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Featured Article

Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study

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Abstract

Introduction: Benzodiazepine use has been associated with increased risk of dementia. However, it remains unclear whether the risk relates to short or long half-life benzodiazepines and whether it extends to other psychotropic drugs.

Methods: Prospective cohort study among 8240 individuals ≥65, interviewed on medication use. Incident dementia confirmed by an end point committee after a multistep procedure.

Results: During a mean of 8 years of follow-up, 830 incident dementia cases were observed. Users of benzodiazepines at baseline had a 10% increased risk of dementia (adjusted hazard ratio [HR], 1.10; 95% confidence interval, 0.90–1.34). However, long half-life (>20 hours) benzodiazepine users had a marked increased risk of dementia (HR = 1.62; 1.11–2.37) compared with short half-life users (HR = 1.05; 0.85–1.30). Users of psychotropics had an increased risk of dementia (HR = 1.47; 1.16–1.86).

Discussion: Results of this large, prospective study show increased risk of dementia for long half-life benzodiazepine and psychotropic use.

Keywords: Cohort studies; Alzheimer's disease; Dementia; Benzodiazepine; Psychotropic medication

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1. Introduction

Benzodiazepines and psychotropic medications are among the most widely used drugs in developed countries [1]. The prevalence of use for benzodiazepines alone among patients aged ≥65 years is estimated to be 30% in France, 20% in Canada and Spain, and approximately 15% in Australia [2–5]. Sleep disorders, anxiety, and depressive symptoms, all of which are frequent in elderly individuals, are the main indications for the use of benzodiazepines and other psychotropic medications [6,7].

Because they are often used in the frail elderly population, the safety and effects of benzodiazepines and psychotropic drugs on cognition and dementia are of great public health interest. Both benzodiazepines and psychotropic medications interact with the neurotransmitter system [8,9], and previous studies have found that benzodiazepine use is associated with an increased risk of dementia [10–13]. Although the results of the small case-control studies that evaluated this association were inconclusive [14–16], the findings of two prospective cohort studies have suggested that the use of benzodiazepines is associated with a 1.5 to threefold increased risk of dementia [12,13]. However, several important questions remain regarding the differences between the use of benzodiazepines with long versus short half-lives [17] as well as whether the effects are limited to benzodiazepine or extend to other psychotropic drugs.

We, therefore, investigated the association between benzodiazepine medication use and the risk of dementia in the Three-City study, a large, population-based cohort study, with a focus on drugs with short versus long half-lives. It also examined the effects of other psychotropic medications on dementia.

2. Methods

Details about the Three-City study were published previously [18]. Briefly, the Three-City study is a population-based longitudinal study that investigated the association between vascular factors and dementia in noninstitutionalized individuals aged ≥65 years starting in 1999. A total of 9294 participants were recruited at baseline (T_0) from the electoral rolls of the cities of Bordeaux, Dijon, and Montpellier in France. Data were collected using a standardized questionnaire and face-to-face interviews as well as by medical examinations conducted at a medical center or hospital. Data were collected at follow-up at T_2 (year 2), T_4 (year 4), T_6 (year 6), T_7 (year 7), and T_{10} (year 10). The study protocol of the Three-City study was approved by the Ethics Committee of the University-Hospital of Kremlin-Bicêtre, France, and written informed consent was obtained from each participant.

2.1. Exposure, outcome, and covariates

At baseline and at follow-up time points T_2, T_4, and T_7, the participants were asked by trained interviewers whether they had used any medication more than once a week during the last month. The interviewers followed a standardized protocol, and the prescriptions and medication packages were systematically checked during a home visit. The drugs were coded based on the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system. All classes of benzodiazepines and their derivative drugs were noted, including anxiolytic (ATC code: N05BA), hypnotic and sedative (N05CD and N05CF), antiepileptic (N03AE), and myorelaxing (M03BX07) drugs. A previous population-based study in France suggested no substantially different associations between prevalent versus incident users of benzodiazepines and the risk of dementia [13]. Here, we used the prevalent users at baseline as the main exposure variable to increase the power and provide an estimation of the association at the population level. Prevalent use was defined as any report of benzodiazepine use at baseline (T_0). In a secondary analysis, we used the incident users of these medications. Incident users (or initiators) were those participants who did not report any benzodiazepine or psychotropic use at baseline but who reported benzodiazepine use at T_2. In addition, the benzodiazepine users were split into two groups, i.e., users of long-acting benzodiazepines (half-life >20 hours) and users of short-acting ones (half-life ≤20 hours). The half-life cutoff time was based on a definition proposed by the French National Agency for Drug Safety (Agence nationale de sécurité du médicament et des produits de santé [ANSM]) and adopted in a previous publication about medication use in the Three-City study [19].

The definition of the use of psychotropic medications (ATC Code: N05, N06) excluded benzodiazepine users to differentiate the two groups and also excluded users of anti-dementia medication (N06D). The medications in this definition include antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, psychostimulants, and nootropics. Prevalent users of psychotropics reported taking the medication at baseline (T_0), whereas initiators were those who began taking psychotropics at T_2 but who did not report any benzodiazepine or psychotropic use at T_0.

2.2. Outcome assessment

The diagnosis of dementia was based on a three-step procedure at each follow-up as described elsewhere [18,20]. First, trained psychologists administered a battery of neuropsychological tests. Second, a neurologist examined all the participants in Bordeaux and Montpellier. In Dijon, owing to the large number of participants, only those who screened positive for dementia using the mini-mental state examination (MMSE) [21] and the Isaacs set test [22] underwent further clinical examination. For subjects suspected of having dementia, further data on cognitive disorders and their consequences on daily activities were collected using a standardized protocol, and the study neurologist or