High prevalence of psychotropic drug use among persons with and without Alzheimer's disease in Finnish nationwide cohort

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Abstract

Psychotropic drugs are used for treatment of behavioral and psychological symptoms of dementia (BPSD) although they are associated with serious adverse drug events. Objective of our study was to investigate prevalence of psychotropic drug use one year after diagnoses of Alzheimer's disease (AD), to compare prevalence to persons without AD and to assess changes in prevalence over time. Data from the MEDALZ (Medication use and Alzheimer's disease) cohort was utilized in the study including all 69,080 community-dwelling persons with new diagnosis of AD during years 2005–2011 in Finland. Four age-, gender- and region of residence-matched persons without AD were identified for each case. Register-based data included prescription drug purchases and comorbidities from Special Reimbursement Register. Annual prevalence of psychotropic drug use one year after diagnosis was determined for each person. Psychotropic drugs were used by 53% of persons with AD compared with 33% of persons without AD during one year after diagnoses. Persons with AD were six times more likely to use antipsychotics and three times more likely to use antidepressants whereas benzodiazepine and related drug (BZDR) use was comparable between persons with and without AD. According to year of AD diagnoses during 2005–2011, antipsychotic use increased from 18% to 20% ($p < 0.0001$) and BZDR use declined from 31% to 26% ($p < 0.0001$) among persons with AD. Widespread utilization of psychotropic drugs was observed among persons with AD. Despite safety warnings of

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antipsychotic use for BPSD, antipsychotic use increased from 2005 to 2011 among newly diagnosed persons with AD in Finland.

1. Introduction

Psychotropic drugs are used in the treatment of behavioral and psychological symptoms of dementia (BPSD) in persons with Alzheimer's disease (AD) (Finnish Medical Society Duodecim, 2010). Antidementia drugs are recommended as the first-line treatment for BPSD. Treatment with psychotropic drugs is recommended only for most severe symptoms and for short-term use if non-pharmacological options are not effective.

Psychotropic drugs have been associated with serious adverse drug events among older persons and persons with dementia. Antipsychotics have been linked to an increased risk of stroke (Mittal et al., 2011). All psychotropic drugs have been associated with falls and hip fractures (Cumming and Le Couteur, 2003; Hartikainen et al., 2007; Coupland et al., 2011; Oderda et al., 2012; Xing et al., 2014). Studies regarding the risk of death associated with psychotropic drug use have been inconclusive. Numerous studies indicate the association between antipsychotic use and an increased mortality risk (Schneider et al., 2005; Wang et al., 2005; Schneeweiss et al., 2007; Ballard et al., 2009; Kales et al., 2012; Gerhard et al., 2014) with some conflicting results (Gardette et al., 2012; Lopez et al., 2013), whereas antidepressant (Ried et al., 2011; Coupland et al., 2011) and benzodiazepine studies (Kripke et al., 1998; Gisev et al., 2011) show mixed results. Antipsychotic and benzodiazepine use has been associated with decline in cognition (Hanlon et al., 1998; Byerly et al., 2001; Paterniti et al., 2002) which counteracts the main goals in the treatment of AD including preservation of cognitive function and delay of institutionalization (Finnish Medical Society Duodecim, 2010).

Few previous studies have investigated psychotropic drug use in persons with incident dementia. Martinez et al. (2013) determined prescribed prevalence of psychotropic drug use at the time of dementia diagnoses during 1995-2011. Schulze et al. (2013a) determined prevalence of antipsychotic use in the year of dementia incidence and studied the impact of safety warnings on prevalence of antipsychotic use (Schulze et al., 2013b). Franchi et al. (2012) investigated changes in antipsychotic use after the safety warnings among persons prescribed with acetylcholinesterase inhibitors. There is a lack of studies concerning prevalence of psychotropic drug use at the time of clinically verified diagnosis of Alzheimer's disease compared with matched comparison persons. Objective of our study was to investigate the prevalence of psychotropic drug use one year after diagnosis of Alzheimer's disease, to compare the prevalence with persons without AD and to assess changes in prevalence between persons diagnosed in 2005-2011.

2. Experimental procedures

Data from the MEDALZ (Medication use and Alzheimer's disease) cohort was utilized in the study. The MEDALZ cohort consists of all 73,005 persons diagnosed with AD between 2005 and 2011 in Finland. Four age-, gender- and region of residence-matched persons without AD were identified from database including all residents, leading to the cohort of 365,011 persons. Persons without AD were chosen based on not having diagnoses of AD or antidementia drug purchases at the index date (date of AD diagnosis for the case) or 12 months after that. Furthermore, non-AD person needed to be alive and not in long-term care facility during the month of AD diagnosis for the case. During the follow-up, some persons in non-AD group developed AD (N=14,343), and they were defined as AD cases and four comparison persons were identified as described.

Persons with AD were identified from the Special Reimbursement Register which includes data on entitlement to special reimbursement of drugs based on clinically diagnosed chronic diseases. Identification of AD cases and registers is described in more detail in Tolppanen et al. (2013). In short, the Finnish Current Care Guideline recommends that all persons with AD are treated with antidementia drugs unless there is a contraindication for the use (Finnish Medical Society Duodecim, 2010). Persons with probable AD need a verified diagnosis completed according to an exact diagnostic protocol monitored by the Social Insurance Institution to be entitled to reimbursed antidementia drugs. The verified AD diagnosis includes computed tomography or magnetic resonance imaging scan, and confirmation of the diagnosis by a neurologist or geriatrician. The special reimbursement for AD medication is not withdrawn when AD progresses to severe stage. Diagnosis of AD was based on the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV criteria (American Psychiatric Association, 1994).

Data of the MEDALZ cohort has been linked to several nationwide registers including Prescription Register (1995-2012), Special Reimbursement Register (1972-2012), Register of Care at Social Institutions (1995-2012), and Hospital Discharge Register (1972-2012). Prescription Register includes information on all purchases of prescribed and reimbursed drugs categorized according to Anatomical Therapeutic Chemical – classification system (ATC) (WHO, 2014). Data were de-identified before submission to the research team and thus, no ethics committee approval was required.

In this study, psychotropic drug purchases one year after index date (i.e. the date of AD diagnosis) were extracted (annual prevalence). The index date of the case was determined as starting date for 12 months follow-up period for comparison persons. Antipsychotics were defined as ATC class N05A excluding lithium. Atypical antipsychotics were defined as ziprasidone, clozapine, olanzapine, quetiapine, risperidone, aripiprazole, asenapine and paliperidone, and other drugs in N05A (excluding lithium) were classified as conventional antipsychotics (chlorpromazine, levomepromazine, dixyrazine, perphenazine, periciazine, thioridazine, haloperidol, melperone, sertindole, flupentixol, chlorprothixene, zuclopenthixol, pimozide, and sulpiride). Antidepressants were defined as N06A and further categorized as tricyclic antidepressants (N06AA), selective serotonin reuptake inhibitors (SSRIs) (N06AB) and other antidepressants (N06AX). Benzodiazepines and related drugs (BZDRs) were defined as N05BA, N05CD and N05CF. BZDRs were further classified as benzodiazepines (BZDs) (N05BA and N05CD) and Z-drugs (N05CF). Most commonly purchased drug substances were calculated for each psychotropic drug class and separately among persons with and without AD. One person may have purchased several drugs during the follow-up and thus, contributed to several substances.

For the present study, persons were excluded if they were in long-term care for over 240 days of the year after AD diagnosis