Epidemiology and Psychiatric Sciences (2013), **22**, 307–308. © Cambridge University Press 2013
doi:10.1017/S2045796013000358

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Corrado Barbui, *Section Editor*

Benzodiazepines and risk of dementia: true association or reverse causation?

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According to a recently published population study conducted in France, exposure to benzodiazepines may be associated with an approximately 50% increase in the risk of dementia in the elderly. However, the clinical interpretation of this finding raised some concerns. A causal link between benzodiazepine use and diagnosis of dementia may be real, but it is nevertheless possible that the increased risk might be due to other confounding factors. In this article, the main strengths and weaknesses of this study are briefly analysed, including the possibility of reverse causation. Implications for research and current practice are discussed.

Received 7 March 2013; Accepted 16 May 2013; First published online 3 July 2013

Key words: Benzodiazepines, dementia, elderly, epidemiology.

Use of benzodiazepines (BDZ) may increase the risk of developing dementia in the elderly. This surprising finding was reached by a recently published population study conducted in France (Billioti de Gage *et al*. 2012). The study involved more than 1000 individuals without dementia, aged 70 years or above, who were followed for 15 years; participants were part of a larger prospective cohort study aimed at describing normal and pathological brain ageing. Eligible participants were classified as new BDZ users if use of BDZ was not reported at baseline and after 3 years of follow up, but was reported after 5 years of follow up; non-users were those individuals without BDZ use at baseline and at 3- and 5-year follow-up interviews. The occurrence of incident dementia was the outcome of interest. All eligible participants were free of dementia at the 5-year follow-up visit, which implies that the exposure variable (BDZ use) preceded the outcome of interest (diagnosis of dementia). At each follow-up, trained psychologists systematically assessed dementia on the basis of the Diagnostic and Statistical Manual of Mental Disorders, third Edition, revised (DSM-III-R) and neurologists further examined suspected cases to confirm the diagnosis.

The main analysis compared cases of incident dementia between the cohort of BDZ users and non-users, after adjustment for several confounding factors. To check the robustness of findings, a complementary case–control study nested into the main study cohort was conducted. Cases were defined as participants with an incident diagnosis of dementia, and controls were participants without a diagnosis of dementia at the time point when a case was diagnosed.

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Within this case–control design, BDZ use was categorized as recent and past, and these exposure categories were compared with the group of those who had never been exposed to BDZ.

In the main analysis, the study found that 12% of the incident cases of dementia were BDZ users, while only 7.6% of participants without dementia were BDZ users. This yielded an adjusted hazard ratio of 1.60 (95% CI 1.08–2.38). In the case–control study, BDZ exposure was associated with an approximately 50% increase in the risk of incident dementia (odds ratio 1.55, 95% CI 1.24–1.95). In comparison with no BDZ use, recent use was associated with a 48% and past use with a 56% increase in the risk of incident dementia. Statistical significance was reached only for past use.

The interpretation of these findings is a compelling issue. A causal link between BDZ use and diagnosis of dementia may be real, but it is nevertheless possible that the increased risk might be due to other factors. In favour of the first interpretation there are several study strengths, including a large representative cohort of elderly participants, a long follow-up period, a reliable definition of incident dementia, a detailed description of BDZ exposure, validated through visual inspection of the patients' medicines, and a careful adjustment for a number of potential confounding factors.

As pointed out by the study authors, another strength is that BDZ exposure preceded a diagnosis of dementia, so that confounding by indication and reverse causation should not have occurred. This point, however, remains highly controversial and debatable, as BDZ use might have been motivated by the presence of psychiatric symptoms, including sleep problems and anxiety symptoms, that are psychopathological features that typically precede dementia by years (Bocti *et al.* 2012; Coyle-Gilchrist *et al.* 2012). If this possibility is plausible, then BDZ use might be a proxy indicator of the presence of underlying risk factors for dementia. This would imply that early symptoms of the outcome of interest preceded BDZ exposure, and therefore reverse causation and confounding by indication cannot be ruled out.

A second concern is biological plausibility with respect to length of follow-up (Bocti *et al.* 2012). Although this prospective cohort study has a long follow-up, the median delay of 6 years between BDZ exposure and onset of dementia seems too short to establish a causal link, in consideration of the epidemiology of dementia, which is a relentlessly progressive degenerative disorder, requiring decades to develop and progress. By contrast, there is evidence suggesting that BDZ use is associated with short-term cognitive effects that may improve by decreasing dosage.

Bearing in mind these strengths and weaknesses, implications for research are a challenge. A typical approach for reducing confounding by indication is limiting the study only to individuals who were exposed to the variable of interest, in this case BDZ. This would make the sample of included individuals more homogeneous, as they would all share the key characteristic of being treated with BDZ, so the confounding effect of the presence of underlying symptoms of dementia should theoretically be mitigated. With such a design, it might be possible to ascertain if different levels of BDZ exposure, say for example, occasional use, frequent use and long-term/chronic use, predict the outcome of interest. The reference group would this way be constituted by individuals who have been exposed to BDZ rather than individuals who have never been exposed. Indubitably, the possibility of residual confounding still remains.

Recommendations for everyday clinical practice are always difficult to make (Barbui & Cipriani, 2011). Common sense strategies include further caution in weighting the expected benefit of BDZ use against the well-established risks, such as for example serious falls and factures, and other potential adverse outcomes, including a risk of worsening cognitive function in the long term. However, as wisely suggested by Coyle-Gilchrist *et al.* (Coyle-Gilchrist *et al.* 2012), practitioners should not over-react to the results of this study by suddenly and radically changing prescribing habits.

Financial Support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of Interest

None

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