

Original Article

Can We Say that Seniors Are Addicted to Benzodiazepines?

MORGANE GUILLOU LANDREAT,¹ CAROLINE VICTORRI VIGNEAU,² JEAN BENOIT HARDOUIN,³ MARIE GRALL BRONNEC,¹ MARIE MARAIS,² JEAN LUC VENISSE¹ AND PASCALE JOLLIET²

¹Addictology Center, CHU Nantes, Nantes, France

²Pharmacology Center, CHU Nantes, Nantes, France

³Biostatistic Center, CHU Nantes, Nantes, France

Introduction: *The elderly are the biggest consumers of Benzodiazepines (BZD) and/or BZD equivalents. However, the risks of developing addiction in this age group are often underestimated. Method: This study describes the nature and extent of addiction in the elderly using DSM IV items. Results: We noted a high prevalence of addiction in our population and identified a two-factor profile in subjects of 65 years of age and older addicted to BZD/equivalents. Conclusion: This profile led us to reconsider anew the definition of addiction, the approach to addiction in this age group, and the way to prescribe treatment by BZD/equivalents in this population.*

Keywords elderly; benzodiazepine; substance use disorders; addiction; prevalence

Introduction

Many studies regularly underline the potential danger of benzodiazepines (BZD) use and their equivalents in subjects aged 65 years and older (Petrovic, Mariman, Warie, Afschrift, and Pevernagie, 2003). Studies have noted increased psychomotor and cognitive risks as a result of pharmacokinetic and pharmacodynamic modifications related to ageing (Briot, 2006; Closser, 1991, Leipzig, Cumming, and Tinetti, 1999; Rouleau, Proulx, O'Connor, Belanger, and Dupuis, 2003). But the risk of developing addiction, widely demonstrated for young consumers of BZD/equivalents, is often underestimated for this age group (Fatseas, Lavie, Denis, Franques-Reneric, and Tignol, 2006). To our knowledge there are no forecast studies proving such addiction. However, persons aged 65 years and older are the biggest

These data were presented at the Albatros Congress, Paris, France, on June 6, 2008.

Address correspondence to Dr. Morgane Guillou Landreat, M.D., CHU, Department of Addictology, 85 Rue St Jacques, 44083 Nantes, France. E-mail: rgane77@hotmail.com

consumers of BZD/equivalents and thus would be especially at risk of addiction (Lagnaoui, Moore, Dartigues, Fourrier, and Begaud, 2001; Pelissolo, Boyer, Lepine, and Bisserbe, 1996; www.insee.fr/, 2007).

The literature shows no studies directly asking seniors about BZD/equivalents use and dependence. Therefore, we decided to perform such a study in order to establish whether there is addiction to BZD and/or their equivalents in seniors. We carried out a forecast study in outpatients aged 65 years and older who were taking BZD/equivalents on a chronic basis in the Nantes area.

Methods

Aim of the Study

The aim of the study was to establish whether there is an addiction to BZD/equivalents in persons aged 65 years or older who were taking BZD/equivalents on a chronic basis, and to carry out a quantitative analysis of their profile.

We used a questionnaire that was based on DSM IV (APA, 1994), and that was filled in by a health professional. This study examined answers to items on drug addiction given by persons aged 65 years and older who took BZD/equivalents on regular basis. To be included in the study, subjects had to be of 65 years or older; they had to be taking BZD/equivalents that had been prescribed via prescription refill orders; and they had to not have any exclusion criteria (e.g., refusing to take part in the study, having a poor understanding of the French language, having a first prescription for BZD/equivalents).

Data were collected in partner pharmacies of the Faculty of Pharmacy of Nantes. The investigators were pharmacy students doing an internship in pharmacies. They were trained to administer the questionnaire according to a standard protocol (i.e., how to obtain consent, complete the questionnaire in 15 minutes, and administer the questionnaire in a separate room within the pharmacies).

The number of subjects to be included in the study was assessed according to feasibility criteria (which took account of constraints of time and staff available to administer the questionnaires). Thus, during a 3-month period, investigators included in the study the first five patients in the pharmacies who met the study criteria for inclusion.

Data were totally anonymous. Consent for participation in the study was oral and consistent with French research standards for studies involving anonymous data.

Questionnaire

The questionnaire was based on DSM IV items on drug addiction; questions were phrased so as to elicit yes-or-no answers. Content and form validity have been consensually approved by a committee made up of addictology, pharmacology, and biostatistics experts.

The questionnaire also collected socio-demographic and medical data (medical history and follow-up). In addition, we asked a question on prescription bypassing by the subjects, that is to say, we wanted to know whether seniors tried to obtain BZD/equivalents through nonformal ways. The formal way to obtain drugs is with a doctor's prescription. The prescription entitles the patient to obtain medications by having one prescription dispensed in one pharmacy.

Statistical Analysis

The statistical analysis was carried out using SAS software.

Descriptive Analysis. Quantitative variables are expressed as means and standard deviations. Qualitative variables are expressed as ratios and percentages.

Comparative Analysis. Univariate comparisons were carried out using standard tests (Student's t, Chi-Square, and Fischer tests).

Multivariate comparisons were carried out by principal component analysis and logistic regressions.

Results

Descriptive Analysis

Population Characteristics. There were 42 investigators who took part in the study; 186 questionnaires were collected during the duration of the study, with an average of 4.4 questionnaires per investigator. Among the questionnaires, 10 were excluded (no BZD/equivalents use and age criteria not respected).

Our population predominantly consisted of females (77.3%). The average age was 75.4 years, ± 7.5 years (range = 65–97 years; median = 75 years).

The family doctor was the only prescribing physician in 90% of the cases.

Addiction to Benzodiazepines. In all 35.2% of the subjects were addicted to BZD/equivalents, that is to say, they met at least three items on addiction according to the DSM IV.

Answers to all items on addiction and to the question on prescription bypassing are presented in Table 1.

What are the Substances Being Prescribed?. Table 2 presents the distribution of BZD/equivalents, in percentages and ranked in order of frequency, prescribed to our sample.

In all 79.5% of the subjects had only one BZD/equivalents substance type prescribed. But 20.5% had more than one substance prescribed.

In addition, some dosages exceeded the doses recommended for use by seniors (in accordance with the notice of the marketing authorization) in 30.2% of the cases.

Table 1
Answers to items on addiction and to the question of bypassing

Items	Yes (%)	No (%)	Never stopped (%)	Not answered (%)
Tolerance	35.2	60.2		4.6
Deprivation signs	51.7	21.6	23.3	3.4
Long-term administration or higher doses	19.9	79.5		0.6
Unsuccessful attempts to stop treatment	31.2	40.3	25.6	2.8
Concerned by treatment	47.2	50.6		2.3
Social consequences	4.5	92.6		2.8
Prescription limitation by the physician	11.9	86.4		1.7
Somatic consequences	13	84.1		2.8
Prescription bypassing	17.6	77.3		5.1

Table 2
Representation of the most
prescribed BZD/equivalents
molecules

Molecule	%
Bromazepam	24.1
Lorazepam	18.1
Zopiclone	12.5
Zolpidem	12.5
Alprazolam	8.8
Oxazepam	6.0
Lormetazepam	3.2
Others	14.8

Moreover, 27.3% of the subjects presented with medical conditions (e.g., respiratory failure, sleep apnea syndrome, liver failure, myasthenia, and kidney failure) for which the use of benzodiazepines and equivalents was contraindicated or required precautions before use in accordance with the recommendations (ANAES, 1995).

Half of the subjects received multiple medications in addition to BZD/equivalents. Moreover, 22% of the subjects admitted resorting to self-medication, mainly for analgesic and homeopathic treatments.

Comparative Study

Univariate Comparative Study. Using a univariate analysis we compared the variables between the addicted and the nonaddicted groups using Chi-Square or Fischer's test. Results are shown in Table 3 in percentages and statistical significance (p -values). Statistical significance was set at $p < .05$.

Multivariate Comparative Analysis. We have carried out a multivariate analysis for exploratory purposes using a principal component analysis (PCA) presented on Figure 1.

Subjects are represented by blue dots for nonaddiction and by red dots for addiction. Items of addiction are represented in green. The variables corresponding to medico-surgical, psychiatric history, alcohol consumption (OH history), and smoking (smoking history) are represented in red (modality 1 for "no," and modality 2 for "yes" answers).

We found that two dimensions explained 42% of the total variance between subjects. Addicted subject groups clearly differ from nonaddicted ones by their coordinates on these dimensions. Moreover, items defining addiction are not gathered on one axis, but a two-factor concept of addiction stands out in this study:

1. The first axis is represented by the following items: "deprivation signs" and "unsuccessful attempts to stop treatment."
2. The second axis is represented by the following items: "Tolerance," "taking higher doses than what has been prescribed," and "concerned by treatment/treatment duration."

Finally, the following variables "alcohol history" and "psychiatric history" seem like illustrative modalities related to addiction.

Table 3
Comparison of variable proportions expressed in percentages (Chi-square)

	Nonaddicted (%)	Addicted (%)	<i>p</i> (Chi-square)
Sex			.1235
Man	26.3	16.1	
Woman	73.7	83.9	
Living place			.045*
City	70.2	83.6	
Countryside	29.8	16.4	
Way of life			.6152
With somebody	50.9	54.8	
Alone	49.1	45.2	
Prescribing physician			.6020
Family doctor	91.1	88.7	
Specialist	8.9	11.3	
Managing treatment			.8465
Independent	87.7	88.7	
Dependant	12.3	11.3	
Independence			.9304
Independent	85.9	85.5	
Dependant	14.1	14.5	
History			
Medical/surgical history	76.9	72.1	.4917
Psychiatric/psychological history	21.2	42.6	.0033**
Smoking history	16.8	26.2	.1393
Alcohol history	3.5	14.7	.0073**
Type of Benzodiazepine			
Bromazepam	63.5	36.5	NS
Lorazepam	58.3	41.7	NS
Zolpidem	48.2	51.8	.0780
Zopiclone	70.4	29.6	NS
Number of benzodiazepines prescribed			.0375*
1 molecule	84.2	15.8	
2 or 3 molecules	71	29	
Items of DSM IV			
Tolerance	18.7	68.8	<.0001***
Deprivation	38.9	79.0	<.0001***
Taking higher doses	4.4	49.2	<.0001***
Unsuccessful attempts to stop treatment	20.9	52.4	<.0001***
Concerns, treatment duration	29.1	82.3	<.0001***
Social consequences	0.9	11.8	.0012*
Physician limitation	54.5	27.9	<.0001***
Somatic consequences	6.3	26.7	.0002**

**p* < .05.

***p* < .01.

****p* < .0001.

Table 4
Goodness-of-fit test of logistic regression for addiction items

Addiction items	Odds ratio	Relative risk
Tolerance	28.630	6.92
Taking higher doses	38.038	4.92
Deprivation	6.741	4.73
Unsuccessful attempts to stop treatment	16.760	4.55

Analysis Using Logistic Regression. We then carried out an analysis using logistic regression to quantify the link between identified variables and addiction in this population.

We chose a multivariate model of logistic regression, i.e., goodness-of-fit test (Hoshmer–Lemeshow test, $p = .89$) with high concordance (93%). Results are presented in Table 4.

The following four items perfectly defined the notion of addiction in this population: “tolerance,” “taking higher doses,” “deprivation signs,” and “unsuccessful attempts to stop treatment.” Moreover, these results totally match those of the PCA. With the logistic regression we also find the two dimensions that stand out with the PCA. These dimensions were represented by “deprivation signs” and “unsuccessful attempts to stop treatment” and by the items “tolerance” and “taking higher doses.”

Discussion

The originality of this study lies in its methodology: This is a forecast study during which we systematically interviewed senior subjects consuming BZD and equivalents concerning their addiction using the items of the DSM IV. We found a high prevalence of addiction, which was not described clearly.

Moreover, we identified a two-factor concept of addiction in this specific population and, insofar as we know, this has not been reported in the literature previously.

First, this can be interpreted as a reflection of a double-conditioning linked with BZD and equivalent consumption in subjects aged 65 years and older. There is a positive conditioning, when looking for psychoactive effects of BZD/equivalents, resulting in the consumption of higher doses than the prescribed ones, and tolerance. Moreover, there is also a negative conditioning: Subjects hardly feel the negative consequences of their consumptions; on the contrary, half of the subjects admitted feeling signs of deprivation. We can therefore consider that negative perception of deprivation signs can easily increase consumption, especially because the harmful effects of BZD/equivalents are hardly felt and it is the positive effects that are experienced by the subjects.

Furthermore, this two-factor concept can also lead us to think about the definition of addiction in seniors. There is no consensus in the literature, as some suggest defining addiction according to the length of time of drug consumption, but this approach is hardly satisfying (Egan, Moride, Wolfson, and Monetteet, 2000; Morgan, Dalosso, Ebrahim, Arie, and Fentem, 1988; Whitcup and Miller, 1987).

In our study we noted that the following items were sufficient to perfectly define the notion of addiction: “tolerance,” “taking higher doses,” “deprivation signs,” and “unsuccessful attempts to stop treatment.”

However, others combined items in the DSM IV, especially the behavioral consequences items, such as “social consequences” and “medical consequences,” were not

specific to BZD/equivalent dependence. We can therefore conclude that these four items (“tolerance,” “taking higher doses,” “deprivation signs,” and “unsuccessful attempts to stop treatment”) better characterize addiction to BZD/equivalents in our sample of seniors.

However, one of limits of our study is that we cannot know whether this stronger place and weight of some items on others is linked to BZD/equivalents having the characteristic of being prescribed drugs unlike other substances or whether it is linked to the age group. Therefore, a comparative study with factor analysis of addiction to BZD/equivalents should be carried out in two groups: one of adults and the other of seniors aged 65 years and older in order to distinguish between the characteristics linked to the substance and those linked to the age.

Moreover, this two-factor concept underlies the overconsumption of BZD/equivalents in seniors, unlike what is often reported in the literature. Indeed, tolerance to BZD/equivalents as well as taking higher doses than what has been prescribed, show that there is treatment overconsumption. Finally, one in five of the subjects of our study admitted bypassing the obtaining of a prescription as a means of obtaining BZD/equivalents and a significant amount of medical prescribing does not respect marketing authorization standards (i.e., prescribing of several BZD/equivalents per prescription in one in five cases, and prescribing higher doses than what is recommended in one in three cases). We can therefore deduce that there is definitely some overconsumption of BZD/equivalents among seniors due to various factors.

Prescribing physicians do not sufficiently respect the BZD/equivalent treatment doses and duration of treatment with BZD/equivalents, as well as the combination of recommended treatment.

The pharmacist is a party to this overconsumption when he or she dispenses medications without a prescription (i.e., treatment “in advance”). Finally, patients tend to self-medicate and overconsume BZD/equivalents beyond the prescribed dose, seeking to obtain treatment by alternate ways bypassing the prescription.

This should encourage everyone involved in the prescribing and dispensing of prescriptions to modify their practices. The prescribing physician should become concerned if a patient describes a tolerance to his/her treatment and asks for higher doses, and should question the patient on their quantitative and qualitative ways of consuming BZD/equivalents. The pharmacist should also be concerned if a patient asks for drugs without a prescription. Finally, as soon as treatment is initiated, patients should be clearly informed about prescription conditions, how to stop treatment, as well as risks related to consumption, and especially the addiction risks. Here therapeutic education of the patient is probably one of the keys to prevent addiction.

Declaration of Interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

RÉSUMÉ

Les sujets âgés sont ils dépendants aux Benzodiazépines?

Introduction: Les sujets âgés sont les plus consommateurs de benzodiazépines ou apparentés. Cependant, les risques de développer une dépendance dans cette tranche d'âge

sont souvent peu évalués ou sous estimés. **Méthode:** Cette étude analyse la prévalence et les caractéristiques de la dépendance chez les sujets âgés à partir des critères de la dépendance aux substances du DSM IV. **Résultats:** Nous avons retrouvé une prévalence élevée de la dépendance aux benzodiazépines ou apparentés dans notre population. Nous avons identifié un profil bifactoriel de la dépendance aux benzodiazépines chez les sujets de 65 ans ou plus dépendants aux benzodiazépines ou apparentés. **Conclusion:** l'identification de ce profil de la dépendance nous a conduit à nous interroger sur la définition de la dépendance chez les sujets âgés et sur les modalités de prescription de traitements par benzodiazépines ou apparentés dans cette tranche d'âge.

RESUMEN

Las personas de edad son adictos a las benzodiazepinas?

Introducción: Los ancianos son los consumidores más de las benzodiazepinas o similares. Sin embargo, los riesgos de desarrollar dependencia en este grupo de edad a menudo no son evaluados o subestimado. **Método:** Este estudio analiza prevalencia y características de la dependencia en los ancianos basada en los criterios de dependencia de sustancias en el DSM IV. **Resultados:** Hemos encontrado una alta prevalencia de la dependencia de benzodiazepina o relacionados en nuestra población. Hemos identificado un doble perfil de factor de la dependencia de benzodiazepina en pacientes de 65 años o más adictos a las benzodiazepinas o similares. **Conclusión:** La identificación de este patrón de dependencia ha llevado a preguntas sobre la definición de la adicción en los ancianos y sobre las modalidades de la prescripción del tratamiento de benzodiazepinas o relacionados con este grupo de edad.

THE AUTHORS



Morgane Guillou Landreat, M.D., works at the addiction center of the hospital of Morlaix (France) and is a scientist at the EA 4275 of University of Nantes. Her areas of interest include benzodiazepine (BZD) use, especially among the elderly, substance use-related disorders, and pathological gambling.



Caroline Victorri Vigneau, Pharm.D., works at the pharmacology center of the University Hospital of Nantes and is a scientist at the EA 4275 of the University of Nantes.



Jean Benoit Hardouin, Ph.D., Assistant Professor of biostatistics at the University of Nantes, is a scientist at the EA 4275 of the University of Nantes.



Marie Grall Bronnec, M.D., works at the addictology center of the hospital of Nantes. She is a scientist at the center for pathological gambling (CRJE) of Nantes and at the EA 4275 of the University of Nantes.



Marie Marais, Pharm.D., works at the pharmacology center of the University Hospital of Nantes.



Jean Luc Venisse, M.D., Ph.D., Director of the addictology center of the University Hospital of Nantes, works as a scientist at the center for pathological gambling of the University of Nantes.



Pascale Jolliet, M.D., Ph.D., Director of the pharmacology center of the University Hospital of Nantes, is a scientist at the EA 4275 of the University of Nantes.

References

- ANAES (1995). Prescription des hypnotiques et anxiolytiques. *Recommandations et Références médicales*, 2:149–165.
- APA (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.) Washington, DC: APA.
- Briot, M. (2006). Rapport sur le bon usage des médicaments psychotropes. Office Parlementaire d'évaluation des Politiques de Santé; Retrieved 23 March, 2007 from www.senat.fr
- Closser, M. H. (1991). Benzodiazepines and the elderly. A review of potential problems. *Journal of Substance Abuse Treatment*, 8(1–2):35–41.
- Egan, M., Moride, Y., Wolfson, C, Monette, J. (2000, Jul) Long-term continuous use of benzodiazepines by older adults in Quebec: prevalence, incidence and risk factors. *Journal of the American Geriatrics Society*, 48(7):811–816.
- Fatseas, M., Lavie, E., Denis, C., Franques-Reneric, P., Tignol, J. (2006, Apr). Auriacombe M. [Benzodiazepine withdrawal in subjects on opiate substitution treatment]. *Presse Medicale*, 35(4 Pt 1):599–606.
- Lagnaoui, R., Moore, N., Dartigues, J. F., Fourrier, A., Begaud, B. (2001, Oct). Benzodiazepine use and wine consumption in the French elderly. *British Journal of Clinical Pharmacology*, 52(4):455–456.
- Leipzig, R. M., Cumming, R. G., Tinetti, M. E. (1999, Jan). Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *Journal of the American Geriatrics Society*, 47(1):40–50.
- Morgan, K., Dallosso, H., Ebrahim, S., Arie, T., Fentem, P. H. (1988, Feb 27). Prevalence, frequency, and duration of hypnotic drug use among the elderly living at home. *British Medical Journal (Clinical Research Edition)*, 296(6622):601–602.

- Pelissolo, A., Boyer, P., Lepine, J. P., Bisserbe, J. C. (1996, May–Jun). Epidemiology of the use of anxiolytic and hypnotic drugs in France and in the world. *Encephale*, 22(3):187–196.
- Petrovic, M., Mariman, A., Warie, H., Afschrift, M., Pevernagie, D. (2003, Jan–Feb). Is there a rationale for prescription of benzodiazepines in the elderly? Review of the literature. *Acta Clinica Belgica*, 58(1):27–36.
- Rouleau, A., Proulx, C., O'Connor, K. P., Belanger, C., Dupuis, G. (2003, Autumn). Benzodiazepine use in the elderly: state of the knowledge. *Sante Ment Que*, 28(2):149–164.
- Whitcup, S. M., Miller, F. (1987, Apr). Unrecognized drug dependence in psychiatrically hospitalized elderly patients. *Journal of the American Geriatrics Society*, 35(4):297–301.
- www.insee.fr/ (2007). “Projections de population pour la France métropolitaine à l’horizon 2050, la population continue de croître et le vieillissement se poursuit” Isabelle Robert-Bobée, division Enquêtes et études démographiques.