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Original Study

Dose-Responsive Effect of Psychotropic Drug Use and Subsequent Dementia: A Nationwide Propensity Score Matched Case-Control Study in Taiwan

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A B S T R A C T

Objective: To test the hypothesis that the load of psychotropic agents was associated with subsequent dementia occurrence by a nationwide database.
Design: Propensity score matched case-control study.
Setting: National Health Insurance Research database.
Participants: A total of 32,649 older people with dementia and 32,649 matched dementia-free older people.
Measurements: Use of psychotropic drugs (anxiolytics, antipsychotics, hypnotics, and antidepressants), defined daily dose (DDD) of psychotropic drugs, diagnosis of dementia, and propensity score.
Intervention: None.
Results: Compared with nonusers, ever use of psychotropic agents was associated with higher odds of subsequent dementia [adjusted odds ratio (OR): 3.73; 95% confidence interval (CI) (3.59–3.88)]. Significantly, the association was stronger with longer term exposure to psychotropic agents. The ORs at exposures of <90 days, 90–180 days, and >180 days, were 3.14 (95% CI 3.01–3.28); 5.48 (5.07–5.93); and 7.54 (6.73–8.44), respectively. A similar and stronger association was identified when cumulative dose was used to measure the exposure of psychotropic agents [<90 DDDs, 3.40 (95% CI 3.26–3.54); 90–180 DDDs 6.38 (5.76–7.07), and >180 DDDs, 7.35 (6.29–8.58)].
Conclusions: We found that a higher burden of psychotropic agents was strongly associated with a higher odds of subsequent dementia. Careful monitoring of any elderly who is prescribed or uptitrated psychotropic agents is highly recommended, especially those who combine use of more than one agent. Furthermore, providing timely assessment for cognitive function for older patients consuming psychotropic drugs is of great importance.

Population aging is a global phenomenon that poses various health care challenges to the world, and dementia has attracted a wide spectrum of attentions internationally.[1] A number of symptoms and signs may appear before the diagnosis of dementia can be made. Among all symptoms and signs related to dementia, behavioral and psychotic symptoms are common presentations that lead family members to search for clinical assistance and may be managed by pharmaceutical intervention.[2] Psychotropic agents, including anxiolytics, antipsychotics, hypnotics (benzodiazepine and z-hypnotics), and antidepressants, are frequently prescribed to treat short-term symptoms of anxiety and insomnia in the elderly.[3,4] Nevertheless, inappropriate long-term consumption of these agents have been reported,[5] which may result in harmful adverse effects, such as impaired cognitive function.[6,7] Specifically, a recent study done by Billioti de Gage S et al[8] clearly showed an increased risk of dementia associated with the use of benzodiazepine, and this phenomenon has

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raised various debates among physicians and public authorities.[8–11] Moreover, these risks may also be significantly increased to older patients with existing dementia. Most of the debates regarding the association between the use of benzodiazepine and the risk of dementia resulted from conflicting outcomes in the existing literature.[12–16] Although in some literature, an increased risk of dementia or cognitive impairment associated with benzodiazepine use was found, others were not conclusive about the potential harmful link.[12–16]

Aside from benzodiazepine, we know little about the effect of other psychotropic agents on the risk of developing dementia in the elderly. This is of particular concern given the high prevalence of use of psychotropic agents in the elderly, and most of them share similar concerns of cognitive decline. Furthermore, accumulating evidence has shown that anxiety and depression are risk factors of dementia,[17] which may be identified early through increased use of anxiolytics and antidepressants in the elderly. On the other hand, insomnia, anxiety, and depression are the main indications for prescribing benzodiazepine[18] that make the clarification of a potential causal relationship between use of benzodiazepine and risk of dementia more difficult. However, the entire picture of the load of psychotropic agents on subsequent dementia was seldom known. Therefore, the main aim of this study was to test the hypothesis that the load of psychotropic agents was associated with subsequent dementia occurrence by a nationwide database.

Methods

Data Source

This is a population-based case-control study using Taiwan's National Health Insurance Research database (NHIRD).[19] The NHIRD is a nationwide database comprising anonymous eligibility and enrollment information, as well as claims for visits, procedures, and prescription medications of more than 99% of the entire population (23 million) in Taiwan. Individual patients are recorded as entering the NHIRD when they are covered by Taiwan's mandatory National Health Insurance (NHI) program since 1996 and remain until death. For each visit, the NHIRD has recorded dates of visits (outpatient visits, admissions, and discharges) and up to 5 diagnoses coded by physicians according to the International Classification of Disease, 9th Edition (ICD-9 CM codes).[20] The completeness and accuracy of the NHIRD are ensured by the Department of Health and the NHI Association of Taiwan. The database has been described in detail elsewhere[21] and has been the source for numerous epidemiologic studies published in peer-reviewed journals.[22–24]

Three subsets of the NHIRD, the Longitudinal Health Insurance Database (LHID) 2000, 2005, and 2010, which contain claims data of 1 million beneficiaries randomly sampled from the NHI Registry of Beneficiaries in year 2000, 2005, and 2010, were used in this study. A total of 3 million individuals, which accounted for 15% of the total population in Taiwan, served as our original cohort. The age and sex distributions of the LHID are not significantly different from those of the original NHIRD cohort. The longitudinal nature of LHID permits one to identify a cohort based upon diagnoses, health services, and drug utilization, track medical history, establish a prescription drug profile, and determine the endpoint of drug treatment.

Definition of Dementia Case and Control

From the LHID 2000, 2005, and 2010, we identified elderly patients who were firstly diagnosed with dementia [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes[5]: 290.0 (senile dementia, uncomplicated), 290.1x (presenile dementia), 290.2x (senile dementia with delusional or depressive features), 290.3 (senile dementia with delirium), 290.4x (arteriosclerotic dementia)] between January 1, 2001 and December 31, 2009. To increase the identification of dementia cases, only those who had at least 3 outpatient or inpatient claim records of dementia-related diagnosis codes were selected as our dementia cases.[25] Date of first diagnosis of dementia was assigned as the index date for all identified demented patients.

For each demented case, a matched control was randomly selected from the NHIRD using the propensity score matching technique to account for baseline differences between demented and non-demented groups. The propensity score was estimated from a multivariable logistic regression model. Covariates included in the model were age, sex, and comorbid diseases (diabetes mellitus, hypertension, heart failure, stroke, transient ischemic attack, osteoporosis, osteoarthritis, chronic obstructive pulmonary disease, and depression).

Use of Psychotropic Drugs

Psychotropic agents with known cognitive effects (antipsychotics [Anatomical Therapeutic Chemical (ATC) code: N05A-, including quetiapine, prochlorperazine, haloperidol, lithium and etc.]), anxiolytics [N05B-, including lorazepam, alprazolam, diazepam and etc.], hypnotics (benzodiazepine derivatives [N05CD-, including estazolam, flunitrazepam, triazolam and etc.] and non-benzodiazepine hypnotics [N05CF-, including zopiclone, zolpidem, and zaleplon (also called as z-hynotics)]), and antidepressants [N06A-, including trazodone, imipramine, fluoxetine and etc.] were included in the study. We have adopted the ATC classification system released by the World Health Organization Collaborating Center for Drug Statistics Methodology.[26] All active substances of psychotropic agents with known cognitive effects are divided into different groups according to the organ or system on which they act (1st level, 1 digit) and their therapeutic (2nd level, 2 digits), pharmacological (3rd level, 1 digit), chemical properties (4th level, 1 digit) and chemical substance (5th level, 2 digits). According to the ATC classification system, all drugs are given a unique 7-digit code. For example, the ATC code of olanzapine is N05AH03 (N: nervous system; N05 psycholeptics; N05A antipsychotics; N05AH: Diazepines, oxazepines, thiazepines, and oxepines; N05AH03: olanzapine).

The cumulative exposure of psychotropic agents was defined as the number of days that psychotropic agents were prescribed prior to the index date. It was calculated as the days from the first to the last prescription of psychotropic agents, adding drug prescribed days. We also calculated the cumulative dose as the defined daily dose (DDD), which is also released by the World Health Organization Collaborating Center for Drug Statistics Methodology.[27] The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. A DDD will only be assigned for drugs that already have an ATC code. The DDD provide a fixed unit of measurement independent of price and dosage form (eg, tablet strength) enabling the researcher to assess drug consumption and to perform comparisons of drug consumption between different categories of drugs. Accumulated DDDs of psychotropic agents during the follow-up for each study subject was used as a categorical variable ($<$90, 90–180, $\geq$180) in the statistical models to measure the exposure to the psychotropic agents more precisely.

Statistical Analyses

Comparison tests for patient demographics and use of psychotropic agents were performed with either the McNemar test for categorical variables or paired *t*-test for continuous variables. The *P* value was 2-sided and α was set to be .05. Multivariable conditional