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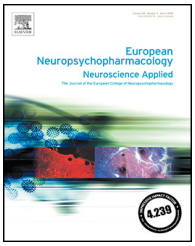

Psychotropic drugs use and psychotropic polypharmacy among persons with Alzheimer's disease

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Abstract
Psychotropic drugs are frequently used for the treatment of behavioural and psychological symptoms of dementia in persons with Alzheimer's disease (AD). Evidence for benefits are limited and concerns have been raised about the safety, especially for the concomitant use of multiple psychotropic drugs. The objective of this study was to investigate prevalence of psychotropic drug and psychotropic polypharmacy (PPP) use and associations with PPP among persons with and without AD, from five years before until four years after AD diagnosis at time points every six months. Data is a part of the nationwide MEDALZ cohort, including all community-dwelling persons who received a clinically verified diagnosis of AD between 2005 and 2011 in Finland ($n = 70{,}719$). Register-based data included purchased prescription drugs, comorbidities, and hospital discharge diagnoses. Prevalence and factors associated with PPP were studied with logistic regression. The prevalence of psychotropic drug use, especially use of antipsychotics and antidepressants, increased during the course of AD. The use of ≥ 2 psychotropic drugs increased from 5.9% five years before to 18.3% four years after AD diagnosis.

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The most frequently used combination was antipsychotics and antidepressants. Predictors for PPP were younger age (< 75 years), female sex and history of psychiatric disease. The use of acetylcholinesterase inhibitors was inversely associated with PPP. The high prevalence of PPP is concerning because of possible higher risks for adverse effects and events.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease and the most common cause of dementia. AD is characterized by a decline in memory, language, problem solving and other cognitive skills that affects a person's ability to perform in activities in daily life (Alzheimer's Association, 2016).

Behavioural and Psychological Symptoms of Dementia (BPSD) are experienced by up to 97% of persons with dementia over a five-year period (Steinberg et al., 2008). Psychotropic drugs are frequently used to treat BPSD even though the evidence for benefits of their use is limited (Wolf et al., 2016; White et al., 2017). Concerns have been raised about the safety of psychotropic drugs in older persons and persons with dementia (Chahine et al., 2010; Johnell et al., 2017), because they are associated with an increased risk of injurious falls (Zdanys et al., al.,2016; Johnell et al., 2017), hip fractures (Saarelainen et al., 2017; Torvinen-Kiiskinen et al., 2017; Koponen et al., 2017a), stroke (Trifirò et al., 2010; Mittal et al., 2011; Taipale et al., 2017), hospitalization (Johnell et al., 2017), and mortality (Huybrechts et al., 2011; Maust et al., 2015; Koponen et al., 2017b). In addition, the use of benzodiazepines and antipsychotics may also be associated with cognitive decline and dementia (Billiote de Gage et al., 2012; Shash et al., 2016; Wolf et al., 2016).

Psychotropic polypharmacy (PPP), the use of two or more psychotropic drugs concomitantly, generally is not recommended for older persons with dementia and should be avoided (Zdanys et al., al.,2016; Finnish Medical Society Duodecim, 2017). PPP is also associated with an increased risk of injurious falls, hospitalization and mortality (Johnell et al., 2017; Koponen et al., 2017b).

In previous observational studies on PPP, prevalence varied between 14% and 50% in persons with dementia (Nijk et al., 2009; Gustafsson et al., 2013; Vasudev et al., 2015; Walsh et al., al.,2016; Breining et al., 2016; Nørgaard et al., al.,2017). These studies were conducted in different settings (including nursing home residents) and countries, some including a limited sample size, and thus, more studies are needed in representative populations. To our knowledge, no previous studies have focused on assessing the prevalence and predictors of PPP before and after the diagnosis of AD. As psychotropic drugs may be used for treatment of behavioral and psychological symptoms of dementia treatment patterns may change when person has received AD diagnosis. On the other hand, older persons in general and persons with AD are susceptible to adverse effects of psychotropic drugs and thus, these drugs should be used with caution. The aim of this research was to determine the prevalence of psychotropic drug use and PPP among persons with Alzheimer's disease and investigate the predictors for concomitant use of two or more psychotropic drugs.

2. Experimental procedures

This study is part of the large nationwide Medication use and Alzheimer's disease (MEDALZ) study and data from this study was utilized. The MEDALZ study has been described in detail elsewhere (Tolppanen et al., 2016). In brief, this cohort included all community-dwelling persons who received their first clinically verified AD diagnosis between 2005 and 2011 in Finland ($n = 70{,}719$). Cohort members were identified from the Special Reimbursement register maintained by the Social Insurance Institution of Finland (SII). Diagnosis of AD was according to the Finnish current care guideline on cognitive disorders (Finnish Medical Society Duodecim, 2017) and based on NINCDS-ADRDA and DSM-IV criteria. The diagnostic protocol for AD include symptoms consistent with AD, exclusion of alternative diagnoses, a CT or MRI scan and confirmation of diagnosis by a neurologist or geriatrician. The medical statement describing the symptoms of a patient and the findings of the diagnostic procedures is sent to the SII for evaluation. The experts at SII evaluate the clinical findings and whether the requirements for AD are fulfilled, i.e. special reimbursement is granted only if the pre-defined criteria for AD are fulfilled. Persons with mixed forms of dementia were granted the special reimbursement if clinical findings and the symptoms were considered to be mainly caused by AD. Our study population consisted of 70,719 persons with AD and 70,719 persons without AD. The mean age of the persons with and without AD at the index date was 80.1 years and 65% were female.

MEDALZ data includes information from several nationwide registers including the Prescription Register (1995–2015), Special Reimbursement Register (1972–2015), and Hospital Discharge Register (1972–2015). No ethics committee approval was required, as data was de-identified by the register maintainers before submission to the research team and participants were not contacted for this study.

Each persons with AD was matched with one control person without an AD diagnosis, at the date of AD diagnoses (index date). The control persons were matched on age, gender and region of residence, and were obtained from a database which contains all residents of Finland. During the follow-up, some persons in the non-AD cohort developed AD, and they were defined as AD cases and matched to one control person.

The Prescription Register includes all reimbursed prescription drug purchases recorded in pharmacies since 1995. In this register, drugs are classified according to Anatomical Therapeutic Chemical-classification system (ATC) and with Defined Daily Doses (DDDs) recommended by the World Health Organization (WHO). Psychotropic drugs were defined as antipsychotics (N05A, excluding N05AN01 – lithium), antidepressants (N06A) and benzodiazepines and related drugs (BZDRs, N05BA, N05CD, N05CF). Use of PPP was

defined as concomitant use of ≥ 2 psychotropic drugs. These could be from the same or different drug classes (i.e. use of two antipsychotics was also considered as polypharmacy as well as use of an antipsychotic together with a BZDR).

Drug utilization was modelled from Prescription Register data to drug use periods with the PRE2DUP method (Tanskanen et al., 2015). This method is based on mathematical modelling of individual purchasing behaviour. By using each person's purchase history for each ATC code, individual drug use periods were defined using temporal sliding averages of daily dose (in DDDs) by taking into account on variation in purchase events, stockpiling of drugs and periods in hospital/institutional care. Concomitant use of multiple psychotropic drugs was studied by combining overlapping use periods of different ATC codes of psychotropic drugs.

Point prevalence of psychotropic drug use was examined from five years before the index date until four years after. Point prevalence was defined every six months. Persons were censored from time points when they were in long-term hospital/institutional care and excluded from time points after death. The total study sample included 141,438 persons, but the sample size varied per time point due to censoring and exclusion. Periods of long-term hospital/institutional care were defined as ≥ 90 days stay, because drugs provided in hospital care and in public nursing homes are provided by the hospital or institution and are not recorded in the Prescription Register.

Comorbidities included in this study were asthma/COPD, rheumatoid arthritis and comparable connective tissue disorders, diabetes, epilepsy and cardiovascular disease (the presence of one or more of the following: chronic heart failure, coronary artery disease, hypertension, chronic arrhythmia). These comorbid diagnosis before the index date were extracted from the Special Reimbursement register data. International Classification of Diseases (ICD-10) codes registered at discharge from hospital were used to define hip fracture (S72.0, S72.1, S72.2), stroke (I60–I64) and history of psychiatric disorder (schizophrenia F20-29; bipolar disorder/mania codes F30-31; and depression codes F32-39) (World Health Organization, 2016). Psychiatric diagnosis were defined as diagnosed at least five years prior to AD diagnosis. Use of acetylcholinesterase inhibitors (AChEIs, N06DA) and memantine (N06DX01) were extracted from drug utilization data.

A sensitivity analysis was performed by excluding both persons from a matched pair when one of them was censored or excluded for a specific time point due to long-term hospital/institutional care or death. By doing this sensitivity analysis both cohorts were equal to each other throughout the whole study.

2.1. Statistical analysis

Descriptive statistical analyses were undertaken using means, standard deviations (SD) and percentages. Characteristics of persons with and without AD, users and nonusers of psychotropic drugs among persons with AD, and polypharmacy and monotherapy users among persons with AD were compared by using logistic regression and reported with unadjusted odds ratios (ORs), adjusted odds ratios (OR_{adj}) and 95% confidence intervals (CIs). Adjusted odds ratios were adjusted for all variables included in Tables 1–3 (age, gender, comorbidities, history of hip fracture, stroke and psychiatric disorders and use of anti-dementia drugs). The covariates were chosen on the basis of previous literature on predictors of psychotropic drug use. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

The mean follow-up time was 3.4 years (SD 1.05) for the AD cohort after AD diagnosis and 3.6 years (SD 0.91) for the matched cohort after the index date. During the follow-up, 38,318 (27.1%) persons died ($n = 24,251$, 34.3% in AD cohort and $n = 14,067$, 19.9% in the matched cohort). History of any psychiatric disorder was present in 4.5% of persons with AD and in 3.8% of persons without AD ($OR_{unadjusted} = 1.20$; 95% CI = 1.14–1.26). Persons with AD were more likely to have diabetes, epilepsy, any cardiovascular disease and history of hip fracture and stroke compared to persons without AD (Table 1).

3.2. Prevalence and predictors of psychotropic drug use

The prevalence of any psychotropic drug use was higher in the AD cohort compared to the matched cohort during the nine-year study period (Fig. 1). The difference was evident already five years before AD diagnosis and highest four years after (49.9% in persons with AD, 25.9% in persons without AD, OR = 2.85, 95% CI = 2.78–2.93). The prevalence of antipsychotic and antidepressant drug use was higher in the AD cohort compared to the matched cohort during the whole study period. Five years before the index date antipsychotic drug use occurred in 2.2% of the persons with AD and in 2.0% of the persons without AD (OR = 1.12, 95% CI = 1.04–1.21). Four years after the index date the prevalence of antipsychotic drug use increased to 23.5% in persons with AD and 3.8% in persons without AD (OR = 7.90, 95% CI = 7.52–8.30). The prevalence of BZDR use was higher in the AD cohort until 2.5 years after AD diagnosis after which there was no difference between the groups. The prevalence of BZDR use four years after the index date was about the same in the AD cohort (18.1%) as in the matched cohort (18.5%) (p-value = 0.13).

On index date, 37.1% of the persons with AD used at least one psychotropic drug compared to 25.5% in the non-AD cohort (OR = 1.73; 95% CI = 1.69–1.77) (Table 1). Of persons with AD, 19.2% used antidepressants, 8.7% used antipsychotics and 21.2% used BZDRs at the index date. There was a steady increase in the years after AD diagnosis for the use any psychotropic drug and for the use of antidepressants and antipsychotics. The prevalence increased to 49.9% for the use of any psychotropic drug, 27.5% for antidepressant drug use and 23.5% for antipsychotic drug use four years after the index date. The use of BZDRs decreased after AD diagnosis to 18.1% four years after the index date. The preva-

Table 1 Characteristics of persons with and without AD at diagnosis date in the MEDALZ cohort (n = 138 211).

	AD ($n = 68\ 413$[1])	Non-AD ($n = 69\ 798$[1])	OR_{adj} (95% CI)[2]
Age, n (%)			
< 65years	2216 (3.2)	2281 (3.3)	
65-75years	12,086 (17.7)	12,376 (17.7)	
75-85years	37894 (55.4)	38,660 (55.4)	
> 85years	16,217 (23.7)	16,481 (23.6)	
Female gender, n (%)	44,566 (65.1)	45,445 (65.1)	
Psychotropic drug use, n (%)	25,400 (37.1)	17,786 (25.5)	1.71 (1.67-1.76)
Any cardiovascular disease, n (%)	35,009 (51.2)	34,766 (49.8)	1.03 (1.00-1.05)
Asthma/COPD, n (%)	6010 (8.8)	6129 (8.8)	0.99 (0.95-1.03)
Rheumatoid arthritis and comparable connective tissue disorders, n (%)	3074 (4.5)	3107 (4.5)	0.99 (0.94-1.04)
Diabetes, n (%)	9134 (13.4)	7853 (11.3)	1.20 (1.16-1.24)
Epilepsy, n (%)	1393 (2.0)	916 (1.3)	1.48 (1.36-1.61)
History of hip fracture, n (%)	3386 (4.9)	2438 (3.5)	1.36 (1.29-1.44)
History of stroke, n (%)	6482 (9.5)	5540 (7.9)	1.16 (1.12-1.21)
History of psychiatric disorders, n (%)	3087 (4.5)	2651 (3.8)	1.28 (1.14-1.43)
Mania/depression/bipolar	2367 (3.5)	1959 (2.8)	1.21 (1.13-1.28)
Schizophrenia	995 (1.5)	899 (1.3)	1.06 (0.96-1.16)

OR_{adj}, adjusted odds ratio; CI, confidence interval; [1] Total number of persons censored/excluded on time of AD diagnosis from study was 3225; [2] Multivariable analysis adjusted for age, gender, comorbidities, history of hip fracture, stroke and psychiatric disorders.

Table 2 Characteristics of non-users and users of psychotropic drugs in AD cohort ($n = 70\ 719$).

	3 years before AD diagnosis ($n = 70\ 479$)[1]			3 years after AD diagnosis ($n = 47\ 915$)[1]		
	Non-users	Users	OR_{adj} (95% CI)[2]	Non-users	Users	OR_{adj} (95% CI)[2]
Number of participants, *n* (%)	52,879 (75.0)	17,600 (25.0)		24,398 (50.9)	23,517 (49.1)	
Age, *n* (%)						
< 65 years	3040 (5.8)	763 (4.3)	0.55 (0.49-0.60)	601 (2.5)	606 (2.6)	1.14 (1.01-1.28)
65-75 years	15,941 (30.2)	4148 (23.6)	0.55 (0.51-0.58)	2915 (12.0)	2855 (12.1)	1.06 (1.00-1.13)
75-85 years	28,744 (54.4)	10,212 (58.0)	0.73 (0.69-0.77)	12,151 (49.8)	11,559 (49.2)	1.02 (0.98-1.06)
> 85 years	5154 (9.8)	2477 (14.1)	1.00	8731 (35.8)	8497 (36.2)	1.00
Female gender, *n* (%)	33,128 (62.7)	12,824 (72.9)	1.51 (1.45-1.57)	15,437 (63.3)	16,800 (71.4)	1.44 (1.38-1.50)
Any cardiovascular disease, *n* (%)	24,529 (46.4)	9834 (55.9)	1.40 (1.35-1.45)	11,910 (48.8)	11,965 (50.9)	1.11 (1.07-1.15)
Asthma/COPD, *n* (%)	3929 (7.4)	1816 (10.3)	1.37 (1.29-1.46)	2017 (8.3)	2227 (9.5)	1.14 (1.07-1.22)
Rheumatoid arthritis and comparable connective tissue disorders, *n* (%)	2106 (4.0)	852 (4.8)	1.15 (1.06-1.25)	1046 (4.3)	1022 (4.3)	0.98 (0.89-1.07)
Diabetes, *n* (%)	5624 (10.6)	2272 (12.9)	1.14 (1.08-1.21)	3618 (14.8)	3317 (14.1)	0.91 (0.86-0.96)
Epilepsy, *n* (%)	750 (1.4)	320 (1.8)	1.20 (1.04-1.38)	630 (2.6)	625 (2.7)	0.99 (0.88-1.11)
History of hip fracture, *n* (%)	1125 (2.1)	652 (3.7)	1.44 (1.30-1.59)	1835 (7.5)	2065 (8.8)	1.12 (1.05-1.20)
History of stroke, *n* (%)	3164 (6.0)	1575 (8.9)	1.48 (1.38-1.58)	2543 (10.4)	2742 (11.7)	1.16 (1.10-1.23)
History of psychiatric disorders, *n* (%)	1130 (2.1)	2095 (11.9)	5.83 (5.33-6.39)	529 (2.2)	1695 (7.2)	3.17 (2.81-3.57)
Mania/depression /bipolar	845 (1.6)	1615 (9.2)	5.53 (5.06-6.04)	395 (1.6)	1289 (5.5)	3.11 (2.77-3.49)
Schizophrenia	340 (0.6)	713 (4.1)	5.39 (4.69-6.19)	159 (0.7)	853 (3.6)	3.11 (2.60-3.72)
Acetylcholinesterase inhibitors (AChEI), *n* (%)				10,873 (44.6)	10,050 (42.7)	0.93 (0.90-0.96)
Memantine, *n* (%)				3681 (15.1)	4619 (19.6)	1.38 (1.31-1.44)
Combination of AChEI and memantine, *n* (%)				6094 (25.0)	6487 (27.6)	1.14 (1.10-1.19)

OR_{adj}, adjusted odds ratio; CI, confidence interval;[1] Total number of persons censored/excluded three years before AD diagnosis was 379 and three years after AD diagnosis 34,270; [2] Multivariable analysis adjusted for age, gender, comorbidities, history of hip fracture, stroke and psychiatric disorders.

Table 3 Characteristics of psychotropic monotherapy and polypharmacy in AD cohort ($n = 70\,719$).

	3 years before AD diagnosis ($n = 70\,479$)[1]			3 years after AD diagnosis ($n = 47\,915$)[1]		
	Monotherapy	Polypharmacy	OR_{adj} (95% CI)[2]	Monotherapy	Polypharmacy	OR_{adj} (95% CI)[2]
Number of participants, *n* (%)	12,639 (17.9)	4961 (7.0)		14,976 (31.3)	8541 (17.8)	
Age, *n* (%)						
< 65 years	442 (3.5)	321 (6.5)	2.11 (1.75-2.53)	348 (2.3)	258 (3.0)	1.38 (1.16-1.64)
65-75 years	2821 (22.3)	1327 (26.8)	1.49 (1.32-1.68)	1736 (11.6)	1119 (13.1)	1.18 (1.08-1.29)
75-85 years	7451 (59.0)	2761 (55.7)	1.26 (1.14-1.41)	7358 (49.1)	4201 (49.2)	1.06 (1.00-1.13)
> 85 years	1925 (15.2)	552 (11.1)	1.00	5534 (37.0)	2963 (34.7)	1.00
Female gender, *n* (%)	9113 (72.1)	3711 (74.8)	1.15 (1.06-1.24)	10,601(70.8)	6199 (72.6)	1.08 (1.02-1.15)
Any cardiovascular disease, *n* (%)	7123 (56.4)	2711 (54.7)	1.03 (0.96-1.10)	7604 (50.8)	4361 (51.1)	1.06 (1.00-1.12)
Asthma/COPD, *n* (%)	1284 (10.2)	532 (10.7)	1.08 (0.96-1.20)	1360 (9.1)	867 (10.2)	1.13 (1.03-1.23)
Rheumatoid arthritis and comparable connective tissue disorders, *n* (%)	621 (4.9)	231 (4.7)	0.93 (0.79-1.09)	652 (4.4)	370 (4.3)	0.98 (0.86-1.12)
Diabetes, *n* (%)	1625 (12.9)	647 (13.0)	0.97 (0.87-1.07)	2184 (14.6)	1133 (13.3)	0.85 (0.79-0.92)
Epilepsy, *n* (%)	196 (1.6)	124(2.5)	1.38 (1.09-1.75)	392 (2.6)	233 (2.7)	0.99 (0.84-1.17)
History of hip fracture, *n* (%)	412 (3.3)	240 (4.8)	1.52 (1.28-1.80)	1291 (8.6)	774 (9.1)	1.07 (0.97-1.18)
History of stroke, *n* (%)	1124 (8.9)	452 (9.1)	1.04 (0.92-1.17)	1775 (11.9)	967 (11.3)	0.96 (0.88-1.05)
History of psychiatric disorders, *n* (%)	887 (7.0)	1208 (24.4)	4.03 (3.67-4.43)	739 (4.9)	956 (11.2)	2.39 (2.12-2.70)
Mania/depression/bipolar	662 (5.2)	953 (19.2)	3.75 (3.36-4.18)	546 (3.7)	743 (8.7)	2.33 (2.07-2.61)
Schizophrenia	296 (2.3)	417 (8.4)	2.69 (2.29-3.17)	252 (1.7)	332 (3.9)	1.91 (1.60-2.26)
Acetylcholinesterase inhibitors (AChEI), *n* (%)				6513 (43.5)	3537 (41.4)	0.87 (0.79-0.96)
Memantine, *n* (%)				2814 (18.8)	1805 (21.1)	1.04 (0.94-1.16)
Combination of AChEI and memantine, *n* (%)				4203 (28.1)	2284 (26.7)	0.89 (0.81-0.98)

OR_{adj}, adjusted odds ratio; CI, confidence interval;l[1] Total number of persons censored/excluded three years before AD diagnosis was 379 and three years after AD diagnosis 34,270; [2] Multivariable analysis adjusted for age, gender, comorbidities, history of hip fracture, stroke and psychiatric disorders.

lence of the most frequently used psychotropic drugs per drug class are shown in Supplementary figure 1.

Psychotropic drug use among persons with AD was associated with female gender, asthma/COPD, hip fracture, stroke, history of psychiatric disorder and any cardiovascular disease (Table 2). Persons aged over 85 years were more likely to use psychotropic drugs three years before AD diagnosis, but three years after the index date persons aged under 65 years were more likely to use psychotropic drugs. The use of anti-dementia drug AChEI was inversely associated with psychotropic drug use, but the use of memantine or the combination of AChEI and memantine was associated with the use of psychotropic drugs.

3.3. Psychotropic polypharmacy among persons with AD

Among persons with AD, PPP increased from 5.9% five years before to 18.3% four years after AD diagnosis (Fig. 2A). The difference in prevalence of PPP was evidently higher in the AD cohort compared to the matched cohort from five years before (5.9% in persons with AD, 4.7% in persons without AD, OR = 1.21, 95% CI = 1.18-1.24) to four years after (18.3% in persons with AD, 6.7% in persons without AD, OR= 2.90, 95% CI = 2.82-2.97) the index date. The most common combination of psychotropic drugs until 2.5 years after AD diagnosis was the combination of BZDRs and antidepressants (Fig. 2B). The prevalence of this combination increased from 3.6% five years before to 7.7% 2.5 years after AD diagnosis. Three years after AD diagnosis, the most frequently used combination was the concomitant use of antipsychotic and antidepressant. The concomitant use of two psychotropic drugs from the same drug class is shown in Fig. 2C. The use of ≥ 2 antipsychotics increased from 0.3% to 1.3% and the use of ≥ 2 antidepressants increased from 0.6% to 2.0%. Six months after AD diagnosis, the prevalence of concomitant use of ≥ 2 BZDRs decreased from 2.5% to 1.7% four years after the index date.

In the multivariate analyses, which included all variables, factors associated with PPP (versus psychotropic monotherapy) were younger age, female gender and history of psychiatric disorder, both three years before and three years after AD diagnosis (Table 3). Having diabetes or using acetylcholine esterase inhibitors (AChEI) or the combination of AChEI and memantine were inversely associated with the use PPP.

3.4. Sensitivity analysis

The sensitivity analysis censored/excluded both persons from a matched pair when one of them was censored/excluded at a specific time point due to long hospital/institutional care or death. The number of participants censored or excluded after sensitivity analysis increased

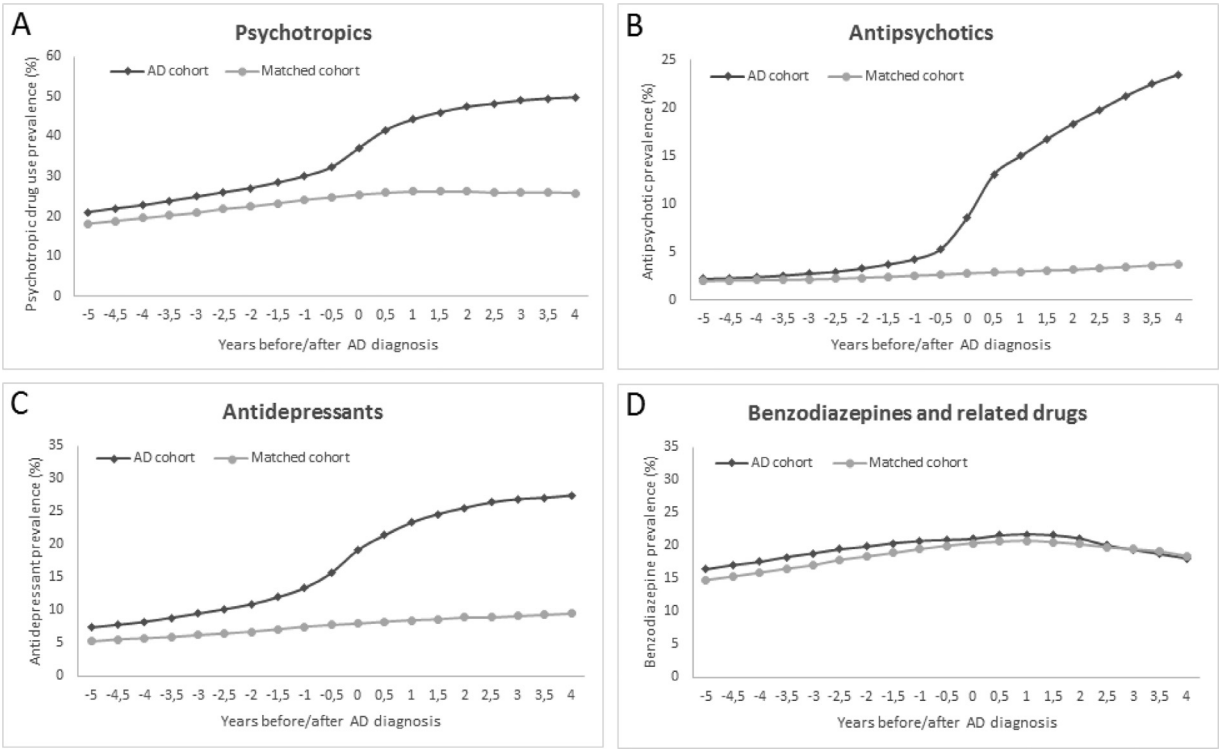

Fig. 1 A: Prevalence of psychotropic drug use, B: prevalence of antipsychotic drug use, C: prevalence of antidepressant drugs use and D: prevalence of benzodiazepine and related drugs use in AD cohort and in matched cohort five years before and four years after AD diagnosis for 2005–2011 cohort. AD diagnosis is specified as 0 on the x-axis.

with 65.5%, from 44,835 before to 74,180. The results found after sensitivity analysis were similar to those found in the main analysis. Sensitivity analysis found that 50.1% of the AD cohort used at least one psychotropic drug four years after AD diagnosis compared to 25.5% in the matched cohort (OR = 2.94; 95% CI = 2.84–3.03; p-value < 0.001). Without sensitivity analysis 49.9% of the AD cohort and 25.9% of the matched cohort used a psychotropic drug at this time point (OR = 2.85; 95% CI = 2.78–2.93; p-value < 0.001). The prevalence of antipsychotic, antidepressant and BZDR use in the AD cohort four years after AD diagnosis was slightly increased in the sensitivity analysis, respectively from 23.5% to 23.7%, 25.5% to 25.8% and 18.1% to 18.2%. The prevalence of use in the matched cohort slightly decreased for antidepressants (1.96% to 1.95%) and BZDRs (18.5% to 18.1%), but the prevalence of antipsychotics slightly increased four years after AD diagnosis from 3.75% to 3.79%.

4. Discussion

To our knowledge, this is the first study reporting psychotropic polypharmacy among community-dwelling persons with AD over a nine year period. We found an increasing prevalence of psychotropic drug use and PPP from five years before until four years after AD diagnosis. Four years after the index date almost half of the persons with AD used some psychotropic drug and almost one fifth used two or more psychotropic drugs. The high prevalence found for psychotropic drug use and PPP is concerning, because of possible higher risks for adverse effects and events.

Previous observational studies among dementia populations have reported prevalence of PPP ranging from 14% to 50% (Nijk et al., 2009; Gustafsson et al., 2013; Vasudev et al., 2015; Walsh et al., al.,2016; Breining et al., 2016; Nørgaard et al., al., 2017). However, most of these studies were conducted in populations that only included persons living in long-term care facilities or special care units and also used different measures to estimate the prevalence of PPP. Breining et al. and Nørgaard et al. included both community-dwelling and nursing home residents into their studies and found a prevalence of respectively 13.8% and 25.3%, but PPP in the study of Breining et al. was defined as the use of three or more psychotropic drugs. Nørgaard et al. found that the annual prevalence of PPP in community-dwelling persons with dementia was 19.7%, which is slightly higher than the prevalence we found. When using annual prevalence to measure PPP it is more likely to capture more users, because the time window is larger than when point prevalence is measured. Therefore, differences can be expected between studies that measure annual prevalence and our study.

We found that factors associated with PPP were younger age (< 75years), female sex and prior psychiatric diagnosis which is in line with a previous study including persons with all types of dementia (Nørgaard et al., 2017). Sensitivity to psychotropic drugs increases with age and older persons are more likely to experience adverse effects than younger adults (Zubenko et al., 2000). The association of PPP and younger age may indicate more careful consideration of risks and benefits among persons aged over 75 years. Alternatively, younger persons with AD may have more se-

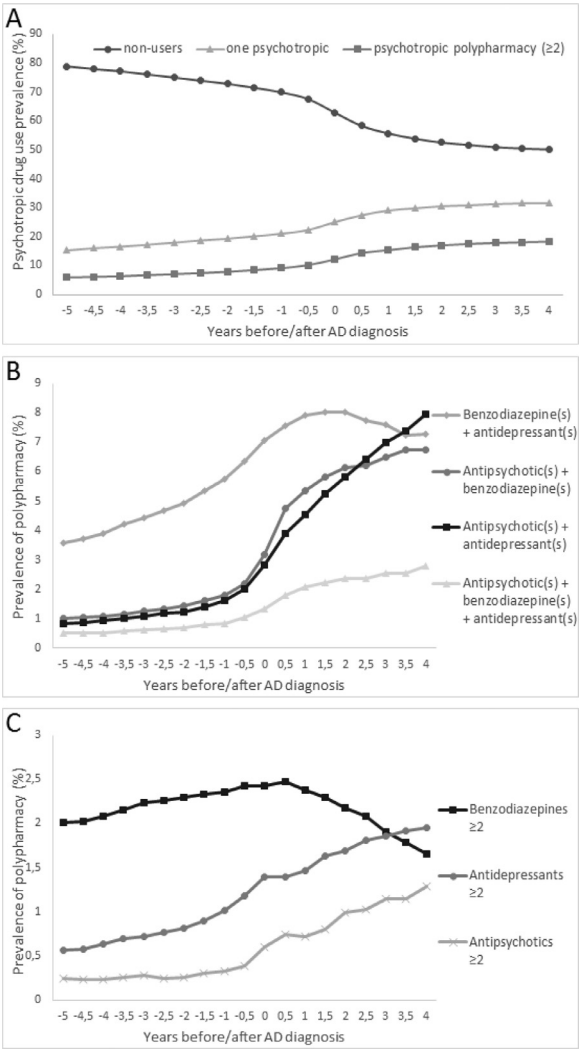

Fig. 2 A: Psychotropic drug use in the AD cohort from five years before to four years after AD diagnosis. Prevalence of non-users, psychotropic monotherapy and psychotropic polypharmacy (≥2 drugs). B: Prevalence of concomitant use of ≥2 different psychotropic drug classes; C: Prevalence of use of ≥2 psychotropic drugs of the same drug class.

vere symptoms, or due to their better physical function, symptoms such as agitation may cause more distress for family caregivers. Previous studies on sex differences in the prevalence of BPSD have reported that women experience behavioural symptoms, especially depressive symptoms, anxiety and delusions, more frequently than men (Steinberg et al., 2006; Lövheim et al., 2009). This might be an explanation for why PPP is more common among women. Persons, especially persons with dementia, with a history of psychiatric disorder have an increased risk for late life depressive disorders compared to persons without any history of psychiatric disorder (Djernes et al., 2006) and therefore are more likely to use PPP. It is possible that behavioural symptoms in persons with pre-existing psychiatric disorder may be more easily attributed to their psychiatric disease and thus, more prone to receive psychotropic drugs.

Previous studies on the prevalence of psychotropic drug use among persons with dementia reported that the use of BZDR's varied from 8.5% to 20% (Rhee et al., 2011; Defrancesco et al., al.,2015), antipsychotics from 12.5% to 19.1% (Guthrie et al., al.,2010; Rhee et al., 2011; Martinez et al., al.,2013) and antidepressants from 22.5% to 29.1% (Guthrie et al., al.,2010; Rhee et al., 2011; Martinez et al., al.,2013). Studies that investigated the prevalence of BZDR use were conducted in smaller samples with dementia, included both nursing home and community-dwelling persons and were not related to time since AD diagnosis. Our findings for the prevalence of BZDR use at the index date, 21%, is higher than in previous studies. However, the prevalence of BZDR use four years after diagnoses (18%) corresponds to previous findings. Martinez et al. investigated the prevalence of antidepressants and antipsychotics from ten years before to four years after AD diagnosis. The prevalence found in our study for the use of antidepressants was lower during the whole study period compared to Martinez et al. At the index date, we found that almost one fifth of the persons with AD used an antidepressant compared to almost a quarter found in Martinez et al. Even more concerning is that we found a higher prevalence for the use of antipsychotics four years after AD diagnosis than previously found. Previous studies with lower prevalence of antipsychotic use also included nursing home residents, who generally show a higher prevalence for psychotropic drug use. However, the results on frequent antipsychotic use are in line with an earlier Finnish study among persons with dementia (Hartikainen et al., 2003). Thus, it seems that despite safety concerns antipsychotic use has remained frequent in Finland throughout the years and more efforts may be required to decrease antipsychotic use, or to increase use of nonpharmacological treatment options in treatment of BPSD.

There was a steady increase in the prevalence of antipsychotic and antidepressant use and the combination of these two drug classes during the period before and after the index date among persons with AD. This increase is not desired, given the concerns about the prescription of antipsychotics in older persons and the risks associated with psychotropic drugs among this vulnerable population. The increase may reflect the changes in prevalence, persistence and severity of behavioural symptoms during the course of AD. A previous study conducted in nursing home setting found that severity of agitation and apathy increased whereas the severity of affective symptoms decreased during follow-up (Selbæk et al., 2014). However, the first-line treatment of BPSD are nonpharmacological treatment approaches and antipsychotics or antidepressants should be used only for symptoms for which there is demonstrated efficacy, when nonpharmacological options have failed or there is risk of harm to the patient or others. In any case, PPP should be avoided among persons with dementia.

In contrast, the use of BZDRs, the concomitant use of two or more BZDRs and the combination of BZDRs and antidepressants decreased from one year after index date. Although the prevalence was still rather high the decrease is welcomed due to the fact that BZDRs are associated with cognitive decline (Billiote de Gage et al., 2012; Shash et al., 2016). In persons with cognitive impairment pharma-

cotherapy should not lead to further decline of cognition. However, it is also important to treat emotional and behavioural symptoms which cause suffering for the patient and support system. Decreasing prevalence of BZDR use may indicate that more focus is paid on the adverse events associated with BZDR use than use of antipsychotics and PPP. Also, regulations have changed over the years which may also affect the prescription of BZDRs.

According to the Finnish guidelines, the use of two or more psychotropic drugs is generally not recommended for older persons with dementia. Therefore, the high prevalence of PPP in our study is concerning. Previous studies report that the use of one psychotropic drug is associated with higher risks of adverse effects and events, such as hip fractures (Saarelainen et al., 2017; Torvinen-Kiiskinen et al., 2017; Koponen et al., 2017a), strokes (Trifirò et al., 2010; Mittal et al., 2011; Taipale et al., 2017), myocardial infarction (Pariente et al., 2012; Yu et al., 2016) and mortality (Huybrechts et al., 2011; Maust et al., 2015; Koponen et al., 2017b). There is a lack of studies concerning the safety of concomitant use of psychotropic drugs among community-dwelling persons with dementia, but because of known serious effects of single psychotropic drug use concomitant use should be avoided in this vulnerable population.

This nationwide cohort included all persons with a clinically verified diagnoses of AD between 2005–2011 and thus, our results represent treatment practice among community-dwelling persons in Finland. All persons with AD were matched on age, gender and index date to a control person. The psychotropic drug use was compared between case and control by using data from the Prescription Register. This data is not subject to recall or reporting bias, because this register contains only actual drug purchases. Only reimbursed drug purchases are recorded in the Prescription Register and some small packages of BZDRs are not reimbursed. This limitation is likely to underestimate exposure to BZDR drugs. Indications (or specific symptoms) for psychotropic drug use and severity of AD were not included in our data which are limitations in our study. As commonly in register-based data, there is no requirement to state indication for drug use in prescriptions, and free dose texts are not stored in the Finnish Prescription register data. In addition, duration of treatment should be analysed in further studies.

In conclusion, we found that the use of two or more psychotropic drugs is frequent in persons with AD. PPP becomes more common during the course of the disease and is associated with younger age (< 75 years), female gender and history of psychiatric disorder. The most frequent combination was the concomitant use of antipsychotics and antidepressants. Psychotropic polypharmacy is concerning and should be avoided in clinical practice. The use of any psychotropic drug have been associated with severe adverse events, but the risks of psychotropic polypharmacy are still unknown and require further investigation.

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Contributors

HT and SH planned the research project. HT, AMT, AT and KO collected data. KO and HT performed statistical analyses and act as guarantor. KO, HT and SH drafted the first version of the manuscript, and all authors revised the draft version and accepted the final manuscript.

Conflict of interest

HT, JT and AT have participated in research projects funded by Janssen and Eli Lilly with grants paid to the institution where they were employed. AT is a member of advisory board of Janssen. JT reports serving as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen-Cilag, Lundbeck, and Organon. He has received fees for giving expert opinions to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka and Pfizer, and lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer. He is a member of advisory board in AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka. Other authors report no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.04.005.

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