Benzodiazepine use and risk of cognitive decline and dementia – systematic review and meta-analysis

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Introduction

Dementia is a syndrome of progressive cognitive impairment that interferes with an individual’s ability to cope with daily living. It is a devastating condition, with an estimated prevalence of >1 million people with dementia in the United Kingdom by 2025. There is no cure for dementia, so the focus has to be on identifying and addressing risk factors. A number of recent studies have suggested that benzodiazepines may be associated with an increased risk of dementia. Moreover, benzodiazepines are used for behavioural symptoms (including sleep disturbance) in dementia and there is conflicting evidence as to whether they can worsen cognition. We aimed to systematically review and analyse the relationship between benzodiazepine use and dementia and cognitive decline in older patients.

Methods

The protocol was registered with PROSPERO (CRD42016039313). We searched MEDLINE and EMBASE (1996-2016) for observational studies of the association between benzodiazepine use and cognitive decline or dementia in participants aged >50 years. The search strategy included terms related to the exposure (benzodiazepines) and the outcomes (dementia or cognitive impairment): * (Benzodiazepine*), and AND * (Cognitive function or Cognitive disorder* or Cognitive impairment or Dementia). Study selection and data extraction was conducted by two reviewers, who recorded key study characteristics, as well as the methods used in ascertainment of cognitive decline/dementia, capture of drug use and handling of confounding. We used ROBINS-I to assess study validity.

Results

We screened 1668 titles and abstracts and included 16 studies in the systematic review. Geographical locations were diverse and included North America, Taiwan, Netherlands, Germany, France, Belgium, UK and Germany. The included studies had a total of 84296 participants (sample size from 226 to 26459) with a mean age of 70. Most of the studies were considered to have serious risk of bias on ROBINS-I. Dementia outcomes: meta-analysis of adjusted data from 8 studies (Figure 2) demonstrated a pooled odds ratio (OR) of 1.45 (95% Confidence Interval [CI] 1.11, 1.90, significant heterogeneity, P=98%) association between benzodiazepine use. One study reported unadjusted data that we have shown separately in Figure 1. Visual inspection of the Forest plot confirms the lack of consistency in the effect estimates. Cognitive decline: meta-analysis of 3 studies (Figure 3) showed that benzodiazepines were associated with decline in cognitive scores, pooled OR of 1.43 (95% CI 1.02, 1.99 with I2=0%). However, there were two other studies that we were unable to include in the meta-analysis because of selective or incomplete reporting (quantitative results for cognitive tests were not fully described for non-quantitative outcomes). Omission of such data means that the meta-analysis of cognitive outcomes may have yielded inflated effect estimates of risk, and we have classified these studies as contributing to critical risk of bias. Dose or duration relationship: Whilst two studies indicated a plausible relationship of a stronger association with ascending exposure, there were three studies with contrary findings where greater exposure to benzodiazepines was actually associated with lower risk of adverse outcomes.

Conclusions

We found substantial inconsistencies in the evidence of cognitive change and dementia associated with benzodiazepine use. The lack of a plausible dose or duration relationship undermines the credibility of any postulated association. The presence of serious risk of bias, confounding by indication, and selective outcome reporting means that we cannot draw robust or reliable conclusions on the true association between benzodiazepine use and cognitive impairment or dementia. Nevertheless, clinicians are advised to minimise the use of benzodiazepines as much as possible, especially in older adults with multiple co-morbidities and at risk of adverse effects of polypharmacy.

Conflicts of interest

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