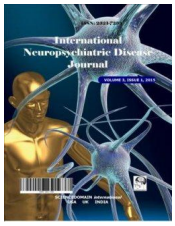

International Neuropsychiatric Disease Journal
4(2): 75-83, 2015; Article no.INDJ.2015.028
ISSN: 2321-7235

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Prolonged Use of Benzodiazepines for Sleep Disturbances in the Elderly: Quality of Sleep and Related Comorbidities

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Authors' contributions

This work was carried out in collaboration between all authors. All authors participated in the design of the study, the performance of the study protocol, and the preparation and approval of the final manuscript.

Article Information

DOI: 10.9734/INDJ/2015/17216
Editor(s):
(1) Weike Mo, Scientific Director for Pharmacogenetics, Molecular Testing Labs, USA.
Reviewers:
(1) Anonymous, Italy.
(2) Matias Carvalho Aguiar Melo, Department of Medical Sciences, Universidade Federal do Ceará, Brazil.
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(4) Anonymous, India.
(5) Anonymous, Universidad Autónoma de Yucatán, México.
(6) Anonymous, University of Bari, Italy.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1005&id=29&aid=9656

Original Research Article

Received 3rd March 2015
Accepted 13th May 2015
Published 8th June 2015

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ABSTRACT

Introduction: Insomnia is frequently found in older people, and may be symptomatic of underlying comorbid conditions. The use of drug therapy for the symptomatic relief of insomnia is widespread, with the most common class of agents used for this indication being benzodiazepines.
Objective: To investigate the relationship between comorbidities and the associated use of benzodiazepines among older people living in the community.
Methods: We evaluated a sample of 27 subjects who were using benzodiazepines for at least 3 months, compared to 33 non-users constituting the control group.
Results: Those using benzodiazepines had higher comorbidity, more impaired cognition, greater anxiety, and poorer sleep quality than controls. However, based on a multivariate logistic regression model, only poor quality of sleep correlated significantly with the prolonged use of benzodiazepines (OR=1.96, 95% CI= 1.34-2.85, p<0.01).
Conclusion: This small study strengthens the need to limit the use of this class of drugs in older people with sleep disturbances.

Keywords: Insomnia; benzodiazepines; elderly; comorbidity.

1. INTRODUCTION

The rise in life expectancy in developed countries has led to a significant increase in the number of older people. In Israel at the end of 2011, about 10.3% of the population was aged 65 years and over [1]. Insomnia and sleep difficulties are frequent symptoms in the elderly. Insomnia is defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) as ‘‘difficulty initiating sleep or difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings or early-morning awakening with inability to return to sleep” and in addition ‘‘the sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning” [2]. The estimated prevalence of insomnia among older patients is between 6 and 38% [3-7]. Common causes of insomnia in older adults include poor sleep habits, inappropriate sleep environment, pain, urinary symptoms, dyspnea, and psychological stress. Insomnia may cause non-specific symptoms in the elderly, such as weakness, tiredness, daytime somnolence, irritability and confusion.

There are various interventions employed for the treatment of insomnia [8], but probably the most common strategy employed is the use of hypnotic medications, with benzodiazepines being one of the most frequent classes of drugs used for this indication [9,10]. Benzodiazepines are more commonly used by older than by younger people [11,12]. Various studies have found that the use of benzodiazepines among the older population living in the community ranges from 10 to over 40 percent [13-17].

The efficacy of benzodiazepines for sleep disturbance varies between studies. A meta-analysis (mean age of patients ranged from 29 to 82 years) found that benzodiazepines prolong total sleep duration by 61.8 minutes, but do not change the sleep latency [18].

A subsequent meta-analysis [19] found that benzodiazepines prolong total sleep time by 34.2 minutes on average, improve sleep quality and reduce the number of awakenings. Yet another meta-analysis [20] found that sleep latency was shortened by 10 minutes, and sleep efficiency and overall sleep quality improved compared to placebo. However, in this study differences in the total sleep time did not reach statistical significance.

Hypnotics in general and benzodiazepines in particular are not free of adverse effects, and older patients experience more adverse effects from benzodiazepines, probably due to the altered pharmacokinetics and pharmaco-dynamics of these drugs in older age [21]. The more frequent adverse effects include daytime sleepiness and dizziness [18], fatigue, headaches, nightmares, nausea and gastrointestinal disorders [19]. In addition, the use of benzodiazepines is associated with a greater frequency of events such as falls and fractures [22], traffic accidents [23], cognitive decline and dementia [19,24,25], and even an increase in mortality [26].

Although there is no evidence in the literature supporting the use of benzodiazepines for more than 14 days [18], it is not unusual for those using these compounds to continue doing so for much more prolonged periods. Thus, in a study

performed in Taiwan, over 20% of those using benzodiazepines continued to use these drugs for more than 6 months [16]. In another study, over two-thirds of those using benzodiazepines used these agents for over a year [14]. In most cases, the initial prescription for benzodiazepines was issued by the family physician [27].

The phrase “comorbid insomnia” emerged from the 2005 National Institutes of Health’s (NIH) State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults, in order to describe the presence of insomnia in the context of a medical or psychiatric disorder [28]. Many studies have examined the relationship between the use of benzodiazepines and comorbid conditions [29]. It is possible that at least in some cases insomnia may be "masking" underlying disease, and that the use of benzodiazepines may actually worsen the underlying condition. For example, benzodiazepines are also inappropriately used for pain [12] and for somatic illnesses [30] that may themselves interfere with normal sleep.

The purpose of our study was to investigate the relationship between comorbidities and the associated use of benzodiazepines among older people living in the community.

2. METHODOLOGY

The study population included patients older than 65 years treated at the Metzada primary care clinic of the Clalit Health Care Services in Beersheva, Israel. The study was conducted in the latter half of the year 2012. The Metzada clinic served almost 11000 clients of varying socioeconomic levels during the period of the study. Of these, 20.4% were aged 65 years and older and 39.4% were men. The medical staff of the clinic comprised 9 doctors, of whom 6 were specialists in family medicine, 1 was a resident in family medicine and 2 were pediatricians. The study was approved by the ethics committee of the Meir Hospital in Kfar Saba, Israel.

From a database generated report looking at the first 4 months of the year 2012, potential subjects who were receiving benzodiazepines on a chronic basis (at least 3 repeat monthly prescriptions) were identified. Of these, 50 subjects were chosen randomly to constitute the study group. A further 50 subjects who were not receiving these compounds were randomly chosen to comprise the control group. All subjects were contacted by their family physician and, after receiving a detailed explanation of the study protocol, were asked to provide their informed consent for participation in the study.

Inclusion criteria were age 65 years and older, Hebrew speaking, and registration as a patient of the Metzada clinic in Beersheva. Exclusion criteria were dementia, schizophrenia, drug or alcohol abuse, or being home-bound.

Subjects underwent an interview in order to confirm the use of benzodiazepines for at least 3 months for sleep disturbances, and were screened for cognitive impairment using the Mini Mental State Examination [31], and for affective disorders using the Geriatric Depression Scale (GDS) [32,33] and the Hamilton Anxiety Rating Scale (HAM-A) [34]. The quality of sleep was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [35] and the presence of comorbidities by means of the Charlson’s Comorbidity Index [36].

2.1 Statistical Analysis

We compared the relationship between the use of benzodiazepines on the one hand and socio-demographic factors, comorbidities, cognitive, affective and sleep quality instruments on the other. The Student's t-test was used for continuous variables and the Fisher's Exact and Chi-Square tests for categorical variables. Statistical significance was determined at $p<0.05$. The effect size between groups was calculated using the Cohen's d test. We used a multivariate logistic regression model to control for confounders. Statistical analysis was performed by means of the SPSS software version 17.

3. RESULTS

Of the study group, 27 (45%) agreed to be interviewed and undergo evaluation, compared to 33 (55%) from the control group. Demographic details of both groups are presented in Table 1.

Of the 27 participants in the study group treated by benzodiazepines, 21 (77.8%) received brotizolam, 4 (14.8%) clonazepam, 3 (11.1%) lorazepam and 1 (3.7%) received diazepam. Two participants (7.4%) received 2 of these agents.

Results of evaluations for comorbidities are presented in Table 2.

Cognitive screening using the MMSE was within the normal range for both groups. However, a

Table 1. Demographics of the study population groups

	Study group (N=27)		Control group (N=33)		p-value
	N	%	N	%	
Gender					
Male	11	40.70%	11	33.30%	0.599
Female	16	59.30%	22	66.70%	
	27		33		
Age					
Mean±SD	74.9±11.0		70.9±7.06		0.029
Range	65-89		65-92		
	27		33		
Marital status					
Married	22	81.50%	25	75.80%	0.755
Not married	5	18.50%	8	24.20%	
	27		33		

statistically significant difference was found between the two groups in favor of the control group (study group 28.37±1.73 vs.29.52±1.21 for controls, p-value = 0.006) with the effect size being moderate (Cohen's d = -0.782).

Comorbidity, as measured by means of the Charlson Comorbidity Index (CCI), was higher in the population that used benzodiazepines (Total Combined Score was 4.48±1.61 vs. 3.55±1.48 in control group, p-value=0.022). After correcting for age, the difference in comorbidity was not statistically significant (Total Score 1.44±1.42 in the study group vs. 1.03±1.16 in controls, p-value=0.22). Screening for depressive symptoms using the GDS score found no difference between the two groups (mean 3.44±4.25 in the study group compared to 1.94±2.69 in the control group, p-value = 0.118). Based on a cut-off level of ≥5, more of those in the study group screened positively for depressive symptoms than controls (29.6% vs. 12.1%). However, this difference did not reach statistical significance. The average score on the Hamilton Anxiety Rating Scale (HAM-A) among participants in the study group was higher compared to untreated participants (15.81±7.85 vs. 10.30±7.86, p-value = 0.009). Based on the HAM-A, 25.9% of the those in the study group were in the range of "mild to moderate anxiety" compared to 18.2% in the control group, with a further 18.5% of those taking benzodiazepines in the range of "moderate to severe anxiety" while none of those in the control group had this degree of anxiety.

Of interest is the report of poor sleep quality in the study group as compared to the controls. The mean PSQI score was significantly different, being 9.9±3.9 in the study group and 4.4±2.7 in controls (p-value <0.001). Based on a PSQI value of 5 or more, 25 subjects (92.6%) in the study group were rated as having poor sleep quality compared to only 10 (30.3%) in the control group (p-value <0.001).

A multivariate logistic regression model was performed to control for those variables shown to be significant in univariate analysis, namely MMSE, CCITCS, HAM-A and PSQI. Age and gender were also included in this model. Based on this analysis, only PSQI remained significant (OR=1.96, 95% CI= 1.34-2.85, p<0.01).

4. DISCUSSION

In this relatively small study performed in a population of community-dwelling people aged 65 years and older, it was found that the chronic use of benzodiazepines was associated with greater comorbidity, more anxiety and inferior sleep quality compared to controls. Using a multivariate logistic regression model, poor sleep quality was highly correlated with the chronic use of benzodiazepines.

The relationship between insomnia and comorbidity is well described in the literature. In a study performed by Vitiello and colleagues, 2954 older people living in the community were rigorously reviewed for comorbidities [37]. The authors found that less than 4% of those with no comorbidity suffered from insomnia, supporting the assumption that insomnia is not a usual feature of healthy aging. Studies have also found an association between the use of benzodiazepines and comorbidity [29], including mental illness [29]. In our study, although general comorbidity as measured by means of the Charlson Comorbidity Index was higher in the study population that used benzodiazepines, this

difference in comorbidity was not statistically significant after correcting for age.

The relationship between the use of benzodiazepines and cognitive changes has been described previously [38], although the question remains as to whether this is a result of reverse causation [39]. In our study, cognitive screening using the MMSE was within the normal range for both groups. However, a statistically significant difference was found between the two groups in favor of the control group. This difference is possibly attributable to the difference in age of the participants. We base this assumption on the calculation that according to Crum and colleagues [40] the age difference of four years between the study (74.9±11.0 years) and control group (70.9±7.06) would manifest as a difference of one point in the age-adjusted MMSE. It should also be emphasized that the MMSE was found to be a non-significant confounder using a logistic regression model.

Depressive symptoms were similar in both groups. In a systematic review [41] the cut-off value used by most studies in out-patient and primary care geriatric settings was five. Although initially we did not evaluate our results based on a cut-off value for the GDS, we did find in a subsequent analysis that more participants in the study group had a score ≥ 5. However, this difference did not reach statistical significance possibly due to the small sample size.

Table 2. Comorbidities, cognitive, affective and sleep quality instruments according to group

	Study group (N=27)		Control group (N=33)		p-value
	N	%	N	%	
MMSE					
Mean±SD	28.37±1.73		29.52±1.21		0.006
Range	25-30		24-30		
	27		33		
CCITS					
Mean±SD	1.44±1.42		1.03±1.16		0.219
Range	0-5		0-4		
	27		33		
CCITCS					
Mean±SD	4.48±1.61		3.55±1.48		0.022
Range	2-8		2-6		
	27		33		
GDS-15					
0-4	19	70.40%	29	87.90%	0.087
5+	8	29.60%	4	12.10%	
Mean±SD	3.44±4.25		1.94±2.69		0.118
Range	0-15		0-10		
	27		33		
HAM					
Mild	15	55.60%	27	81.80%	0.018
Mild to moderate	7	25.90%	6	18.20%	
Moderate to severe	5	18.50%	0	0.00%	
Mean±SD	15.81±7.85		10.30±7.86		0.009
Range	2-29		0-25		
	27		33		
PSQI					
<5	2	7.40%	23	69.70%	<0.0001
≥5	25	92.60%	10	30.30%	
Mean±SD	9.85±3.91		4.42±2.73		<0.0001
Range	4-18		0-12		
	27		33		

CCITS- Charlson Comorbidity Index- Total Score; CCITCS -Charlson Comorbidity Index- Total Combined Score; MMSE- Mini Mental State Examination; GDS- Geriatric Depression Scale, 15 questions; HAM- Hamilton Anxiety Rating Scale; PSQI- The Pittsburgh Sleep Quality Index; a score of 5 or greater indicates poor quality of sleep
SD – Standard Deviation

Although we found that those treated with benzodiazepines experienced more symptoms of anxiety, this association was not significant on logistic regression analysis. One of the known symptoms of anxiety is insomnia [42-44]. Thus it is not surprising that those complaining of insomnia had received treatment for anxiety, and continued to suffer from anxiety, possibly due to inadequate treatment [45]. Additional less-likely explanations for this phenomenon are that the interview took place in the afternoon with treatment for insomnia being administered in the evening, thus raising the possibility of a withdrawal reaction due to of the use of short-acting BZP drugs [46].

An interesting finding of our study was the poor satisfaction with the quality of sleep in the study group, a finding that remained highly significant using a logistic regression model. This was in spite of the fact the use of benzodiazepine-type drugs in these patients was meant specifically to improve sleep quality. Similar findings have been reported previously [47,48]. It is suggested that not only do these compounds not improve the quality of sleep, but may even lead to poorer sleep quality [47-49]. In addition, the use of hypnotics as symptomatic therapy for insomnia does not necessarily treat possible underlying causes of this symptom, such as depression, anxiety, or pain, among others.

Our study has a number of limitations. The small number of subjects and the inclusion of subjects from a single clinic limit the generalizablity of our findings. As well, only about half of those chosen randomly (45% in the study group and 55% of the controls) agreed to undergo evaluation, and this selection bias may have affected our results. Also, evaluations were performed by means of screening instruments and not by comprehensive clinical assessments. Although the groups were similar regarding comorbidities, we did not analyze for specific conditions, such as cardiovascular disease or risk factors. As a cross-sectional study, we cannot determine whether factors such as poor quality of sleep or cognitive impairment are a cause or a consequence of the use of benzodiazepine drugs. In addition, those taking benzodiazepines were not questioned specifically about the need for continuing the use of these drugs in spite of ongoing symptoms of anxiety or sleep disturbance. While all subjects studied had been taking benzodiazepines for at least 3 months, the exact dose of these drugs and the total duration of therapy were not studied. Also, data was not obtained regarding the use of associated psychotropic and non-psychotropic drugs. Further studies should address these issues. A strength of our study is the comparison with a well-matched control group. Also, to the best of our knowledge, this is the first such study looking at an older Hebrew-speaking population group.

5. CONCLUSION

In this small study of randomly-chosen older people, we found that patients receiving benzodiazepines continue to suffer from poor sleep quality. The study emphasizes the need for a careful search for the causes of insomnia and strengthens the need to limit the use of benzodiazepines in the older population with sleep disturbances. Our findings should be further validated in larger randomized controlled studies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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