Elderly Benzodiazepine Users at Increased Risk of Activity Limitations: Influence of Chronicity, Indications, and Duration of Action—The Three-City Cohort

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Objective: *To examine the cross-sectional and longitudinal associations between benzodiazepine use and daily activity limitations, according to drug indications and duration of action.* **Design:** *Prospective cohort study.* **Setting:** *Population-based three-city study.* **Participants:** *6,600 participants aged 65 years and over included between 1999 and 2001 and followed after 2, 4, and 7 years.* **Measurements:** *Benzodiazepine users were separated into hypnotic, short-acting anxiolytic, and long-acting anxiolytic users and compared with non users. Three outcomes were examined assessing restrictions in mobility, instrumental activities of daily living (IADLs) and social participation.* **Results:** *In multivariate simple or mixed logistic models adjusted for sociodemographic variables, impairments and comorbidity, and for anxiety, insomnia, and depression, hypnotic benzodiazepines were moderately associated with mobility limitation prevalence and IADL limitation incidence. Short-acting and long-acting anxiolytics were associated with IADL limitation prevalence and with mobility limitation prevalence and incidence and long-acting anxiolytics were also associated with IADL limitation incidence. Chronic benzodiazepines users were at a marked risk of developing restrictions for the three outcomes; odds ratio: 1.71 (95% CI: 1.23−2.39) for mobility, 1.54 (95% CI: 1.14−2.10) for IADL, and 1.74 (95% CI: 1.23−2.47) for participation limitations.* **Conclusions:** *Benzodiazepine users are at increased risk of activity limitations regardless of the duration of action or indication. Chronic use of benzodiazepines should be avoided in order to extend disability-free survival.* (Am J Geriatr Psychiatry 2014; ■:■−■)

Received May 2, 2014; revised October 15, 2014; accepted October 28, 2014. From INSERM U1061 (IC, TM, JN, IJ, CB, KR, MLA), Montpellier, France; Université Montpellier I, U1061 (IC, TM, JN, IJ, CB, KR, MLA), Montpellier, France; INSERM ISPED, Centre Inserm U897-Epidemiologie-Biostatistique (KP, AE), Bordeaux, France; Université Bordeaux, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique (KP, AE), Bordeaux, France; CHRU Dijon, Centre Mémoire Ressources et Recherche (OR), Dijon, France; and the Faculty of Medicine, Imperial College (KR), London, United Kingdom. Send correspondence and reprint requests to Isabelle Carrière, Ph.D., INSERM U1061, Neuropsychiatry: Epidemiological and Clinical Research, Hôpital La Colombière, 39 Avenue Charles Flahault, BP 34493, 34093 Montpellier Cedex 05, France. e-mail: isabelle.carriere@inserm.fr

http://dx.doi.org/10.1016/j.jagp.2014.10.006

Key Words: Benzodiazepines, activity of daily living, aging, longitudinal study, random-effect model

Because of their extensive use and well-known side effects, the safety of benzodiazepines has received particular attention in older people. Benzodiazepines are usually prescribed for their sedative, anxiolytic, hypnotic, and muscle-relaxant effects. They can, however, produce excessive sedation, anterograde amnesia, and motor coordination deficits, and long-term usage induces problems of tolerance (decreasing pharmacological effect over time) and physical dependence.[1] The likelihood of such adverse neurological reactions increases with age due to depletion of the neurotransmitter system, hormonal changes, decreased cerebral availability of glucose and oxygen, possibly greater penetration of drugs into the central nervous system,[2] but also pharmacodynamic alterations with a decreased renal clearance and hepatic metabolism leading to increased elimination time. As a consequence, the use of benzodiazepines is an established risk factor for falls[3–5] and hip fractures[6–9] in the elderly as well as for driving impairment and motor vehicle collisions.[10] More controversially, new elderly users were recently found at increased risk of incident dementia,[11] although the risk decreased after discontinuation in former users,[12] and chronic users were found at risk of cognitive impairment but not cognitive decline.[13]

Together, these findings suggest a possible adverse effect on daily activities that require physical and cognitive capacities. Given that anxiety disorders[14] and poor sleep quality[15,16] are also associated with incident activity limitations in the community-dwelling population, the global risk-benefit balance of treatment with benzodiazepines remains to be assessed. Increasing disability-free life expectancy and promoting good social functioning and participation for older people are foreground goals in aging populations; yet few studies have analyzed the effects of benzodiazepines on daily activity limitations.[17–21]

Furthermore, these studies have several methodological limits: 1) not taking into account temporality between the exposure and the outcome and possible reverse causality; 2) insufficient control of indication confounders (sleep and anxiety disorders); 3) not taking into account pharmacological and pharmacokinetic properties of the drugs and the chronicity of their use; and 4) not exploring the differential effects according to the degree of severity of the activity limitations.

The purpose of this study was to examine the cross-sectional and longitudinal associations between benzodiazepine use and activity limitations in a large elderly community-dwelling cohort, for which information on a large number of potential confounding factors, including sleep and anxiety disorders, was available. The analyses are based on three scales corresponding to different activity and participation restrictions and focus on the influence of benzodiazepine indications (hypnotic and anxiolytic) and duration of action (short- and long-acting).

METHODS

Study Sample

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001.[22] The study protocol was approved by the ethics committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. A standardized evaluation with a face to face interview and clinical examination was undertaken at baseline, and at 2, 4, and 7 years. Of the 9,080 dementia-free participants included in the cohort, 6,600 were included in the cross-sectional analysis and 5,766, 3,484, and 5,651 in the longitudinal analyses of the incidence of participation restriction, mobility, and instrumental activities of daily living (IADL) limitations, respectively (Fig. 1).

Compared with the analyzed sample, those not included in the cross-sectional analysis were more frequently benzodiazepine users, female, older, living alone, had lower education, lower income, cognitive impairment, cardiovascular and non-cardiovascular chronic pathologies, depression, insomnia, anxiety, and hearing impairment ($p < 0.0001$). They also had