**Association between Benzodiazepines and Dementia: Nested Case-Control Study**

**Introduction**

Dementia is a syndrome of acquired, chronic, progressive cognitive impairment which interferes with an individual’s ability to cope with daily living. It is predicted to affect over 1 million people in the United Kingdom by 2025, with financial costs estimated at £26 billion per year. Recent research has raised concerns that some pharmacological agents (e.g., benzodiazepines) may increase the risk of dementia in older people. However, the existing studies have serious methodological limitations and have yielded conflicting findings.

We aimed to design and conduct an observational study that addresses key methodological issues (selection bias and confounding) in evaluating the association between long-term benzodiazepine use and dementia.

**Methods**

We conducted a nested case-control study using the UK Clinical Practice Research Datalink. We selected participants of age 65-99 years (time period 2006-2015) based on new dementia diagnosis or new prescription for a dementia drug and subsequent dementia diagnosis, with up to 7 controls matched on gender, age, deprivation index and data history.

Exposures of interest were benzodiazepine derivatives and Z-drugs, with relevant exposure period 4-20 years prior to incident dementia, and we assessed dose-response using Defined Daily Doses. New users were those first prescribed benzodiazepines/z-drugs, with no prescriptions in 12 months prior to the exposure period. We collected information on time-varying covariates measured at start, and end of drug exposure period (DEP)

We used conditional logistic regression to estimate adjusted odds ratios (aOR) and 95% Confidence Intervals (CI) for dementia and drug use, adjusted for potential confounders e.g. lifestyle, BMI, comorbidities, medication. Significance was set at p<0.01 to account for multiple testing. Sensitivity analyses included: (1) new versus prevalent users and (2) timing of measurement of covariates.

**Results**

We selected 40,770 dementia cases (see Figure 1) and 283,933 controls, median age 74 years, 60% female. Mean drug exposure period was 7.8 years. Key covariates are shown in Table 1. Overall, we did not find a statistically significant association between Benzodiazepine (aOR 0.99, 95% CI 0.96, 1.02) and Z-drug (aOR 1.05, 95% CI 1.01, 1.10) use and dementia (adjusted for baseline covariates).

Primary analysis (Table 2): We did not identify a plausible cumulative dose-response relationship for the link between dementia and defined daily doses (DDD) of benzodiazepines or Z-drugs. The highest level of benzodiazepine exposure (DDD=1460+) had the lowest risk and appeared to have a protective effect.

Sensitivity analysis (Tables 2 and 3): comparing new users to non-users (adjusted for baseline comorbidities and aOR adjusted benzodiazepine use was not associated with a significant risk of dementia (aOR 1.02, 95% CI 0.96, 1.06) whereas Z-drugs had a small association with dementia (aOR 1.07, 95% CI 1.02, 1.11). Analysis restricted to prevalent users (which is prone to selection bias) showed that benzodiazepines had an apparent protective effect. In another sensitivity analysis, the strength of the association was affected by the timing of measurement of the confounding covariates.

Strengths of our study include the evaluation of new users and reduction of proophylactic bias by defining a window of exposure distant to the diagnosis of dementia. We recognise that dementia can be under-diagnosed or misclassified, resulting in bias towards the null. A further limitation is the potential for residual or unmeasured confounding.

**Conclusions**

Our results do not support the hypothesis that long-term benzodiazepine use is associated with an increased risk of dementia. We have demonstrated that methodological issues (participant selection and timing of measurement of confounders) can greatly affect the results, and this may explain the conflicting findings from other studies.

Despite the findings of our nested case-control study, benzodiazepines can cause a wide range of other adverse effects, and clinicians should continue to follow guidelines on avoiding potentially inappropriate prescription of long-term benzodiazepines, even in the absence of a definitive evidence of any association with dementia.

**Conflicts of interest**

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