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Benzodiazepines: dementia in the elderly?

Abstract

● **About twenty benzodiazepines and related drugs, such as *zolpidem* and *zopiclone*, are used to treat sleep disorders and anxiety, and also as anticonvulsants. Their short-term adverse effects include confusion and cognitive disorders that regress only slowly after treatment withdrawal, especially in elderly patients. Questions have been raised as to persistent cognitive effects in case of long-term benzodiazepine exposure.**

● **A case-control study of 1796 patients over 66 years of age showed that benzodiazepine exposure 5 to 10 years previously was statistically significantly more frequent among those who developed Alzheimer's disease.**

● **Five other epidemiological studies provided similar results. However, some studies showed no relation with the duration of exposure or the cumulative dose; this is an argument against a causal relationship between benzodiazepine use and dementia.**

● **These studies provide only weak evidence and thus fail to establish a causal relationship. In addition, early symptoms of dementia can cause anxiety, which may lead to benzodiazepine prescription in the period preceding diagnosis. The results of these studies do not, however, rule out a long-term risk of persistent cognitive impairment.**

● **In practice, the known adverse effects of benzodiazepines are a sufficient reason to avoid these drugs, especially in elderly patients. The possibility of irreversible cognitive impairment is another reason not to prescribe them.**

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About 20 benzodiazepines and related substances such as *zolpidem* and *zopiclone* are used in sleep disorders and anxiety, and also as anticonvulsants (1). Their short-term adverse effects include confusion and cognitive disorders that regress slowly after treatment withdrawal, especially in elderly patients (1,2).

This raises questions as to persistent cognitive effects in the long term, especially a risk of dementia.

Increased risk of Alzheimer's disease after more than 3 months of cumulative exposure?

In 2014, a Franco-Quebec team used Quebec's health insurance database to identify 1796 Alzheimer's patients over 66 years of age who had been followed for at least 6 years before diagnosis (3). Each case (patient with Alzheimer's disease) was matched with 4 controls (persons without Alzheimer's) from the same database, matched for age, sex and length of follow-up (the index date was the date of diagnosis for the case). A total of 7184 controls were selected.

Only benzodiazepine exposure during the period from 5 to 10 years before the index date was taken into account (3). Patients who had not taken benzodiazepines at all or who had taken them less than 5 years before the index date were considered "non-users". *Zopiclone* and zolpidem were not included among the study drugs.

Benzodiazepine exposure five or more years before the date of diagnosis was significantly more frequent among the patients with Alzheimer's disease than among the controls. After adjustment for anxiety, depression and insomnia, the estimated relative risk (RR), expressed as the odds ratio, was 1.4 (95% confidence interval: 1.3 to 1.6) (3).

The increased risk of Alzheimer's disease appeared to be higher with cumulative benzodiazepine exposure, from 1.05 for less than 3 months, to 1.3 for 3 to 6 months, and 1.7 (95%CI: 1.5 to 2.0) for more than 6 months (3).

Convergent results from epidemiological studies

Several studies have examined the risk of dementia in individuals who had taken benzodiazepines (4-10). The relative risks mentioned here are estimates adjusted for various confounding factors, in particular early symptoms of dementia that can lead to benzodiazepine prescription.

Three cohort studies. A prospective cohort of 3777 persons aged 65 years and over was randomly selected between 1987 and 1989 in the French departments of Gironde and Dordogne (4). Of these, 1063 persons with a mean age of 78 years did not develop dementia during the first 5 years of follow-up and never took benzodiazepines during the first 3 years. Ninety-five patients reported taking a benzodiazepine during the fifth year of follow-up and were considered new users, while the remaining 968 patients who denied having taken a benzodiazepine formed the "non-user" group, regardless of any subsequent exposure.

After a median follow-up of 6 years, the risk of dementia was significantly higher among the "new users" than among the "non-users", with an estimated RR of 1.6 (95%CI: 1.1 to 2.4), after adjusting for confounding factors such as educational level, marital status, wine consumption, diabetes, hypertension, and cognitive decline, based on test performance, compared to baseline (4).

Another cohort study conducted in Wales analysed data on 1134 men followed for an average of 22 years, 93 of whom developed dementia (5). Dementia was three times more frequent among the 103 men who had taken benzodiazepines regularly than among non-users (RR = 3.0, 95%CI: 1.2 to 7.5) after adjustment for age, alcohol consumption, smoking, anxiety and psychological distress (5).

Another French cohort study (conducted in Bordeaux, Dijon and Montpellier)

compared the risk of dementia after exposure to selected benzodiazepines. Patients who were not taking psychotropic drugs at inclusion in the cohort served as reference. This study showed a statistical link between the onset of dementia and benzodiazepine exposure, but only in the subgroup of patients taking benzodiazepines with a plasma elimination half-life generally exceeding 20 hours (6).

Two other case-control studies. Two case-control studies used data from Taiwan's health insurance database. One study compared benzodiazepine exposure between 779 patients with dementia and 4626 dementia-free controls matched for age and sex. The patients with dementia were more likely than controls to have taken a benzodiazepine, zolpidem or zopiclone for more than 6 months (estimated RR = 1.3, 95%CI 1.1 to 1.6) (7).

The other study involved 8434 patients with dementia and 16 706 controls matched for age, sex and the start date of follow-up (8). Exposure to a benzodiazepine or related drug was 2.7 times more frequent among the patients with dementia (RR = 2.7, 95%CI 2.45 to 3.0 (8).

Benzodiazepine prescription for early symptoms of dementia?

These studies have generated controversy regarding potential biases such as benzodiazepine use for early symptoms of dementia (9,10). Some analyses attempted to take this bias into account, but the early symptoms of dementia are often vague. Early symptoms of dementia can provoke anxiety that may lead to benzodiazepine prescription in the period preceding diagnosis. In addition, dementia is often difficult to diagnose, especially in the early stages (11). Finally, people who use benzodiazepines may have more contact with the healthcare system and may thus be more likely to be diagnosed early.

Other studies do not support a causal link between dementia and benzodiazepines or related drugs.

No link to the duration of exposure. A UK case-control study used a general practice database in which 26 459 patients aged 65 years or older had Alzheimer's disease or vascular dementia (12). The risk of Alzheimer's disease was analysed according to the duration of benzodiazepine exposure before the index date (case diagnosis). This study showed a statistical link between diagnosis of Alzheimer's disease and initiation of benzodiazepine therapy 1 to 2 years previously, but not with longer exposure. These data are consistent with benzodiazepine use to control early symptoms of Alzheimer's disease (12).

No link to the cumulative dose. In a US cohort study of 3434 people over the age of 65 years who were followed for 7.3 years on average, 797 participants were diagnosed with dementia (Alzheimer's disease in 637 cases)(13). Compared to a control population not exposed to benzodiazepines or related drugs, the increase in the adjusted relative risk of dementia was statistically significant only for the lowest cumulative doses, and not the highest doses, despite similar statistical power. This is an argument against a causal relationship between benzodiazepine use and development of Alzheimer's disease.

Avoid benzodiazepines in the elderly

Pharmacoepidemiological studies conducted in several countries tend to support a link between long-term benzodiazepine exposure and dementia. However, such studies can only provide weak evidence and are not sufficient for establishing a causal relationship.

A causal relationship is nonetheless plausible, given the short-term cognitive adverse effects of benzodiazepines. But the lack of a causal relationship is also plausible as the observed relationship might be due to benzodiazepine prescription for anxiety related to early symptoms of dementia in the period preceding diagnosis.

In practice, faced with this uncertainty, it is best to err on the side of caution and to consider that benzodiazepines and the related drugs *zolpidem* and *zopiclone* can cause dementia (14).

The known adverse effects of benzodiazepines are already sufficient reason to avoid using these drugs whenever possible, especially in the elderly. The possibility of irreversible cognitive impairment is another reason not to use benzodiazepines.

Review produced collectively by the Editorial Staff: no conflicts of interest

Literature search and methodology

Our literature search was based on continuous prospective monitoring of the contents of major international journals and member newsletters of the International Society of Drug Bulletins (ISDB) at the *Prescrire* library; and routine consultation of clinical pharmacology textbooks (Martindale The Complete Drug Reference, Stockley's Drug Interactions). In addition, we accessed the following databases up to 4 April 2016: Medline (1946-5th week of March 2016), EMBASE (1996-2016 week 14), Reactions (1983-April 2016) and the following websites: ANSM, EMA and FDA.

This review was prepared using the standard *Prescrire* methodology, which includes verification of the choice of documents and their analysis, external review, and multiple quality controls.

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2- Prescrire Rédaction "Réussir l'arrêt d'une benzodiazépine" Infos-Patients Prescrire updated January 2016: 1 page.
3- Billioti de Gage S et al. "Benzodiazepine use and risk of Alzheimer's disease: case control study" *BMJ* 2014; 349: 10 pages.
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14- Prescrire Rédaction "Quelques points-clés pour une lecture critique efficace" *Rev Prescrire* 2008; **28** (298): 589-591.