The risk of cognitive impairment in older community-dwelling women after benzodiazepine use

SIR—Long-term benzodiazepine (BZD) use has been associated with cognitive impairment that was reversible [1, 2] or not [3]. Few cohort studies have examined the association between BZD use and incident cognitive decline or dementia [4]. Chronic BZD users had a significantly increased risk of cognitive impairment, while episodic or recurrent users had not [5]. In the French community-dwelling persons, BZD use was associated with an increased risk of dementia [6]. Nevertheless, the study design did not allow us to rule out a protopathic bias, whereby BZDs could be prescribed for early symptoms of cognitive impairment resulting in a spurious association. Another study reported a lower incidence of dementia in older persons using BZDs [7]. Since subjects exposed only at baseline were not distinguished from those exposed both at baseline and follow-up assessments, a depletion of susceptible effect may explain the protective effect finding [8], as BZDs may have been discontinued in subjects with incident cognitive impairment. To help clarify the association between BZD use and cognitive decline, a case-control analysis was carried out using data from a large representative cohort of Canadian older women, in order to examine the association between BZD use and the occurrence of cognitive decline including dementia.

Material and methods

Study population

The source population for our study was that of Quebec community-dwelling women aged 65 years or more who participated in nation-wide study on dementia, the Canadian Study of Health and Aging (CSHA) [9, 10]. In 1991–92, a random sample of older Canadians residing in the community and institutions was drawn (CSHA-1). In 1996–97, a follow-up study (CSHA-2) was carried out to estimate the incidence of dementia and to study risk factors. In Quebec, 3,903 community older persons were randomly sampled. For the present study, the cohort consisted of all women who met the following criteria: (i) community-dwelling resident of Quebec for at least 2 years prior to CSHA-1, (ii) provided a valid Health Insurance Number (HIN) and (iii) screened normal (MMMS score ≥ 78) at CSHA-1 and participated in CSHA-2. Cases were found to be demented or cognitively impaired but not yet demented (CIND) at CSHA-2. Controls did not develop dementia or CIND between CSHA-1 and CSHA-2. The interview included general health questions and the Modified Mini-Mental Status examination (MMMS) to screen for cognitive impairment [11]. Those who screened positive and a random sample of those who screened negative underwent a clinical assessment. An independent diagnosis using the DSM-III-R criteria was made by the physician and the neuropsychologist, who were unaware of the subjects' MMMS scores: diagnosis of dementia, CIND or no cognitive loss [12, 13]. The index date was the date of the screening test (i.e. MMMS) in CSHA-2 which preceded the date of diagnosis.

Exposure to benzodiazepines and covariates

Data on the use of BZDs and other drugs were obtained from the Régie de l’Assurance Maladie du Québec (RAMQ) prescription database. The linkage between CSHA-1, CSHA-2 and RAMQ databases through the HIN produced a dataset that included long-term exposure to drugs for all study subjects along with demographic and clinical characteristics. We classified exposure to BZDs into two mutually exclusive categories: current use, defined as dispensing of at least one prescription within 365 days preceding the index date, and past use. Past use covered the time prior to 365 days before index date and up to CSHA-1. Non-users were not dispensed a BZD during the follow-up period. Covariates included age, institutionalisation since CSHA-1, the activities of daily living scale (ADL) [14], education, mean number of drugs used per week during the year preceding the index date, exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or estrogens during the study period.

Statistical analysis

The association between BZD use and cognitive impairment was measured through unconditional multivariate logistic regression. We explored the association between the risk of cognitive decline and BZD exposure (current or past), controlling for the covariates.

Results

Of the 590 women who were eligible for the study, 510 (86.4%) were included in the analysis while 80 were excluded because of missing data on BZD use. Seventy-three received a diagnosis of cognitive impairment at CSHA-2 (Table 1). Of the 73 cases, 14 (19.2%) had a diagnosis of dementia and 59 were classified as CIND. Current use of BZDs did not influence the risk of cognitive decline (Table 2). Former use
was non-significantly associated with a 50% increase in the risk of cognitive decline compared to non-use.

**Discussion**

This study had some methodological limitations. First, the small number of patients included in this study and the relatively low effect size of the association between BZD use and cognitive impairment could explain the absence of statistically significant results using the conventional level of significance of 0.05. For example, keeping the same conditions, the detection of an odds ratio as low as 1.5 or greater would have required 509 cases and 3,054 controls. Such figures are unrealistic when one considers the frequency of the disease in the source population. The number of cases and controls retained in our analysis provided a statistical power of 86% to detect an odds ratio of 2.5 or greater which allows us to rule out a strong association between BZD and cognitive impairment. Second, the definition of former use of BZD included long- and short-term use. The association between BZD use and cognitive decline, if any, is more likely to imply long-term use. Unfortunately, the small number of subjects exposed to BZD did not permit stratification by pattern of use (dose, duration, etc.), or type of BZDs. Lastly, indication for BZD treatment was not available and might correspond to early symptoms of dementia. However, the index date was the date of the early screening test which took place several months before the consensus diagnosis, allowing us to rule out a protopathic bias.

The strengths of the study were that the data were derived from a representative sample of community-dwelling older people, with the controls drawn from the same population as the cases. The results could be generalized to the population of older women. BZD use was assessed using RAMQ prescription database, based on drugs dispensing, while, in most studies, it was reported by the participants leading to recall bias.

Even if not statistically significant, these results are consistent with the findings of our prior nested case-control study where former use of BZD was associated with an increased risk of dementia, while current use did not increase this risk [6]. Although the effect size of such association, if any, is probably not strong, the public health impact may not be negligible since a significant number of cases of dementia may be induced by exposure to BZDs considering the high prevalence of BZD use in the older people [15–17]. The next step would be to determine whether specific patterns of BZD use, such as chronic or long-term use, are particularly associated with an increased risk of cognitive decline.

**Key points**

- The use of benzodiazepines has been suggested as a risk factor for cognitive impairment and possibly for dementia.
- In the present study, former use of benzodiazepines was associated with a 50% increase in the risk of cognitive decline including dementia, but without statistical significance. No association was found between current use of benzodiazepines and risk of cognitive decline.
- The present findings rule out a strong association between benzodiazepines and cognitive decline.
Research letters

- The next step would be to determine whether specific patterns of benzodiazepine use, such as chronic use, are particularly associated with an increased risk of cognitive decline.

Acknowledgements

Marie Tournier is a recipient of an award from the Fondation pour la Recherche Médicale of France. We thank Fabrice Rouah, Anne Perrault, Professor Hélène Verdoux and the Department of Evaluation at the Régie de l’Assurance-Maladie du Québec.

Conflicts of interest

There are no conflicts of interest.

Funding

The present study was an independent study funded by the Fonds de la Recherche en Santé du Québec (FRSQ) and supported by the Senior’s Independence Research Program, through the National Health Research and Development (NHRDP) of Health Canada, by the Health Activity Program of the Medical Research Council of Canada and the Pharmaceutical Manufacturers Association of Canada; by Bayer; and by the British Columbia Health Research Foundation.

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Published electronically 9 December 2008

doi: 10.1093/ageing/afn277

Restoring continence in frail older people living in the community: what factors influence successful treatment outcomes?

SIR—The prevalence of urinary incontinence (UI) in frail older people is high, yet it is often overlooked, and if identified, poorly assessed and managed conservatively [1–6] by pad provision [3] or catheterisation [7]. Providers generally perceive low potential for restoring continence in frail older people. There are few studies of UI management and outcomes in home-dwelling frail older people. A 2-month RCT of oxybutynin and bladder retraining improved urinary frequency but not UI [8]. Another study concluded that after 4 weeks of oxybutynin for urge UI, impaired cognition,