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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Impact of long-term benzodiazepine use on cognitive functioning in young adults: the VISAT cohort

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Abstract
Purpose Results from a number of studies have suggested a relationship between cognitive alteration and benzodiazepine use in the elderly. The aim of this study was to determine the impact of benzodiazepine use on cognitive functions in a young adult population.
Methods This study included 1,019 French salaried workers from the VISAT (Aging, Health and Work) cohort whose objective was to determine the long-term impact of working conditions on health and aging. Data were collected during interviews by occupational physicians in 1996, 2001 and 2006. Cognitive function was assessed using five cognitive tests (immediate free recall test, delayed free recall test, recognition test, Digit Symbol Substitution Subtest and visual search speed test). Cognitive scores obtained after a 10-year follow-up were investigated among three categories of benzodiazepine users, namely, non-users, occasional users and long-term users, using analysis of covariance models adjusted for several potential confounders in men and women separately.
Results In the course of the 10 year-follow-up, 3.9% of subjects were defined as occasional users of benzodiazepine and 7.5% as long-term users. The analysis revealed a significant alteration of long-term memory in women whereas there was no significant association in men.
Conclusions Long-term use of benzodiazepine leads to specific impairment in long-term memory only in women.

Keywords Cognition · Benzodiazepine · Gender · Young adult · Observational cohort study

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Introduction

Psychotropic drug use is common in most industrialized countries and particularly so in France [1]. This high prevalence of use is also observed in the context of work environments [2–4], and it has been documented that several job and social constraints lead to chronic use of these medications [5–7]. In addition to the risk of abuse as well as road or work-related injuries related to psychoactive drug use [8, 9], another major public health question is whether long-term use may induce permanent cognitive deficits. Experimental and clinical studies have documented the acute effects of psychoactive drugs on cognitive performance, showing changes in vigilance and memory with benzodiazepine use [10]. It has also been determined that the duration of psychoactive drugs use commonly exceeds the recommended duration of therapy, especially in the elderly [11, 12], with many patients are receiving long-lasting treatment which can stretch to several years.

A number of studies carried out in the early 1980s investigated the relationship between benzodiazepine

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consumption and cognitive decline. Since then, several authors have shown the impact of these drugs on attention, memory and psychomotor speed after an acute administration [10, 13]. Most of pharmacoepidemiological studies assessing the effect of psychoactive drugs on cognitive function have focused on elderly subjects who are most likely to consume and to develop cognitive deficits [14]. Moreover, these studies used mostly cross-sectional surveys that did not distinguish between psychopathology and drug consumption. In 2002, Paterniti et al. [15] published the first longitudinal study that emphasized a negative impact of long-term benzodiazepine consumption on cognitive functions. These results were confirmed by Bierman et al. [16] who found a negative effect of chronic use of benzodiazepines on long-term memory. Consequently, the effect of chronic benzodiazepine use has been well explored in the elderly, with some studies reporting a lower risk of cognitive decline or no association [17] and other studies finding an increased risk of cognitive decline or dementia among psychotropic drug users [15, 16, 18–20].

The aim of the study reported here was to investigate the effects of benzodiazepine use (occasional and long-term use) over a period of 10 years on cognitive efficiency in a young adult population according to gender.

Materials and methods

Participants

Details regarding the population sampling in the VISAT study (Aging, Health and Work) have been described elsewhere [21]. A total of 4,258 current and former salaried workers were randomly selected from the worker's list of 94 occupational physicians in three areas in the South of France in 1996. Of these, 3,237 subjects agreed to participate in a prospective cohort study. The sample consisted of 1,660 men and 1,577 women aged 32, 42, 52 and 62 years when selected. Recruitment and data collection occurred during the compulsory medical examination by the occupational physician, who was trained for this survey. Data were collected at three cross-sectional time points in 1996, 2001 and 2006. In 1999, an intermediate data collection was conducted to obtain information only on medications (no other information was collected). Six subjects (0.2%) at baseline (or during the follow-up) presented a serious psychiatric disease and were excluded from the study due to the potential impact of their psychiatric disease on cognitive functioning. We included 1,019 subjects in our analysis who completed the 10-year follow-up for whom a complete data set was available.

Data collection

Self-administered questionnaire

A self-administered questionnaire was completed by the subjects regarding their social, familial and occupational status and lifestyle. Educational level (number of years of schooling) was divided into three categories: <10 years of schooling; 10–13 years; >13 years. Subjects who reported the use of alcohol at least daily were defined as daily alcohol consumers. Smoker status was categorized as "current smoker" or "non-smoker". We used the marital status question to identify the subjects involved in cohabitation (yes/no). In the same way, we created dichotomous variables: from the Likert scale assessing physical activities (yes/never) and from shiftwork (currently/not currently).

Clinical examination

For each data collection time point, questionnaires regarding former and current medical conditions and a clinical examination were administered by physicians. All medical histories were reported [subject currently affected by a disease (yes/no)]. We created one dichotomous variable (yes/no) coding for the medical history for each disease if the subject was affected at least once during the follow-up by depression, diabetes, hypercholesterolemia, trauma, thyroid disease and cardiovascular disorders (high blood pressure, cerebrovascular accident, ischemic attack transient, angina pectoris or myocardial infarction).

Exposure to benzodiazepines was defined from data collected in 1999, 2001 and 2006 (this information was not available in the 1996 survey). In 1999, 2001 and 2006, subjects reported all drugs taken during the previous month, and these drugs were then classified according to the Anatomical, Therapeutic and Chemical Classification. Benzodiazepines (and benzodiazepine-related drugs) were identified by following codes: N05CF and N05CD (hypnotics), N05BA (anxiolytics), M03BX07 (tetrazepam) and N03AE (clonazepam). The questionnaire also contained one question to determine whether subjects used these drugs for at least 1 year. According to the answers at the different times of the study, we defined three mutually exclusive categories of benzodiazepine users: (1) "non-users", no reported use in 1999, 2001, 2006; (2) "occasional users", reported use in one survey or for less than 1 year; (2) "long-term users", reported use in two or three successive surveys or for at least 1 year.

Neuropsychological assessment was evaluated in 1996, 2001 and 2006 using the same cognitive tests

each time. Five tests were administered in the following order:

- An immediate free recall test adapted from the Rey auditory verbal learning test with only three trials and 16 words learned [22].
- The WAIS (Wechsler Adult Intelligence Survey) digit symbol substitution subtest (DSST) [23]
- A selective attention test derived from the Sternberg's test [24] and composed of two subsets. The first subset was to scan as quickly as possible a line of 58 alphabetic characters to find a target letter shown in the margin and then cross it out. This task was repeated six times. The second subset also included six lines of 58 characters, but the memory load was greater because the target was to locate one of the four letters shown in the margin.
- A delayed recall test in which subjects had to write down all of the words they could remember from the word list given in the first test.
- A recognition test in which participants had to find the 16 words learned previously from a list of 32 words.

Three cognitive functions, namely, memory, information processing speed component and visual attention, were evaluated in these tests. The results for the word list learning tests, delayed free recall and recognition tasks are given as a mean number of cited words, those for the DSST are given as a mean score, and those for the selective attention test are given as the mean time taken to perform the test (in minutes). Thus, in all analyses, a better performance corresponds to a higher score for word lists and DSST, whereas it corresponds to a lower score (shorter time) for the selective attention test. All tests were run by physicians specifically trained for this study.

Statistical analysis

All analyses were conducted with the SAS ver. 9.2 statistical packages (SAS Institute, Cary, N.C.). A descriptive analysis investigated the socio-demographic and medical characteristics of the study sample, the prevalence of benzodiazepine exposure and cognitive performance during the follow-up. Paired t and χ^2 tests were used to compare the sample's characteristics. Effect sizes were calculated following the method set out by Hedges and Olkin [25] according to gender. The effect size represents the difference between the benzodiazepine user (occasional or long-term) group and the non-user group divided by the pooled standard deviation. Therefore, a negative effect size indicates that the performance of the subject was poorer than that of the reference group (non-users). We stratified multivariate analyses on the gender variable because cognitive functioning and psychoactive drug use are known to differ between the sexes [26]. We therefore performed a multivariate analysis of covariance to evaluate the impact of long-term benzodiazepine use through changes in cognitive scores after 10 years of follow-up. The non-user group was the reference group. We included in the model all variables identified as expected confounding factors: age, cognitive score at the baseline, education level, cohabitation life, tobacco use, physical activity, shiftwork, daily alcohol use, BMI (body mass index) [27] and medical histories of diabetes, depression, trauma, cardiovascular and thyroid diseases. The beta (β) coefficient for each variable indicates the amount of change one could expect in various cognitive test scores given a one-unit change in the value of that variable.

Results

In the VISAT cohort study, 3,237 subjects were enrolled in 1996, 2,288 in 2001 and 1,308 in 2006. The number of subjects lost to follow-up was more important between 2001 and 2006 because subjects were older and retired. The VISAT survey took place in the context of the occupational medicine department of each company so those subjects who retired during study were more difficult keep in the study than current workers. In our study, we included 1,019 subjects who participated in all surveys and who had been diagnosed to be free of dementia or psychiatric disease at the time (Table 1). The age classes of 32 years and 42 years were the most highly represented (two-thirds of the sample), and one-third of the sample had a high level of education. In 1996, 29.6% were current smokers, 28.4% reported daily alcohol consumption (only six subjects were identified as clinically abusive consumers by occupational physicians in 2006). We determined many differences according to gender in the categories of employment and consumption of alcohol (41.2% in men and 14.1% in women, $p<0.001$).

However, 2,201 subjects were not included in our analysis because they were lost to follow-up or presented a serious psychiatric disease at the evaluation time point (Table 1). Subjects lost to follow-up were overall older, comprised fewer supervisors (9.5 vs. 12.5% in the included population, $p<0.05$) and more blue collar workers (24.8 vs. 20.4%, $p<0.01$) and presented a lower educational level than the included population (26.8 vs. 33.4%, $p<0.01$). Finally, our study population presented better cognitive performance than the population not included in all tests except for the DSST.

In our population, 3.9% of subjects were considered as occasional benzodiazepine users (women 4.8%, men 3.2%). We identified 7.5% of the population (women 8.3%, men 6.7%) as long-terms benzodiazepine users. The most

Table 1 Comparison of characteristics of the study population and the not-included population in 1996

Cohort characteristics	Study population, n=1,019 (32.6%)	Not-included population, n=2,201 (68.4%)
Sex		
Men	536 (52.6)	1115 (50.7)
Women	483 (47.4)	1086 (49.3)
Age at baseline		
32 years	322 (31.6)	569 (25.9)**
42 years	318 (31.2)	651 (29.6)
52 years	242 (23.8)	652 (29.6)**
62 years	137 (13.4)	329 (15.0)
Occupational status		
Executives	127 (12.5)	210 (9.5)*
Technicians/supervisors	298 (29.2)	641 (29.1)
White collar	359 (35.2)	758 (34.4)
Blue collar	208 (20.4)	546 (24.8)**
Education level		
<10 years	246 (24.1)	589 (26.8)
10–13 years	433 (42.5)	1023 (46.5)*
>13 years	340 (33.4)	589 (26.8)**
Cohabitation lifestyle	829 (81.4)	1749 (79.5)
Shiftwork	135 (13.3)	447 (20.3)**
Physical activity	757 (74.3)	1564 (71,1)
Current smoker	302 (29.6)	706 (32.1)
Daily alcohol consumption	289 (28.4)	624 (28.4)
Body mass index (mean ± SD)	24.7 ± 3.9	24.7 ± 4.2
Cognitive scores (mean ± SD)		
Immediate free recall	8.2 ± 2.1	7.9 ± 2.0**
Delayed free recall	7.9 ± 2.9	7.4 ± 2.7**
Recognition test	13.2 ± 2.5	12.9 ± 2.5**
Digit Symbol Substitution Test	51.2 ± 14.6	50.4 ± 15.1
Selective attention test	3.4 ± 1.6	3.7 ± 1.6**

*p<0.05, **p<0.01

SD, Standard deviation

Data are presented as the number (n) with the percentage in parenthesis unless indicated otherwise

frequently reported benzodiazepines were bromazepam, with 2.7% of the population identified as long-term users, with a definite preference for benzodiazepines by women (3.9 vs. 1.7% in men, p<0.05), followed by zopiclone (1.7%) and zolpidem (1.3%). Tetrazepam (fourth position, 1.1% of long-term users) and clonazepam (fifth position, 0.7% of long-term users) use was also reported.

At baseline, women scored better on all cognitive tests than men (Table 2). During the follow-up, we identified a slight increase in cognitive performance between 1996 and 2001 which we attributed to a familiarity with the cognitive tests by the participants (effect which decreases with age). This transient period was followed by a natural decrease (or stabilization) in cognitive scores related to the aging population.

The effect sizes and 95% confidence intervals for the performance of subjects on different cognitive tests according to their benzodiazepine consumption are given in Figs. 1 and 2. The results are different according to gender. Among the men, only occasional users performed worse than non-users, while among the women, long-term users performed more poorly than non-users in free recall tests. However, these results must take into account all confounding factors.

Table 3 presents the results of the multivariate models of covariance analysis for each score in 2006 according to gender. In all models, scores at baseline, age and education level were the strongest associated factors explaining the value observed in 2006. In women, the long-term consumption of benzodiazepines presented a significant alteration of scores in delayed free recall (β=−2.13±0.67, p< 0.01), which evaluates the long-term memory of subjects. We also found a significant interaction between benzodiazepines and thyroid disease in this model. There was no statistically significant difference in cognitive scores for men.

Table 2 Mean cognitive scores during the follow-up for men and women

Cognitive test	Year of test	Total (n=1,019)	Men (n=536)	Women (n=483)
Immediate free recall	1996	8.2 ± 2.1	7.9 ± 2.1	8.6 ± 2.1***
	2001	8.7 ± 2.1	8.3 ± 2.0	9.1 ± 2.1***
	2006	8.6 ± 2.2	8.1 ± 2.1	9.1 ± 2.1***
Delayed free recall	1996	7.9 ± 2.9	7.2 ± 2.8	8.7 ± 2.8***
	2001	8.3 ± 2.9	7.7 ± 2.8	8.9 ± 2.9***
	2006	8.1 ± 3.0	7.5 ± 2.8	8.8 ± 3.0***
Recognition test	1996	13.2 ± 2.5	12.7 ± 2.6	13.7 ± 2.2***
	2001	13.5 ± 2.3	13.1 ± 2.4	13.9 ± 2.1***
	2006	13.4 ± 2.3	12.9 ± 2.5	14.0 ± 2.0***
Digit symbol substitution subtest	1996	51.2 ± 14.6	48.4 ± 13.9	54.2 ± 14.8***
	2001	53.7 ± 17.7	51.4 ± 19.8	56.2 ± 14.5***
	2006	53.5 ± 17.0	50.3 ± 14.6	56.9 ± 18.7***
Selective attention test	1996	3.4 ± 1.6	3.4 ± 1.6	3.4 ± 1.5
	2001	3.3 ± 1.5	3.3 ± 1.5	3.3 ± 1.5
	2006	3.4 ± 1.5	3.5 ± 1.6	3.3 ± 1.4*

*p<0.05, ***p<0.0001 (comparison between men and women)

Data are presented as the mean cognitive score ± SD

Discussion

The aim of this study was to investigate the impact of long-term benzodiazepine use on cognitive functioning in young adults according to gender. Adverse events following acute administration of benzodiazepines on attention, memory and psychomotor speed are well described in the literature [10]. Most studies have reported a negative effect of long-term benzodiazepine use on cognitive functioning [15, 16, 28–31], but the results are heterogeneous [17, 19, 32]. There is currently no data that establish a causal link between benzodiazepine consumption and cognitive decline in young adults, and few studies have taken an interest in men and women separately in their analysis. However, sex differences in cognitive abilities are well documented [33–37], and several studies suggest that men and women differ significantly in terms of their specific cognitive functions [38]. Men excel in visuospatial abilities whereas women excel at fine motor skill tasks and verbal fluency. Bremner et al. [39] found different patterns of activation in brain regions among women compared to men during the remembrance of emotional words. Other studies have

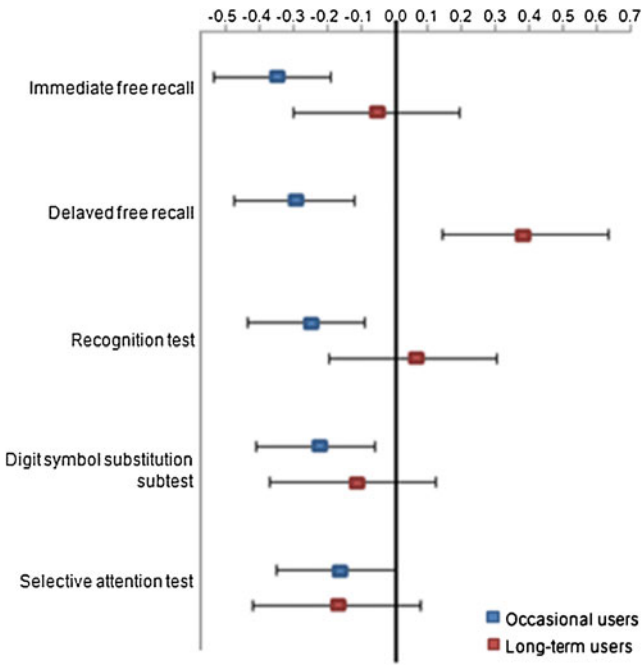

Fig. 1 Effect sizes and 95% confidence intervals for the performance of men on tests of cognitive function categories according to benzodiazepine use

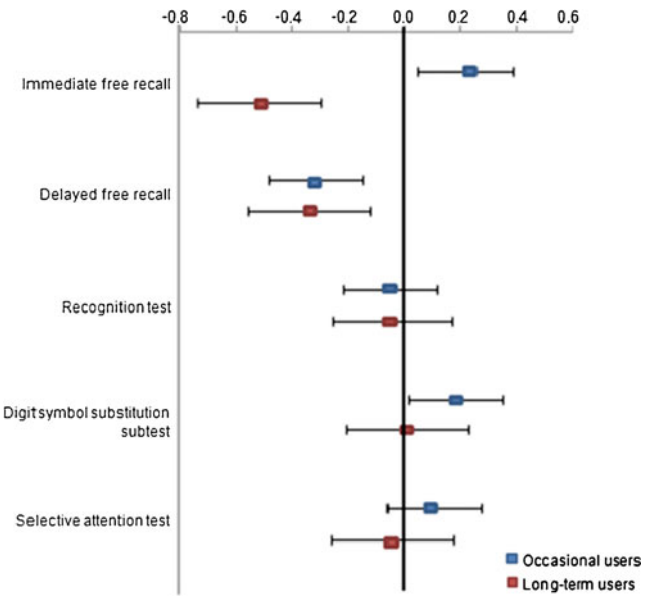

Fig. 2 Effect sizes and 95% confidence intervals for the performance of women on tests of cognitive function categories according benzodiazepine use

Table 3 Results of multivariate covariance analysis according to gender

Cognitive test	Category of drug use	β[a]	
		Men (n=526)	Women (n=483)
Immediate free recall	Non-users	0	0
	Occasional users	-0.01 ± 0.36	−0.55 ± 0.35
	Long-term users	-0.40 ± 0.25	0.52 ± 0.28
Delayed free recall	Non- users	0	0
	Occasional users	0.77 ± 0.50	−0.14 ± 0.97
	Long-term users	−0.80 ± 0.42	−2.13 ± 0.67**
Recognition test	Non-users	0	0
	Occasional users	−0.10 ± 0.47	−0.06 ± 0.33
	Long-term users	-0.57 ± 0.34	−0.12 ± 0.26
Digit symbol substitution subtest	Non- users	0	0
	Occasional users	−1.66 ± 2.46	−0.91 ± 3.46
	Long-term users	-0.32 ± 1.70	4.48 ± 2.65
Selective attention test	Non-users	0	0
	Occasional users	−0.04 ± 0.29	0.37 ± 0.26
	Long-term users	−0.30 ± 0.20	0.01 ± 0.21

*p<0.05, **p<0.01

Data are adjusted for age group, cognitive score at baseline, education level, cohabitation life, tobacco use, physical activity, shiftwork, daily alcohol use, body mass index and medical history of diabetes, cardiovascular disease, trauma, thyroid disease and depression.

[a] β indicates the amount of change in cognitive tests compared to non-users. Value is given as the score ± SD

focused on the impact of sexual hormones on cognitive functioning and decline [40]. These sex differences must be taken into account in cognitive performance studies. To the best of our knowledge, this is the first study to investigate the evolution of cognitive performance according to benzodiazepine use throughout a 10-year follow-up in a large sample of healthy young adults (<62 years). Indeed, most studies have focused on the impact of psychotropic drugs in elderly patients [15–19], whereas psychoactive drug consumption often begins before the age of 60 years and continues after this age. As cognitive functions are very sensitive to factors related to aging, it is important to assess changes in performance in several psychometric tests regardless of age and especially among patients whose mental health is good enough to perform their job during the period of observation. In our study, we analyzed benzodiazepine use taking into account other psychosocial and behavioral variables, such as tobacco use, cohabitation life or medical history, which may be important potential confounders in the relationship between drug use and cognitive functions. We observed that the long-term consumption of benzodiazepines was associated with a negative impact on cognitive performance; this negative impact was especially evident for long-term memory in women only (β=−2.13±0.67). Among our study cohort, the consumption of benzodiazepines did not seem to have any impact on the cognitive performance in men.

Some limitations of our study must be discussed. The first limitation is that the VISAT population was not strictly population based, even if the overall distribution into socio-professional categories is close to that observed at the national level in France [21]. Due to the manner in which the data were obtained from the medical examinations conducted by occupational physicians, we were led to restrict the study cohort to wage earners who were still working or just retired. This eliminated other categories of people who were out of work when the sample was set up, non-salaried workers and non-working individuals of working age. The second limitation is related to attrition for two reasons. Firstly, because we did not include subjects lost to follow-up and, secondly, because the cognitive performances at baseline were better in our study population than in the not-included population. Therefore, there was a selection bias of subjects which is related to the "healthy worker effect" (subjects with good health are more likely to be at work at the inclusion and during the follow-up than subjects of poor health status), which may have led to a possible underestimation of the impact of psychoactive drug use on cognitive functions. Patterns of benzodiazepine use in our sample were similar to those observed in other studies [2, 5]. We defined the category of drug use (non-users/occasional users/long-term users) according to methodology reported in other studies investigating cognitive decline and drug use in the elderly [15, 18]. We put forward the hypothesis that individuals reporting benzodiazepine use during the month preceding the interview for two of the surveys or who reported benzodiazepine treatment for at least 1 year would be classified as long-term users because in France the prescription recommendations for these drugs must not exceed 4 weeks for hypnotics and 12 weeks for anxiolytics. This hypothesis on the longitudinal use of drugs extrapolated from four data collection times could lead to a misclassification bias. Despite these limitations, we believe that the misclassification bias likely did not

greatly affect our group of long-term users because these patients reported the same drug or a similar drug in 2001 and/or 2006, strongly suggesting chronic use.

In our population, the prevalence of long-term psychoactive drug consumers was 9.0%, of whom the most were benzodiazepine users (82.6%). We identified 7.5% of the study cohort as long-term users of benzodiazepines (or related benzodiazepines). According to the French product characteristic summary of these drugs, the prescription period should not exceed 4 weeks for hypnotics and 12 weeks for anxiolytics. There is therefore a real problem in the prescription habits for these drugs. Moreover, the risk of dependence associated with the long-term consumption of benzodiazepines is well documented. We chose to analyze benzodiazepines because these drugs are the most extensively used psychoactive drugs in the French population [3].

Our results are in accordance with many published reports which underline that the long-term use of benzodiazepines is associated with a negative effect on cognitive functions[15, 16, 27]. In 2002, Paterniti et al. [15] performed the first longitudinal study to identify the negative impact of long-term benzodiazepine consumption in the elderly. The authors used data from the cohort EVA (Epidemiology of Vascular Aging), which included 1,176 subjects aged 59–69 years followed-up for 4 years and identified that the long-term use of benzodiazepines seemed to be a risk factor for cognitive decline. Bierman and al. [16], in a 9-year follow-up, cohort study (Longitudinal Aging Study Amsterdam), confirmed the negative impact on long-term memory and word retention among subjects aged 55–85 years. In their meta-analysis of clinical studies involving a minimum benzodiazepine exposure time of 1 year, Barker and al. [41] included 13 studies in which neuropsychological tests were used to evaluate cognitive performance of 12 cognitive domains (as working memory, psychomotor speed, visuospatial, attention…). The mean duration of benzodiazepine use was 9.9 years. The authors found that long-term benzodiazepine users were more impaired than the controls across all cognitive domains.

The major limitation of these studies was the use of data from elderly populations because in the elderly, it remains difficult to distinguish whether individuals use drugs as a response to cognitive impairment or whether the long-term use of these substances increases age-related cognitive impairment. Therefore, we observed the same impact of benzodiazepines on memory. We attributed this effect in women based on our separate analysis of men and women.

Finally, in our model evaluating the impact of benzodiazepines on long-term memory in women, we found a strong interaction between benzodiazepines and thyroid disease. Several published studies have emphasized the impact of the hypothyroidism on anxiety and depression, which could lead the patient to consume benzodiazepines [42, 43].

Conclusions

In conclusion, our study determined that long-term benzodiazepine use begins during adult life, even if its prevalence increases with age. Of our study cohort, 7.5% of young workers were benzodiazepene used. This is the first study to evaluate cognitive performance according to gender in an adult population and to show that long-term benzodiazepine exposure leads to specific impairment in long-term memory only in women. We need further investigations over a longer period of observation to determine whether or not these alterations are associated with a risk of developing dementia in old age.

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Conflict of interest statement The authors declare that they have no conflicts of interest regarding the content of this article.

References

1. Ohayon MM, Lader MH (2002) Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. J Clin Psychiat 63(9):817–825
2. Jacquinet-Salord MC, Lang T, Fouriaud C, Nicoulet I, Bingham A (1993) Sleeping tablet consumption, self reported quality of sleep, and working conditions Group of Occupational Physicians of APSAT. J Epidemiol Community Health 47:64–68
3. Boeuf-Cazou O, Lapeyre-Mestre M, Niezborala M, Monstruc JL (2009) Evolution of drug consumption in a sample of French workers since 1986: the 'Drugs and Work' Study. Pharmacoepidemiol Drug Saf 18(4):335–343
4. Chau N, Baumann M, Falissard B, Choquet M, the Lorhandicap Group (2008) Correlates and inequalities of psychotropic drug use among young adults: a population-based questionnaire study. Int J Equity Health 7(1):3–14
5. Lapeyre-Mestre M, Sulem P, Niezborala M, Ngoundo-Mbongue TB, Briand-Vincens D, Jansou P, Bancarel Y, Chastan E, Montastruc JL (2004) Taking drugs in the working environment: a study in a sample of 2106 workers in the Toulouse metropolitan area. Therapie 59(6):615–623
6. Ngoundo-Mbongue TB, Niezborala M, Sulem P, Briant-Vincens D, Bancarel Y, Jansou P, Chastan E, Montastruc JL, Lapeyre-Mestre M (2005) Psychoactive drug consumption: performance-enhancing behaviour and pharmacodependence in workers. Pharmacoepidemiol Drug Saf 14(2):81–89
7. Boeuf-Cazou O, Niezborala M, Marquié JC, Lapeyre-Mestre M (2010) Factors associated with psychoactive drug initiation in a sample of workers in France: results of the VISAT cohort study. Pharmacoepidemiol Drug Saf 19(3):296–305
8. Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, MacDonald TM (1998) Association of road-traffic accidents with benzodiazepine use. Lancet 352(9137):1331–1336
9. Khlat M, Ravaud JF, Brouard N, Chau N (2008) Occupational disparities in accidents and roles of lifestyle factors and disabilities: a population-based study in north-eastern France. Public Health 122(8):771–783

10. Curran HV (1991) Benzodiazepines, memory and mood: a review. Psychopharmacology 105(1):1–8
11. Taylor S, McCracken CF, Wilson KC, Copeland JR (1998) Extent and appropriateness of benzodiazepine use: results from an elderly urban community. Br J Psychiatry 173(5):433–438
12. Kirby M, Dehinan A, Bruce I, Radic A, Coakley D, Lawlor BA (1999) Benzodiazepine use among the elderly in the community. Int J Geriat Psychiatry 14(4):280–284
13. Woods JH, Katz JL, Winger G (1992) Benzodiazepines: use, abuse, and consequences. Pharmacol Rev 44(2):151–347
14. Hanlon JT, Horner RD, Schmader KE, Fillenbaum GG, Lewis IK, Wall WE, Landerman JR, Pieper CF, Blazer DG, Cohen HJ (1998) Benzodiazepine use and cognitive function among community-dwelling elderly. Clin Pharmacol Ther 64(6):684–692
15. Paterniti S, Dufouil C, Alperovitch A (2002) Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study. J Clin Psychopharmacol 22(3):285–293
16. Bierman EJ, Comijs HC, Gundy CM, Sonnenberg C, Jonker C, Beekman AT (2007) The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent? Int J Geriatr Psychiatry 22(12):1194–1200
17. Allard J, Artero S, Ritchie K (2003) Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance. Int J Geriatr Psychiatry 18(10):874–878
18. Lagnaoui R, Depont F, Fourrier A, Abouelfath A, Bégaud B, Verdoux H, Moore N (2004) Patterns and correlates of benzodiazepine use in the French general population. Eur J Clin Pharmacol 60(7):523–529
19. Dealberto MJ, McAvay GJ, Seeman T, Berkman L (1997) Psychotropic drug use and cognitive decline among older men and women. Int J Geriatr Psychiatry 12(5):567–574
20. Verdoux H, Lagnaoui R, Begaud B (2005) Is benzodiazepine use a risk factor for cognitive decline and dementia? A literature review of epidemiological studies. Psychol Med 35(3):307–315
21. Marquie JC, Jansou P, Baracat B, Martinaud C, Gonon O, Niezborala M, Ruidavets JB, Fonds H, Esquirol Y (2002) The VISAT (aging, health, & work) prospective study: overview and methodology. Le Travail Humain 65(3):243–260
22. Mitrushina M, Satz P, Chervinsky A, d'Elia L (1991) Performance of four age groups of normal elderly on the Rey Auditory Verbal Learning test. J Clin Psychol 47(3):351–357
23. Hoyer WJ, Stawski RS, Wasylyshtn C, Verhaeghen P (2004) Adult age and digit symbol substitution performances: a meta-analysis. Psychol Aging 19(1):211–214
24. Sternberg S (1975) Memory scanning: new findings and current controversies. Q J Exp Psychol 27(1):1–32
25. Hedges LV, Olkin I (1985) Statistical methods for meta-analysis. Academic Press, New York
26. Aartsen MJ, Martin M, Zimprich D (2004) Gender differences in level and change in cognitive functioning: results from the Longitudinal Aging Study Amsterdam. Gerontology 50(1):35–38
27. Cournot M, Marquié JC, Ansiau D, Martinaud C, Fonds H, Ferrières J, Ruidavets JB (2006) Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology 67(7):1208–1214
28. McAndrews MP, Weiss RT, Sandor P, Taylor A, Carlen PL, Shapiro CM (2003) Cognitive effects of long-term benzodiazepine use in older adults. Hum Psychopharmacol Clin Exp 18(1):51–57
29. Golombok S, Moodley P, Lader M (1988) Cognitive impairment in long-term benzodiazepines users. Psychol Med 18(2):368–374
30. Gorenstein C, Bernik MA, Pompeia S, Marcourakis T (1995) Impairment of performance associated with long-term use of benzodiazepines. J Psychopharmacol 9(4):313–318
31. Lagnaoui R, Bégaud B, Moore N, Chaslerie A, Fourrier A, Letenneur L, Dartigues JF, Moride Y (2002) Benzodiazepine use and risk of dementia: a nested case-control study. J Clin Epidemiol 55(3):314–318
32. Fastom J, Forsell Y, Winblad B (1998) Benzodiazepines may have protective effects against Alzheimer disease. Alzheimer Dis Assoc Disord 12(1):14–17
33. Kimura D, Hampson E (1993) Neural and hormonal mechanisms mediating sex differences in cognition. In: Vernon PA (ed) Biological approaches to the study of human intelligence. Ablex Publishing, New York
34. Halpern DF (1992) Sex differences in cognitive abilities, 2nd edn. Erlbaum, Hillsdale
35. Maccoby E, Jacklin C (1974) The psychology sex differences, edn. Stanford University Press, Stanford
36. Geary DC, DeSoto MC (2001) Sex differences in spatial abilities among adults from the United States and China. Evolution Cognition 7(2):172–177
37. Kimura D, Hampson E (1994) Cognitive pattern in men and women is influenced by fluctuations in sex hormones. Curr Dir Psychol Sci 3:57–61
38. Feingold A (1996) Cognitive gender differences: where are they, and why are they there? Learn Indiv Diff 8(1):25–32
39. Bremner JD, Soufer R, McCarthy G, Delaney R, Staib LH, Duncan JS, Charney DS (2001) Gender differences in cognitive and neural correlates of remembrance of emotional words. Psychopharmacol Bull 35(3):55–78
40. Richards M, Kuh D, Hardy R, Wadsworth M (1999) Lifetime cognitive function and timing of the natural menopause. Neurology 53(2):308–314
41. Barker MJ, Greenwood KM, Jackson M, Crowe SF (2004) Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 18(1):37–48
42. Larisch R, Kley K, Nikolaus S, Sitte W, Franz M, Hautzel H, Tress W, Müller HW (2004) Depression and anxiety in different thyroid function states. Horm Metab Res 36(9):650–653
43. Demet MM, Ozmen B, Deveci A, Boyvada S, Adigüzel H, Aydemir O (2003) Depression and anxiety in hypothyroidism. West Indian Med J 52(3):223–227