of TPC approved this study (study protocol number = B20140815-2 and date of approval = September 17, 2014) with the waiver not to obtain any signatures from the study patients.

Study participants were dichotomized into non-BZDR users and BZDR users. BZDR users were defined as exposure to at least one kind of BZDRs after the index date from medical records. Non-BZDR users were defined as no exposure to any kind of BZDRs. All drugs were coded according to the System by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) [20], as BZDs (alprazolam, brotizolam, bromazepam, clonazepam, diazepam, estazolam, fludiazepam, flurazepam, lorazepam, nimetazepam, nordazepam, oxazolam, and triazolam) and non-BZDs (zopiclone and zolpidem). We classified BZDRs into three groups according to their half-life values (www.benzo.org.uk), as defined by the World Health Organization: short-acting (less than 5 h), intermediate-acting (from 5 to 24 h), and long-acting (more than 24 h). We also counted the defined daily dose (DDD) [21] of BZDR prescriptions and collected the AEs recorded in medical charts.

The average prescribed daily dose (PDD) of the BZDRs used was calculated for each patient and compared to the DDD provided by the WHOCC. The WHOCC defines DDD as the average dose used for each drug for its main indication in adult patients [21]. The PDD/DDD ratio has been used to assess whether appropriate doses were used [22]. High dose is defined as a PDD/DDD ratio ≥ 1.

This is a retrospective study. Therefore, the decisions of initiations, changes or discontinuation of BZDRs were depended on physicians' clinical judgment at that time.

Data collection

Patterns of treatment with BZDRs during the two-year follow-up period, including the medications used, doses, and duration, were obtained through reviewing the medical records. We also collected the data of AEs and admissions to the hospital as psychiatric hospitalizations during the study period. Sociodemographic data including gender, age, marital status, education, and clinical data including the severity of dementia, and other physical and psychiatric comorbidities were collected and measured at the index date. The severity of dementia was assessed using clinical dementia rating (one item, score range: 1–5, higher score means higher severity) [23]. Comorbid psychiatric disorders included delirium, schizophrenia, delusional disorder, bipolar disorder, anxiety disorder, depressive disorder, alcohol use disorder, and amphetamine use disorder. We also used the Charlson comorbidity index (CCI) [24], to calculate the severity of comorbidities. The CCI is a method of categorizing comorbidities of the patients based on the *ICD* diagnosis codes. Each comorbidity category has an associated weight (from 1 to 6), based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient [25]. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use. We removed dementia

diagnosis from the CCI because the whole study patients were all patients with dementia. Therefore, it is meaningless to put dementia diagnosis in the CCI in this study.

Statistical analysis

The comparison groups included the BZDR users versus non-BZDR users in all the study patients. We used independent *t*-test for continuous variables with normal distribution, Mann–Whitney U-test for continuous variables with nonnormal distribution, Pearson Chi-square or Fisher's exact test for categorical variables, and unconditional logistic regression model to identify the predictors of BZDR users and BZDR polypharmacy in BZDR users. We included covariates in the multivariate logistic regression model if we deemed them to be of clinical significance, such as age and physical comorbidities, or if they had a univariate $p < 0.05$. Adequacy of the multivariate models was assessed by the Homer–Lemeshow goodness-of-fit test.

A $p < 0.05$ was considered significant. The data were analyzed using the Statistical Analytic System software version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Table 1 shows the characteristics of those participants. Of those 308 participants, the mean age of the population was 77.42 years. Female (60.7%), literacy (61.0%), and severe dementia (61.0%) were in the majority of study participants. The most popular BZDRs in the study were estazolam (50/308, 16.2%), followed by zopiclone (35/308, 11.4%), zolpidem (23/308, 7.5%), lorazepam (17/308, 5.5%), and clonazepam (17/308, 5.5%).

Table 2 presents the distribution of BZDR use. The average days of BZDR use was 263.34 ± 19.71 days. The PDD/DDD ratio of estazolam, zolpiclone, and zolpidem was 0.70, 1.13, and 0.96, respectively. In this study, the prevalence of AEs in BZDR users was 17.2%. The most common AEs were delirium (6.0%), followed by somnolence (4.6%), fall (2.0%), and weakness (1.3%). What's more, one case was recorded death (0.7%). The other rare AEs (0.7%) were chocking, dizziness, pneumonia, and odd taste.

Table 3 displays the characteristics of BZDR users as compared with nonusers, and the prevalence of BZDR use was 49.0%. Univariate analysis showed that BZDR users were more prevalent in patients with illiterate (44.4% vs. 33.8%, $p < 0.05$) and one-point CCI score (34.4% vs. 19.7%, $p < 0.05$). The variable of age was close to but did not reach statistically significant difference.

To explore the risk factors for BZDR use, we used unconditional multivariable logistic regression model and we found that a factor was significantly associated with BZDR use: One point of CCI score was significantly increased the risk of BZDRs use, compared with the reference group of 0 points of CCI (adjusted odds ratio = 2.097, 95% confidence interval = 1.225–3.589, and $p < 0.01$). But Hosmer–Lemeshow goodness-of-fit test was not significant.

Table 1. Demographic data and clinical characteristics of the 308 study patients

Descriptions	Mean ± SD or *n* (%)
Age (years)	77.42 ± 6.78
Gender	
Male	121 (39.3)
Female	187 (60.7)
Marital status	
Married	156 (50.6)
Single/divorced/widowed	152 (49.4)
Accommodation	
Solitary/institutions	59 (19.2)
Live with family	249 (80.8)
Education	
Illiteracy	120 (39.0)
Literacy	188 (61.0)
Duration of dementia (years)	4.72 ± 2.96
Number of admission	0.77 ± 0.87
CDR	
Mild	24 (7.8)
Moderate	113 (36.7)
Severe	171 (55.5)

CDR, clinical dementia rating; SD, standard deviation

Table 2. The distribution of benzodiazepines and related drug use among the study population (*N*=308)

BZDR classification	*n* (%)
BZDR use	151 (49.0)
Short-acting benzodiazepines	
Brotizolam	4 (1.3)
Medium-acting benzodiazepines	
Alprazolam	3 (1.0)
Lorazepam	17 (5.5)
Estazolam	50 (16.2)
Long-acting benzodiazepines	
Fludiazepam	2 (0.6)
Clonazepam	17 (5.5)
The Z-drugs	
Zopidem	23 (7.5)
Zopiclone	35 (11.4)
Non-BZDR use	157 (51.0)

BZDR, benzodiazepines and related drug

Discussion

To our knowledge, this is the first study to examine the prevalence, AEs, and risk factors of BZDR use in patients with dementia in specialized psychiatric hospital settings. The diagnosis of all study patients was all confirmed and issued catastrophic illness certificates by Taiwanese government. This study (Table 3) showed that patients with a physical comorbidity were more significantly to use BZDRs than those without physical comorbidities ($p < 0.05$). Our study implies that physical comorbidities play an important rôle for BZDR prescription for patients with dementia.

The high prevalence of BZDR use was up to 49% (151 out of 308 patients) (Table 3) in our study, compared to previous reports of 8%–20% among community-dwelling patients [11, 18]. The distinct characteristics of our population

may attribute to this discrepancy. More than 70% of the study patients were moderate-to-severe dementia. Patients with higher dementia severity are associated with more BPSD [26] and receive more prescription of BZDRs [27]. Up to 50% of nursing home residents with comorbid dementia receive BZDRs to treat BPSD [28]. Besides, the doctor-shopping phenomenon of Taiwan may also contribute to the high prevalence of hypnotic use in our study. The copayment of visiting specialist directly without referring from general practitioners is low in Taiwan. Therefore, people can visit the clinics of any hospitals easily and some patients visit several physicians at the same time and take several kinds of BZDRs [28, 29].

In our study, Table 3 shows that only one variable (one-point score of CCI) existed significantly increased the risk of BZDR use ($p < 0.05$). Even though a number of variables have been found to be associated with BZDR use in previous studies, physical health factors (chronic illness or other health problems) and pain complaints are found to be associated in previous reports [15, 30]. The presence of specific organic vulnerability or somatic pathology might worsen the development of anxiety symptoms, leading to a subsequent demand for BZDRs alleviating discomforts. A previous study has displayed major systemic illness increasing the needs for BZDRs [30]. But initiating BZDRs to demented patients with multiple physical illnesses can cause more undesirable morbidities [31]. We speculate that clinicians might be vigilant when initiating BZD prescriptions for more vulnerable subjects, particularly when patients are chronically ill [32, 33].

Our study (Table 2) showed that estazolam, an intermediate-acting BZDR, was the most frequent prescriptions (16.2%), followed by zolpiclone (11.4%) and zolpidem (7.5%). These results are not in line with other studies in which short-acting BZDRs are the most popular medications [7, 8]. Some literature suggested that the use of long-acting BZDRs is prevalent in mild-to-moderate Alzheimer's dementia in community-dwelling patients in real-life clinical settings [12]. Medium-acting BZDRs even are the initial drugs for 47.4% of BZDR users with Alzheimer's dementia, in comparison with non-Alzheimer's dementia [11]. Previous studies also showed that the severity of BPSD is associated with the use of BZDRs, resulting in the chance of using long half-life BZDRs increase [11, 27]. With proven efficacy and improved safety profiles compared with BZDs, our results also highlighted that Z-drugs are common in dementia patients as consistent with previous reports [34]. And Z-drugs are the most commonly prescribed hypnotics among the elderly in Taiwan [34]. Zolpidem was well-known for having a rapid onset (usually within several minutes), short duration of action (the peak time is 2 h, half time is 1.5–5.5 h), low tolerance, and a low incidence of adverse effects in treating insomnia.

The average days of BZDR prescription were 263.34 ± 19.71 days in this study, against the recommendation of not exceeding 4 to 8 weeks from most guidelines [35]. It is because that long-term BZDRs treatment can increase the risk of adverse effects and induce BZDRs tolerance [12]. In this study, the PDD/DDD ratio was used to assess whether appropriate doses were prescribed for patients with dementia. Zolpiclone has been found to be prescribed commonly and inappropriately (PDD/DDD > 1) in demented patients. The average PDDs of most BZDRs in our study are higher than the current guidelines [36, 37]. Gustafsson et al. also reported that a good tolerance can be developed to the hypnotic/sedative effect of high-dose BZDRs [38]. Moreover, the dose of BZDRs should be adjusted to one-third to one-half of the adult population due to decreased renal clearance among the geriatric population [39]. But some studies showed that complicated BPSD may increase the frequency and duration of BZDR use [27]. Therefore, the long duration and high dose of BZDR use in this study may be due to the high proportion of moderate-to-severe dementia in the study patients.

Recent studies also revealed that various disruptive behaviors tend to be distressing to the caregivers [40, 41]. For instance, delusions of persecution and infidelity, agitation and aggression, and various disturbing behaviors may create tension between the caregiver and the care-recipient, resulting in causing increased the severity of patient's neuropsychiatric

Table 3. Comparisons between nonbenzodiazepines and related drug users and benzodiazepines and related drug users

	Non-BZDR users (n = 157), n (%)	BZDR users (n = 151), n (%)
Age (years), mean ± SD	78.14 ± 6.804	76.66 ± 6.685
Gender		
Male	61 (38.9)	60 (39.7)
Female	96 (61.1)	91 (60.3)
Marital status		
Married	78 (49.7)	69 (45.7)
Single/divorced/widowed	79 (50.3)	82 (54.3)
Accommodation		
Solitary/institutions	35 (22.3)	24 (15.9)
Live with family	122 (77.7)	127 (84.1)
Duration of dementia (years), mean ± SD	4.86 ± 3.161	4.58 ± 2.741
Education		
Illiteracy	53 (33.8)	67 (44.4)
Literacy	104 (66.2)	84 (55.6)
CDR		
Mild	9 (5.7)	15 (9.9)
Moderate	59 (37.6)	54 (35.8)
Severe	89 (56.7)	82 (55.5)
Comorbid psychiatric diagnosis	38 (24.2)	40 (26.5)
CCI*		
0	95 (60.5)	76 (50.3)
1	31 (19.7)	52 (34.4)
≥2	31 (19.7)	23 (15.2)
Suicidal history	18 (11.5)	22 (14.6)
Family history of dementia	2 (1.3)	7 (4.6)

*$p < 0.05$ using Chi-square test or t-test or when appropriate (N = 308). CCI, Charlson comorbidity index; BZDRs, benzodiazepines and related drugs; SD, standard deviation; CDR, clinical dementia rating

symptoms. It might cause physicians to prescribe higher dose of medications including BZDRs, to relieve caregivers' agony.

The prevalence of BZDR-related adverse events was 17.4% (26 out of 151 patients) in this study. AE prevalence in this study was higher than those in other reports [42]. Previous studies showed that the prevalence of side effects among BZDR users with Alzheimer's dementia is between 5% and 10% [19, 43]. The discrepancy of AE prevalence between this study and others may be due to three reasons.

- The prevalence of adverse drug reactions for people with dementia may have been underestimated in previous studies. Physicians are difficult to identify AEs in patients with dementia because those patients cannot express their symptoms well due to cognitive impairment.
- The severity of dementia is higher in this study than other studies. The study of Rossat et al. revealed that some objective side effects of BZDR users are related to Mini Mental State Examination score [43]. Hence, the majority of patients in this study were with moderate-to-severe dementia might associate with higher BZDR AEs.
- Our study method of chart review was easily carried out to improve data collection of AEs records in clinical documents.

The prevalence of delirium was high, up to 6% (9 out of 151 patients), among BZDR users in our study. BZDRs might be related to cognitive dysfunction and patients with dementia were susceptible to this side effect, resulting in fluctuated consciousness [44]. Falls in older population are associated with poor prognosis. The prevalence of fall was 2% (3 out of 151 patients) and there were no falling-related fractures in our study. But numerous previous studies showed that falls are associated with BZDR use and the annual incidence is up to 60%–80% [45, 46]. This discrepancy might be due to our method of medical charts review, recording falls with overt physical harms, resulting in low prevalence in the study. Further, patients' shame and denial fall accidents and family member's lack of their awareness of falls make physician to obtain relevant information [47]. Brotizolam, short-acting anxiolytics, was recorded in our one case of all-cause mortality. Weich et al. conducted a retrospective cohort study [48] revealed that anxiolytic and hypnotic drugs are associated with twice the risk for mortality even after adjusting relevant variables.

Study limitations

The readers are warned not to over-interpret the study result in this study because of three limitations:

- The generalization of our findings to other hospitals or community population may be limited due to it was a single-hospital study.
- The method of this study is a retrospective, chart review design. The causal relationship between BZDR use and related factors was difficult to judge.
- Some variables are related to BZDR treatment for geriatric studies but are difficult to retrieve from a retrospective study. The information includes the profiles and severity of BPSD, family support, doctors' and patients' attitude toward BZDRs, previous history, and treatment responses of BZDRs and other medications.

Summary

Although this study has above limitations, it has the strength of large sample size and the diagnosis of dementia was confirmed by the National Health Insurance Bureau of Taiwan. Furthermore, the results still have three implications for psychiatrists:

- The prevalence of BZDR use and BZDRs-related AEs was high for people with dementia.
- The patients with dementia and one physical illness were associated with more BZDR use but not the patients with two or more physical illnesses in this study, which may imply that clinicians need caution the initiating BZDRs in patients with several physical vulnerable conditions.
- Delirium was a common AE during the period of BZDR treatment for people with dementia.

Clinicians should aware the possible side effects of BZDRs for demented patients with comorbid physical and mental illnesses and take precautions. More studies focusing on BZDR prescriptions for people with dementia are recommended to help physicians make appropriate decision.

Acknowledgements

The funding body played no role in study design, analysis, or interpretation of data in this paper. SC Tien and JJ Chen contributed equally as the first authors of this article.

Financial Support and Sponsorship

This work was supported by a research grant from TPC, Ministry of Health and Welfare of Taiwan (TYPC-201401).

Conflicts of Interest

The authors declare no conflicts of interest for this paper.

References

1. Schroeck JL, Ford J, Conway EL, et al.: Review of safety and efficacy of sleep medicines in older adults. *Clin Ther* 2016; 38: 2340-72.
2. Shih HI, Lin CC, Tu YF, et al.: An increased risk of reversible dementia may occur after zolpidem derivative use in the elderly population: A population-based case-control study. *Medicine* (Baltimore) 2015; 94: e809.
3. Paul SM, Marangos PJ, Skolnick P: Benzodiazepine-GABA-chloride ionophore receptor complex: comom site of minor tranqulizer action. *Biol Psychitry* 1981; 16: 213-29.
4. Kales HC, Gitlin LN, Lyketsos CG: Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015; 350: h369.
5. Kozman MN, Wattis J, Curran S: Pharmacological management of behavioural and psychological disturbance in dementia. *Hum Psychopharmacol* 2006; 21: 1-2.
6. Finkel SI: Behavioral and psychological symptoms of dementia: A current focus for clinicians, researchers, and caregivers. *J Clin Psychiatry* 2001; 62 (Suppl 21): 3-6.
7. APA Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, et al.: American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other

dementias. Second edition. *Am J Psychiatry* 2007; 164: 5-6.
8. The American Geriatrics Society Beers Criteria Update Expert Panel: American Geriatrics Society 2015 Updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geri Society* 2015; 63: 2227-46.
9. McCleery J, Cohen DA, Sharpley AL: Pharmacotherapies for sleep disturbances in Alzheimer's disease. Cochrane Database Syst Rev 2014; 3: CD009178.
10. Wang J, Yu JT, Wang HF, et al.: Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: A systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2015; 86: 101-9.
11. Saarelainen L, Taipale H, Koponen M, et al.: The incidence of benzodiazepine and related drug use in persons with and without Alzheimer's disease. *J Alzheimers Dis* 2016; 49: 809-18.
12. Montastruc F, Gardette V, Cantet C, et al.: Potentially inappropriate medication use among patients with Alzheimer disease in the REAL. FR cohort: be aware of atropinic and benzodiazepine drugs! *Eur J Clin Pharmacol* 2013; 69: 1589-97.
13. Ashton H: The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry* 2005; 18: 249-55.
14. Vinkers CH, Olivier B: Mechanisms underlying tolerance after long-term benzodiazepine use: a future for subtype-selective GABA(A) receptor modulators? *Adv Pharmacol Sci* 2012; 2012: 416864.
15. Manthey L, van Veen T, Giltay EJ, et al.: Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). *Br J Clin Pharmacol* 2011; 71: 263-72.
16. Maher RL, Hanlon J, Hajjar ER: Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014; 13: 57-65.
17. Hajjar ER, Cafiero AC, Hanlon JT: Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007; 5: 345-51.
18. Defrancesco M, Marksteiner J, Fleischhacker WW, et al.: Use of benzodiazepines in Alzheimer's disease: a systematic review of literature. *Int J Neuropsychopharmacol* 2015; 18: pyv055.
19. Markota M, Rummans TA, Bostwick JM, et al.: Benzodiazepine use in older adults: dangers, management, and alternative therapies. *Mayo Clin Proc* 2016; 91: 1632-9.
20. Sivananthan SN, Lavergne MR, McGrail KM: Caring for dementia: a population-based study examining variations in guideline-consistent medical care. *Alzheimers Dement* 2015; 11: 906-16.
21. Wong CY: Predictors of psychiatric rehospitalization among elderly patients. *F1000Res* 2015; 4: 926.
22. Phelan EA, Borson S, Grothaus L, et al.: Association of incident dementia with hospitalizations. *JAMA* 2012; 307: 165-72.
23. Grimmsmann T, Himmel W: Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? *Eur J Clin Pharmacol* 2011; 67: 847-54.
24. Waite L, Grayson D, Jorm AF, et al: Informant-based staging of dementia using the clinical dementia rating. *Alzheimer Dis Assoc Disord* 1999; 13: 34-7.
25. Charlson ME, Pompei P, Ales KL, et al.: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-83.
26. Tanaka H, Hashimoto M, Fukuhara R, et al.: Relationship between dementia severity and behavioural and psychological symptoms in early-onset Alzheimer's disease. *Psychogeriatrics* 2015; 15: 242-7.
27. Nobili A, Pasina L, Trevisan S, et al.: Use and misuse of antipsychotic drugs in patients with dementia in Alzheimer special care units. *Int Clin Psychopharmacol* 2009; 24: 97-104.
28. Stevenson DG, Decker SL, Dwyer LL, et al.: Antipsychotic and benzodiazepine use among nursing home residents: findings from the 2004 National Nursing Home Survey. *Am J Geriatr Psychiatry* 2010; 18: 1078-92.
29. Wu MH, Wu MJ, Chou LF, et al.: Patterns of nonemergent visits to different healthcare facilities on the same day: a nationwide analysis in Taiwan. *Sci World J* 2014; 2014: 627580.
30. Luijendijk HJ, Tiemeier H, Hofman A, et al.: Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *Br J Clin Pharmacol* 2008; 65: 593-9.
31. Simpson RJ, Power KG, Wallace LA, et al.: Controlled comparison of the characteristics of long-term benzodiazepine users in general practice. *Br J Gen Pract* 1990; 40: 22-6.
32. Palmaro A, Dupouy J, Lapeyre-Mestre M: Benzodiazepines and risk of death: results from two large cohort studies in France and UK. *Eur Neuropsychopharmacol* 2015; 25: 1566-77.
33. Kaufmann CN, Spira AP, Alexander GC, et al.: Trends in prescribing of sedative-hypnotic medications in the USA: 1993-2010. *Pharmacoepidemiol Drug Saf* 2016; 25: 637-45.
34. Lan TY, Zeng YF, Tang GJ, et al.: The use of hypnotics and mortality–a population-based retrospective cohort study. *PLoS One* 2015; 10: e0145271.
35. Petek Šter M, Cedilnik Gorup E: Psychotropic medication use among elderly nursing home residents in Slovenia: cross-sectional study. *Croat Med J* 2011; 52: 16-24.
36. Bourgeois J, Elseviers MM, Azermai M, et al.: Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages. *Eur J Clin Pharmacol* 2012; 68: 833-44.
37. Rancourt C, Moisan J, Baillargeon L, et al.: Potentially inappropriate prescriptions for older patients in long-term care. *BMC Geriatr* 2004; 4: 9.
38. Gustafsson M, Karlsson S, Gustafson Y, et al.: Psychotropic drug use among people with dementia – a six-month follow-up study. *BMC Pharmacol Toxicol* 2013; 14: 56.
39. Wang PS, Bohn RL, Glynn RJ, et al.: Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry* 2001; 158: 892-8.
40. Chiao CY, Wu HS, Hsiao CY: Caregiver burden for informal caregivers of patients with dementia: a systematic review. *Int Nurs Rev* 2015; 62: 340-50.
41. Cheng ST: Dementia caregiver burden: a research update and critical analysis. *Curr Psychiatry Rep* 2017; 19: 64.
42. Onder G, Gambassi G, Scales CJ, et al.: Adverse drug reactions and cognitive function among hospitalized older adults. *Eur J Clin Pharmacol* 2002; 58: 371-7.
43. Rossat A, Fantino B, Bongue B, et al.: Association between benzodiazepines and recurrent falls: a cross-sectional elderly population-based study. *J Nutr Health Aging* 2011; 15: 72-7.
44. Airagnes G, Pelissolo A, Lavallée M, et al.: Benzodiazepine misuse in the elderly: Risk factors, consequences, and management. *Curr Psychiatry Rep* 2016; 18: 89.
45. Mecocci P, von Strauss E, Cherubini A, et al.: Cognitive impairment is the major risk factor for development of geriatric syndromes during hospitalization: results from the GIFA study. *Dement Geriatr Cogn Disord* 2005; 20: 262-9.
46. Anstey KJ, von Sanden C, Luszcz MA: An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. *J Am Geriatr Soc* 2006; 54: 1169-76.
47. Chou WC, Tinetti ME, King MB, et al.: Perceptions of physicians on the barriers and facilitators to integrating fall risk evaluation and management into practice. *J Gen Intern Med* 2006; 21: 117-22.
48. Weich S, Pearce HL, Croft P, et al.: Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ* 2014; 348: g1996.