Benzodiazepine use and risk of Alzheimer’s disease

A Canadian observational study found that past benzodiazepine use was associated with an increased risk of Alzheimer’s disease. The study suggests that taking benzodiazepines for more than 3 months and the use of agents with longer half-lives strengthen the association, but potential biases in the study limit the conclusions that can be drawn. Prescribers should continue to follow NICE and MHRA guidance to restrict benzodiazepines to short-term use of no more than 2 to 4 weeks and only for specific indications.

Overview and current advice

Risks associated with the long-term use of benzodiazepines have been well recognised for many years. These include falls, accidents, cognitive impairment, dependence and withdrawal symptoms. As long ago as 1988, the Committee on Safety of Medicines advised that benzodiazepine hypnotics should be used only if insomnia is severe, disabling or causing the person extreme distress. The lowest dose that controls symptoms should be used, for a maximum of 4 weeks and intermittently if possible. The NICE clinical guideline on generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults supports this and advises that a benzodiazepine should only be offered for the treatment of generalised anxiety disorder as a short-term measure during crises. Furthermore, NICE clinical guidelines on depression in adults and depression in adults with a chronic physical health problem give recommendations on benzodiazepine prescribing for people who develop side effects early in antidepressant treatment. Short-term benzodiazepine treatment (no longer than 2 weeks) can be considered if anxiety, agitation or insomnia are problematic, except in people with chronic symptoms of anxiety.


See the NICE Evidence topic pages on insomnia, anxiety and depression for a general overview of these conditions. The NICE Pathways on generalised anxiety disorder and depression bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

Published evidence on the relationship between benzodiazepines and dementia is limited and inconsistent, although 2 recent observational studies suggested that benzodiazepine use is associated with an increased risk of dementia. See the Eyes on Evidence commentary: Benzodiazepines and the risk of dementia.
New evidence

A Canadian case-control study\(^3\) investigated the link between past benzodiazepine use and the risk of Alzheimer's disease using data from a prescription drug insurance plan. The study involved 8980 people aged 66 years or over living in Quebec between 2000 and 2009, who were members of the Public Prescription Drug Insurance Plan, with data on prescription and medical services taken from an administrative claims database. Cases (n=1796) with a diagnosis of Alzheimer's disease recorded during the study period who had at least 6 years of follow-up before the diagnosis were matched to controls (n=7184) by sex, age and duration of follow-up.

Benzodiazepines included in the study were bromazepam, alprazolam, chlordiazepoxide, lorazepam, clonazepam, oxazepam, diazepam, flurazepam, midazolam, nitrazepam, temazepam, triazolam and clonazepam.

The authors acknowledged that people may experience anxiety, insomnia and depression in the years before a diagnosis of dementia, and that some benzodiazepine prescribing may be treating such symptoms during the prodromal phase. To minimise the risk of such reverse causality bias, benzodiazepine treatment started in the 5 years before a diagnosis of Alzheimer's disease was not considered. This was extended to 6 years before diagnosis as part of the sensitivity analysis.

During the study period, 894 people with Alzheimer's disease (49.8%) and 2873 controls (40.0%) had used benzodiazepines, and 64.8% of cases and 60.6% of controls were taking benzodiazepines at the time of diagnosis. Use of benzodiazepines during the study period was associated with an increased risk of Alzheimer's disease (adjusted odds ratio [OR] 1.51, 95% confidence interval [CI] 1.36 to 1.69). No difference was seen between groups when cumulative exposure to benzodiazepines was less than 3 months (OR 1.09, 95% CI 0.92 to 1.28). However, the risk of Alzheimer's disease increased with prolonged exposure to benzodiazepines; OR 1.32 (95% CI 1.01 to 1.74) for between 3 and 6 months use and OR 1.84 (95% CI 1.62 to 2.08) for exposure longer than 6 months. The association with Alzheimer's disease was also stronger for long-acting (half-life of 20 hours or more) benzodiazepines (OR 1.70, 95% CI 1.46 to 1.98) than for short-acting (half-life less than 20 hours) agents (OR 1.43, 95% CI 1.27 to 1.61). Sensitivity analysis excluding benzodiazepine use for 6 years before diagnosis, and further adjustment for symptoms thought to be potential prodromes for dementia (such as anxiety, depression and insomnia) did not meaningfully alter the results.

Commentary

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Previous observational studies\(^1,2\) have suggested a link between long term benzodiazepine use and the future development of Alzheimer's disease, but this association has not been demonstrated in all studies. The same group of investigators had previously shown a link in a prospective population based study\(^2\).

Both Alzheimer's disease and benzodiazepine use are very common, and there was much debate as to whether the association was related to causation, or if benzodiazepines were often prescribed for pre-clinical manifestations of early dementia.
As a clinician working with patients who are often long-term benzodiazepine users it can be hard to know how to counsel these patients about the continued use of these drugs, and the potential effect it may have on their cognition.

This case control study from Canada, took significant steps to reduce potential biases and confounders, but did rely on databases rather than patient data. The study showed a cumulative and dose effect association between benzodiazepine use and the risk of developing Alzheimer’s, and a greater risk with long acting benzodiazepines. However, there is no pathophysiological mechanism known for benzodiazepines to cause Alzheimer’s dementia.

This study adds to the evidence base for the possible harmful effects of long-term benzodiazepine therapy and reminds us of the importance of counselling patients prescribed these drugs. It helps reinforce guidance from NICE and CSM that benzodiazepines should only be considered for short-term use.

**Study sponsorship**

The case-control study was supported by IRESP (Institut de Recherche en Santé Publique); the French Ministry of Health (Direction Générale de la Santé); and the Funding Agency for Health Research of Quebec (Fonds de la Recherche en Santé du Québec, FRSQ).

**References**


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