

## **Alzheimer's disease: increased risk of pneumonia observed in people treated with benzodiazepines**

An [observational study](#) using a large Finnish database found that people with Alzheimer's disease who received benzodiazepines were around 30% more likely to develop pneumonia compared with those people not taking benzodiazepines. People were at the highest risk during the first 30 days of benzodiazepine treatment. The authors suggested that the sedation associated with benzodiazepines may increase the risk of aspiration, leading to pneumonia. Although further studies would be required to establish causation, this study acts as a reminder of the need for care when prescribing benzodiazepines, especially in populations who may be frail, have co-morbidities or be at particular risk of adverse events or interactions.

Reference: Taipale H, Tolppanen AM, Koponen M *et al.* [Risk of pneumonia associated with incident benzodiazepine use among community dwelling adults with Alzheimer disease](#) CMAJ. 2017. 189 (14): E519-E529

### **What do we know already?**

- Alzheimer's disease is the most common form of dementia. In addition to cognitive dysfunction, people with Alzheimer's disease may exhibit non-cognitive symptoms and behaviour that challenges, including changes in personality, emotional control, social behaviour, depression, agitation, hallucinations and delusions. Benzodiazepines and Z-drugs are frequently used in people with Alzheimer's disease, with many people receiving long-term treatment.
- Incidence of pneumonia increases with age. It has been suggested that sedation may lead to pneumonia because of an increased risk of aspiration ([Taipale \*et al.\*, 2017](#)).
- Studies that investigated the association between benzodiazepine use and pneumonia have reported conflicting results. In a UK based nested case-control study by [Obiora \*et al.\* \(2013\)](#), benzodiazepines were associated with a 50% increased risk of pneumonia in adults of all ages. In contrast, a US case-control study did not find an increased risk of pneumonia in older people taking benzodiazepines ([Dublin \*et al.\* 2011](#)).
- The [NICE guideline on dementia](#) recommends that healthcare professionals who use medication in the management of violence, aggression and extreme agitation in people with dementia should understand the cardiorespiratory effects of the acute administration of benzodiazepines (and antipsychotics) and the need to titrate dosage to effect.

### **What does this evidence add?**

- This [observational study](#) found that people with Alzheimer's disease treated with benzodiazepines were at increased risk of pneumonia, particularly during the first month of treatment.
- The authors noted that although no significant association between Z-drugs and pneumonia was found, we should not come to the conclusion that Z-drugs are safer than benzodiazepines. The study was not designed to compare the two classes of medication, and it is likely that prescribers have different attitudes to benzodiazepine and Z-drug prescribing (for example, possibly favouring Z-drugs in more fragile patients).
- The authors concluded that risk of pneumonia should be considered when choosing whether to prescribe benzodiazepines for people with Alzheimer's disease.
- The observational nature of this study means it has a number of limitations.
  - Although the researchers were able to adjust for confounders including asthma, COPD and previous pneumonia, the register-based data did not include information on smoking status, an important predictor of pneumonia.

- The study only included cases of pneumonia that resulted in a hospital admission or death; cases of pneumonia treated in primary care were not included. This meant only the most severe infections were captured.
- The researchers also did not have information on severity of Alzheimer's disease, the presence of behavioural symptoms or the indications that medicines were prescribed for.

## Study details

### Participants:

- The study included all community-dwelling adults who were diagnosed with Alzheimer's disease in Finland between 2005 and 2011 using the [Medication use and Alzheimer's disease \(MEDALZ\) cohort](#) (n=70,718). Within the MEDALZ cohort there were 49,484 people with Alzheimer's disease who had no history of benzodiazepine use and were included in the study.
- The mean age of the included participants was 80 years and 62.7% were women. The researchers limited the study to incident use of benzodiazepines because prevalent users are more likely to have developed tolerance to drug effects.

### Intervention and comparison:

- In total, 5,232 people were taking benzodiazepines and 3,269 were taking Z-drugs; both groups were matched 1:1 to 8,501 people who were not taking these drugs.
- Benzodiazepines prescribed in this study included diazepam, nitrazepam, chlordiazepoxide, clobazam, oxazepam, alprazolam, lorazepam and temazepam. The Z-drugs included zopiclone and zolpidem. The authors did not report the doses used.

### Outcomes and results:

- Use of benzodiazepines and Z-drugs (analysed together) was associated with an approximate 20% increased risk of pneumonia (8.10 vs. 6.32 pneumonia cases per 100 person-years, adjusted [hazard ratio](#) [HR] 1.22, 95% [confidence interval](#) [CI] 1.05 to 1.42). When the 2 classes of medication were analysed separately the association with benzodiazepine use remained [statistically significant](#) (adjusted HR 1.28, 95% CI 1.07 to 1.54), although Z-drug use was not (adjusted HR 1.10, 95% CI 0.84 to 1.44).
- The risk of pneumonia associated with benzodiazepine use was highest within the first 30-days of use (adjusted HR 2.09, 95% CI 1.26 to 3.48). Analysis of benzodiazepine use beyond 30 days (for example, days 31 to 180, days 181 to 365, days 366 to 1095 and beyond day 1096) found no statistically significant association with pneumonia.

### Level of evidence:

Level 2 (limited quality patient-oriented evidence) according to the [SORT criteria](#)

### Study funding:

No source of funding is reported for this observational study