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Original article

Antipsychotic treatment effects on cardiovascular, cancer, infection, and intentional self-harm as cause of death in patients with Alzheimer's dementia

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ABSTRACT

Background: Alzheimer's disease (AD), the most common disease causing dementia, is linked to increased mortality. However, the effect of antipsychotic use on specific causes of mortality has not yet been investigated thoroughly.
Methods: Utilizing the Danish nationwide registers, we defined a cohort of patients diagnosed with AD. Utilizing separate Cox regressions for specific causes of mortality, we investigated the effects of cumulative antipsychotic dosage after diagnosis and current antipsychotic exposure in the time period 2000–2011.
Results: In total, 45,894 patients were followed for 3,803,996 person-years. A total of 6129 cardiovascular related deaths, 2088 cancer related deaths, 1620 infection related deaths, and 28 intentional self-harm related deaths are presented. Current antipsychotic exposure increased mortality rate with HR between 1.92 and 2.31 for cardiovascular, cancer, and infection related death. Cumulative antipsychotic dosages were most commonly associated with increased rates of mortality for cardiovascular and infection as cause of death, whereas the associations were less clear with cancer and intentional self-harm as cause of death.
Conclusions: We showed that cumulative antipsychotic drug dosages increased mortality rates for cardiovascular and infection as cause of death. These findings highlight the need for further investigations of long-term effects of treatment and of possible sub-groups who could benefit from treatment.

1. Introduction

Alzheimer's disease (AD) has been linked to increased mortality in several studies [1]. Autopsy studies in dementia have shown infection and cardiovascular events as the most common causes of death, with cancer being a less common cause [2,3]. Some data suggests that cancer is less common in patients diagnosed with or suspected of suffering from AD [4]. Suicide as cause of death in AD is less investigated, as well as passive forms of self-harm, although small studies [5,6] have shown both to be more frequent in patients with AD.

Current antipsychotic treatment in patients diagnosed with AD increases all-cause mortality, as well as death from specific causes, e.g. cerebrovascular events in which an increased risk has been demonstrated using evidence from randomized controlled trials [7,8]. Nevertheless, other studies have shown benefits from short-term antipsychotic treatment in reducing Behavioural and Psychological Symptoms in Dementia (BPSD), although studies with long follow-up have been sparse [9]. We have previously shown that lifetime cumulative antipsychotic drug dosages and all-cause mortality are associated [10], suggesting that the negative effects on mortality by antipsychotics could not be outweighed by the effects of antipsychotics on BPSD. So far, no studies have investigated the effects of cumulative antipsychotic treatment in patients diagnosed with AD for specific causes of death. As cardiovascular events and infection are the two most common causes of death in this population, we chose to include these as outcome measures. The choice to include cancer was undertaken, as antipsychotics have been proposed to increase the risk of cancer development, and as cancer is a common cause of death in elderly

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patients. Lastly, we chose to include intentional self-harm, as this outcome is very rare, and would most likely only be investigated utilizing larger datasets, as ours.

In this study, we examine the effect of cumulative antipsychotic drug dosages, as well as the effect of current antipsychotic exposure, on the rate of different causes of death in patients diagnosed with AD.

2. Methods

2.1. Design

A nationwide, population-based, retrospective cohort study of specific cause mortality (cardiovascular, cancer, infection, and intentional self-harm) in patients diagnosed with dementia in AD.

2.2. Sample

We formed a cohort of newly diagnosed patients with AD, which we defined as either receiving an ICD-10 F00x. (Dementia in Alzheimer's disease) or a G30x. (Alzheimer's disease) diagnosis or picking up a prescription for anti-dementia drugs (ATC N06D), from January 1, 2000 to December 31, 2011 from the total Danish population. Persons previously diagnosed with an ICD-8 dementia diagnosis in the period from January 1, 1980 throughout 1993, or an ICD-10 diagnosis of dementia in the period from January 1, 1994 throughout 1999 were excluded from the analysis, as well as patients picking up a prescription for anti-dementia drugs in the period January 1, 1998 to December 31, 1999.

2.3. Measures

2.3.1. Medication

All medication variables were coded as time-dependent variables, with patients being coded as non-exposed until first prescription.

Antipsychotics were defined as ATC N05A, excluding lithium (ATC N05AN).

The current exposure variable was based on the use of antipsychotics over the previous year and grouped as present or absent, with index defined as a prescription for an antipsychotic drug. The cumulative antipsychotic dosages from dementia diagnosis until end of study for each participant were calculated and divided into 5 groups:

- baseline: no antipsychotic treatment at all;
- more than zero daily defined dosages (DDD) < 90;
- ≥ 90 DDDs < 365;
- ≥ 365 DDDs < 730;
- ≥ 730 DDDs.

Because of the definitions, no patients currently exposed to antipsychotics could be in the baseline cumulative exposure group. The groups were defined arbitrarily, but the definition has been utilized before in a similar study [10].

2.4. Co-variables

2.4.1. Severity of AD

The current Danish registers do not include data on severity of AD, and cognitive function. To compensate for these deficits, we used the following variables as proxy markers of disease severity: number of psychiatric bed days, number of psychiatric outpatient contacts, and accommodation status after diagnosis. All markers were examined after incident dementia diagnosis (as defined by either the ICD-10 diagnosis or the first prescription of anti-dementia drug).

Accommodation status was dichotomized as a time-dependent variable (never previously lived in an institution or lived in an institution at some point in time after the diagnosis).

2.4.2. Psychiatric co-morbid disorder

We defined a psychiatric co-morbidity score ranging from zero to five and determined by the aggregated diagnosis status in the following categories: psychosis, affective disorders, substance misuse, other psychiatric diagnosis, and intentional self-harm. The score was computed for each patient, and could increase over time, if more diagnoses were given. The score was cumulative for all patients since the initiation of the Danish Psychiatric Central Research Registry in 1969. The score has previously been utilized in a similar study [10].

2.4.3. Somatic co-morbid disease

We divided somatic diseases into the following groups: cardiovascular disease, cancer, infection, diabetes, epilepsy, lower respiratory disease, and other somatic diseases. For the somatic co-morbid score, one point was added for a diagnosis in each of the groups unless the diagnosis occurred before the age of 51 years for males and 56 years for females, where two points were added due to an increased risk associated with early onset of disease. The score was computed for each patient, and could increase over time, if more diagnoses were given. The score was cumulative for all patients since the initiation of the Danish Nation Patient Registry in 1977. The score has previously been utilized in a similar study [10].

2.4.4. Cardiovascular risk factors

The current Danish registers do not include data on blood pressure or blood test results, such as lipid and glucose levels. Besides, general practitioners examining and treating the majority of patients diagnosed with hypertension, increased lipids, or type II diabetes do not register diagnoses in the Danish registers. To make up for this information gap, we used the following proxy measures of arterial hypertension, increased cholesterol, and diabetes: data on the prescription of antihypertensive drugs (ATC C02), drugs used to lower lipids (ATC C10), and drugs for treatment of diabetes (blood glucose lowering drugs (excl. insulins): ATC A10B, A10XA; insulins: ATC A10A), in addition to the actual diagnoses (see above under somatic co-morbid disease). All medication variables were coded as time-dependent variables, with patients being coded as non-exposed until first prescription.

2.5. Statistical analysis

Cox regressions with event defined as specific cause of mortality were conducted using cumulative antipsychotic dosage and current antipsychotic exposure as explanatory variables, and adjusting for variables defined above. All variables were coded as time-dependent.

In order to investigate the effects of an association between cumulative exposure and current exposure, secondary analyses were conducted for the different specific causes of death listed above, excluding current exposure as an explanatory variable.

Statistical analyses were performed with Stata 13 at the Statistics Denmark server with remote access.

3. Results

3.1. Demography

In total, 45,894 patients (17,082 males and 28,812 females) were followed for 3,803,996 person-years, presenting 27,894 deaths (10,818 males and 17,076 females) in the study population.

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