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RESEARCH PAPER

Trends of use and characterisation of anti-dementia drugs users: a large multinational-network population-based study

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Abstract

Background: An updated time-trend analysis of anti-dementia drugs (ADDs) is lacking. The aim of this study is to assess the incident rate (IR) of ADD in individuals with dementia using real-world data.
Setting: Primary care data (country/database) from the UK/CPRD-GOLD (2007–20), Spain/SIDIAP (2010–20) and the Netherlands/IPCI (2008–20), standardised to a common data model.
Methods: Cohort study. Participants: dementia patients ≥40 years old with ≥1 year of previous data. Follow-up: until the end of the study period, transfer out of the catchment area, death or incident prescription of rivastigmine, galantamine, donepezil or memantine. Other variables: age/sex, type of dementia, comorbidities. Statistics: overall and yearly age/sex IR, with 95% confidence interval, per 100,000 person-years (IR per 10^5 PY (95%CI)).
Results: We identified a total of (incident anti-dementia users/dementia patients) 41,024/110,642 in UK/CPRD-GOLD, 51,667/134,927 in Spain/SIDIAP and 2,088/17,559 in the Netherlands/IPCI. In the UK, IR (per 10^5 PY (95%CI)) of ADD decreased from 2007 (30,829 (28,891–32,862)) to 2010 (17,793 (17,083–18,524)), then increased up to 2019 (31,601 (30,483 to 32,749)) and decrease in 2020 (24,067 (23,021–25,148)). In Spain, IR (per 10^5 PY (95%CI)) of ADD decreased by 72% from 2010 (51,003 (49,199–52,855)) to 2020 (14,571 (14,109–15,043)). In the Netherlands, IR (per 10^5 PY (95%CI)) of ADD decreased by 77% from 2009 (21,151 (14,967–29,031)) to 2020 (4763 (4176–5409)). Subjects aged ≥65–79 years and men (in the UK and the Netherlands) initiated more frequently an ADD.
Conclusions: Treatment of dementia remains highly heterogeneous. Further consensus in the pharmacological management of patients living with dementia is urgently needed.

Keywords: dementia, drug utilization studies, cohort studies, older people

Key Points

- A large heterogeneity in the incident prescription of ADDs in the UK, Spain and the Netherlands is observed.
- A large treatment gap exists among patients with dementia in the three countries (UK, Spain and the Netherlands).
- Patients aged ≥65 to 79 years are initiated with an ADD more frequently than those over 79 years.
- The higher ADD incidents rates in UK and Dutch men, suggest a possible gender inequity.

Introduction

Due to the greater longevity and lifestyle of the population, dementia incidence is expected to increase and become a great challenge for public health care systems worldwide. The Global Burden of Diseases, Injuries and Risk Factors Study in 2019 estimated that dementia would affect 152.8 million people in 2050 [1].

Although new therapies have been recently approved [2–4], their use in real-world settings is still limited, and evidence on their long-term safety and efficacy remains scarce. To date, dementia patients remain treated with acetylcholinesterase inhibitors and N-Methyl-D-Aspartate receptor antagonist, which are mainly symptomatic medications with no disease modifying effects [5].

Previous drug utilisation studies showed an increasing trend in the use of anti-dementia drugs (ADDs) [6–10], especially in women [6, 11] and older patients [6, 8–10]. However, these studies are outdated and might not reflect the current use of these drugs. Recent observational data are more limited and conflicting [12–14] with reports of either an increase [12], stabilisation [13] or decrease in the use of ADDs [14].

Both acetylcholinesterase inhibitors and N-Methyl-D-Aspartate receptor antagonists are recommended in dementia guidelines [15, 16]. Nonetheless, uncertainties regarding the prescription of these drugs, due to adverse events [17, 18], and the lack of evidence on long-term benefits and increased costs [19–22], could be hampering their use. A reflection of this is the withdrawal of these drugs from state funding in France in 2019 due to their limited effectiveness [23].

The drug-utilisation studies published until now focus mainly on the prevalent use of anti-dementia treatments [6–10, 12–14, 24] in the overall population [6–9, 11–13, 24] but not on those with a dementia diagnose, for whom these drugs are recommended. Overall, these limitations prevent us from understanding the current incident prescription of these drugs among dementia patients.

Considering the increasing trends of dementia and the controversies regarding the use of anti-dementia treatments, an updated time-trend analysis of their incident use is necessary to understand the effect of policies and clinical guidance in dementia management. Therefore, the aim of this study is to characterise and assess the trend in the incident rate (IR) of ADDs in individuals with dementia diagnosis in Spain, the UK and the Netherlands using real-world data.

Methods

Study design, setting and data sources

We conducted a population-based cohort study using data from the *Information System for Research in Primary Care* (SIDIAP/Spain [25]), *Clinical Practice Research Datalink* (CPRD-GOLD/UK [26, 27]) and the *Integrated Primary Care Information* (IPCI/the Netherlands) [28], standardised to the Observational Medical Outcomes Partnership common data model [29] (Appendix 1).

Study participants and follow-up

Patients with a first diagnosis of dementia who were ≥ 40 years old and had ≥1 year of previous data were identified from 1 January 2010 to 31 December the 2020, for SIDIAP; from 1 January 2007 until 31 December 2020, for CPRD-GOLD and from 1 January 2008 until 31 December 2020, for IPCI (according to the accessibility and/or quality of the data in each database). Dementias due to acute infections, intoxications, traumas or neoplasms were excluded. Patients were observed until (each or overall) the incident prescription of rivastigmine, galantamine, donepezil and memantine, death, transfers out of catchment area or end of study period.

Variables

Patients' age and sex were extracted, as well as information on other medical conditions (such as type of dementia, Parkinson's disease, Huntington's disease, multiple sclerosis or cancer diagnosis) based on the Systematized Nomenclature of Medicine Current Terminology (SNOMED CT) using a web-based integrated platform (ATLAS tool: https://atlas.ohdsi.org/). Outcomes included the overall and yearly incidence rate (IR) of the study drugs (RxNorm codes) (see Appendix 2). The full study protocol is available in The European Union Electronic Register of Post-Authorisation Studies (EUPAS104349).

Statistical analysis

The IR of rivastigmine, galantamine, donepezil and memantine (separately or together) per 100,000 person-years was calculated for the population diagnosed with dementia using the IncidencePrevalence R package [30]. The denominator included patients with a diagnosis of dementia who were alive and currently registered in each database in the same year. Overall, age groups (≥40 to 64, 65 to 79 and ≥ 80 years) and sex (men and women) yearly IRs were calculated by excluding patients who were prescribed any of the individual ADDs in the previous year for the any ADD cohort, and for each of the ADDs in the individual drug cohorts (memantine, rivastigmine, galantamine and donepezil). Continuous variables were described using absolute numbers (considering both valid and missing cases), means with standard deviations, and median values, depending on the distribution of the data. Categorical variables were described as percentages. Missing data were quantified and treated as specific categories in the analysis. Statistical analysis was conducted using R version 4.1.3.

Ethical considerations

The study was developed in accordance with the declaration of Helsinki on ethical aspects and the rules of Good Practice

in Research, and in agreement with Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016, on Data Protection, and Organic Law 3/2018 of 5 December on the protection of personal data and guarantee of digital rights. Patient-level data used in this study were obtained through the respective Institutional Review Boards of each country; application to the Clinical Practice Research Datalink (CPRD) GOLD (application number 22_001849), Institutional Review Board approval of the IDIAPJGol (SIDIAP, 22/041-EOm) and approval during the meeting on 7 April 2022 for IPCI (IPCI nr 6/2022). In accordance with current European and national law, results with fewer than five individuals were blinded and reported as <5. Consent to participate was not required as only anonymized retrospective data were used for this study and no patient or GP contact was required.

Results

Baseline characteristics

A total of 134,927 subjects (85,538 women) with dementia were followed for 254,230 person-years in Spain (2010–20), 110,642 subjects (69,147 women) with dementia were followed for 165,745 person-years in the UK (2007–20) and 17,559 subjects (10,845 women) with dementia were followed for 30,614 person-years in the Netherlands (2008–20). The baseline characteristics of the incident users of ADDs are reported in Table 1. The proportion of patients with dementia who initiated an ADD during the study period in all three databases was 2094 (11.9%) in the Netherlands, 41,024 (37.1%) in the UK and 51,667 (38.3%) in Spain. The majority of the incident ADD users were women (ranging from 57% in the Netherlands to 65% in Spain) and had a diagnosis of Alzheimer's disease (ranging from 60% in the Netherlands to 65% in Spain).

Incidence rates (overall and per individual ADD)

Incident rate per 100,000 person-years (IR per 10^5 PY) with a 95% confidence interval (95% CI) of the overall ADDs prescription in the UK, Spain and the Netherlands are reported in Figure 1.

In the UK, the IR per 10^5 PY of the overall ADD prescription followed three different patterns; a decrease from 2007 (IR (95% CI) of 30,829 (28,891 to 32,862)) to 2010 (IR (95%CI) of 17,793 (17,083 to 18,524)), an increase from 2011(IR of 19,712 (19,022 to 20, 422)) to 2019 (IR of 31,601 (30,483 to 32, 749)) and a final decrease in 2020 (24,067 (23,021 to 25,148)). Individually, the IR per 10^5 PY of donepezil followed the same trend as the overall ADD prescription cohort, while rivastigmine and galantamine remained low during the whole study period, and memantine showed an increasing trend especially after 2010. The most frequently prescribed ADD during the whole study period was donepezil (IR per 10^5 PY (95%CI) of 12,459 (12,308 to 12,612)) followed by memantine (IR of 5,156 (5,069 to 5,244)), rivastigmine (IR of 2,026 (1,973 to 2,080)) and galantamine (IR of 1,872 (1,821 to 1,925)).

In Spain, a 72% decrease in the IR per 10^5 PY of the overall ADD prescription was observed during the study period from 2010 (IR (95% CI) of 51,003 (49,199–52,855)) to 2020 (IR (95% CI) of 14,571 (14,109–15,043)), which was more pronounced between 2010 and 2013. Donepezil, memantine and rivastigmine had similar IR per 10^5 PY during the study period (donepezil (IR (95% CI) of 5,413 (5,340 to 5,486)), memantine (IR (95% CI) of 5,128 (5,060 to 5,197) and rivastigmine (IR (95% CI) of 5,896 (5,820 to 5,973)), which were higher than those observed for galantamine (IR (95%CI) of 1,435 (1,400 to 1,470)).

In the Netherlands, the IR per 10^5 PY ADD prescriptions was calculated from 2009 onward. A 77% decrease was observed during the study period, from 2009 (IR (95%CI) of 21,151 (14,967–29,031)) to 2020 (IR (95% CI) of 4,763 (4,176–5,409)). During this period, only a small peak was observed in 2012 (IR (95%CI) of 12,514 (10,689–14,563)) with little differences between rivastigmine, memantine and galantamine.

Age and sex stratification

Incident rate per 100,000 person-years (IR per 10^5 PY) with a 95% CI of ADDs in the UK, Spain and the Netherlands stratified by age and sex are reported in Figures 2–4.

In the UK, ADDs were more frequently prescribed to patients aged ≥65 to 79 years (IR per 10^5 PY (95%CI) of 34,845 (34,287–35,409)) followed by those of aged ≥40 to 64 years (IR of 23,984 (22,693–25,329)) and those aged ≥80 years (IR of 22,879 (22,587–23,173)). The trend in the incident ADD prescription in patients of ≥65 years followed the same pattern as the one reported for the overall population. Donepezil was the most prescribed ADD in all age strata, followed by memantine in subjects ≥65 years old. Memantine was the only ADD with an increasing trend after 2012 in subjects ≥65 years old (IR per 10^5 PY of 5,115 (4,603–5,668) in 2012 to IR of 9,903 (8,956–10,923) in 2020 among subjects ≥65 to 79 years old and IR per 10^5 PY of 4,091 (3,770–4,432) in 2012 to IR of 8,459 (7,836–9,120) in 2020 among patients ≥80. A higher IR per 10^5 PY of ADD prescription was observed in men (IR (95%CI) of 25,470 (25,071–25,875)) compared with women (IR (95%CI) of 24,333 (24,035–24,633)). The trend in both sexes showed an initial decrease in the IR up to 2010, a >1.8 and >1.6-fold increase from 2010 to 2019 in men and women, respectively, and a subsequent decrease in 2020. Donepezil was the most frequently prescribed drug in both sexes, followed by memantine. Memantine was the only drug that continuously increased in both sexes, from 2011 to 2019.

In Spain, ADDs were mostly prescribed to persons aged ≥65 to 79 years (IR per 10^5 PY (95%CI) of 36,031 (35,536–36,531)), followed by persons aged ≥80 years (IR per 10^5 PY (95%CI) of 17,131 (16,929–17,336)) and by persons aged ≥40 to 64 years (IR per 10^5 PY (95%CI) 14,482

Table 1. Baseline characteristics of the incident antidementia drug users

	CPRD-GOLD *N* = 110,642 (with dementia)					SIDIAP *N* = 134,927 (with dementia)					IPCI *N* = 17,559 (with dementia)				
	Any ADD *N* = 41,024	Donepezil *N* = 25,921	Galantamine *N* = 5068	Memantine *N* = 13,461	Rivastigmine *N* = 5554	Any ADD *N* = 51,667	Donepezil *N* = 21,536	Galantamine *N* = 6641	Memantine *N* = 21,444	Rivastigmine *N* = 23,012	Any ADD *N* = 2088	Donepezil *N* = 20	Galantamine *N* = 813	Memantine *N* = 243	Rivastigmine *N* = 1253
Median Age (years)	81	81	80	82	80	81	80	81	82	80	78	77	77	80	79
Women, n(%)	25,484 (62)	16,746 (65)	3257 (64)	7950 (59)	3025 (54)	33,637 (65)	14,397(67)	4092 (62)	14,640 (68)	14,908(65)	1198 (57)	14 (70)	471 (58)	142 (58)	713 (57)
Type of Dementia diagnosis															
Fronto temporal dementia, n (%)	15 (0.0)	10 (0.0)	0	7 (0.0)	<5	176 (0.3)	63 (0.3)	17 (0.3)	74 (0.4)	80 (0.4)	5 (0.2)	0	<5	0	<5
Alzheimer Disease, n (%)	25,328 (61.7)	17,687 (68.2)	3191 (63.0)	7957 (59.1)	2532 (45.6)	33,678 (65.2)	15,238 (70.8)	4035 (60.8)	15,806 (73.7)	14,978 (65.1)	1248 (59.8)	14 (70.0)	563 (69.2)	156 (64.2)	682 (54.4)
Vascular dementia, n (%)	5026 (12.3)	2480 (9.6)	673 (13.3)	2236 (16.6)	635 (11.4)	4504 (8.7)	1300 (6.04%)	1308 (19.7)	1913 (8.9)	1663 (7.2)	68 (3.3)	<5 (15.0)	14 (1.7)	11 (4.5)	49 (3.9)
Lewy-Body Dementia, n (%)	1158 (2.8)	323 (1.3)	59 (1.2)	233 (1.7)	830 (14.9)	1087 (2.1)	199 (0.9)	46 (0.7)	254 (1.2)	944 (4.1)	92 (4.4)	0	13 (1.6)	<5	86 (6.8)
Mixed/ unspecified dementia, n (%)	13,478 (32.9)	7882 (30.4)	1679 (33.1)	4699 (34.9)	2200 (39.6)	18,274 (35.4)	6934 (32.2)	2179 (32.8)	8129 (37.9)	8242 (35.8)	796 (38.1)	6 (30.0)	265 (32.6)	101 (41.6)	508 (40.5)
Comorbidities associated with cognitive impairment or dementia															
Creutzfeldt Jakob Disease, n (%)	0	<5	NA	NA	0	<5	0	0	<5	<5	0	0	0	0	0
Cancer (all excluded skin), n (%)	4138 (10.1)	2594 (10.0)	432 (8.5)	1410 (10.5)	563 (10.1)	7042 (13.63)	2893 (13.4)	895 (13.5)	2884 (13.5)	3145 (13.7)	269 (12.9)	5 (25.0)	102 (12.5)	27 (11.1)	170 (13.5)
Parkinson's disease, n (%)	1518 (3.7)	406 (1.6)	83 (1.6)	300 (2.2)	1078 (19.4)	2236 (4.3)	442 (2.1)	154 (2.3)	628 (2.9)	1735 (7.5)	42 (2.0)	0	<5	<5	41 (3.3)
Multiple Sclerosis n (%)	43 (0.1)	31 (0.1)	5 (0.1)	10 (0.1)	<5	20 (0.04)	13 (0.1)	0 (0%)	11 (0.1)	5 (0.0)	0	0	0	0	0

ADD: anti-dementia drug, CPRD: Clinical Practice Research Datalink, SIDIAP: Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primària, IPCI: Integrated Primary Care Information database

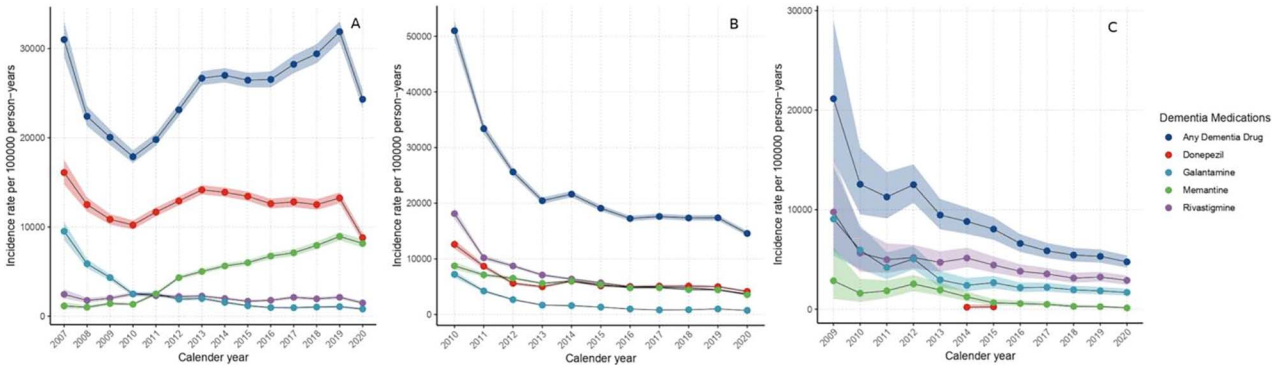

Figure 1. Overall and individual ADD prescriptions incidence rate per 100,000 person-years: (A) Clinical Practice Research Datalink (CPRD-GOLD), (B) Information System for Research in Primary Care (SIDIAP) and (C) Integrated Primary Care Information (IPCI).

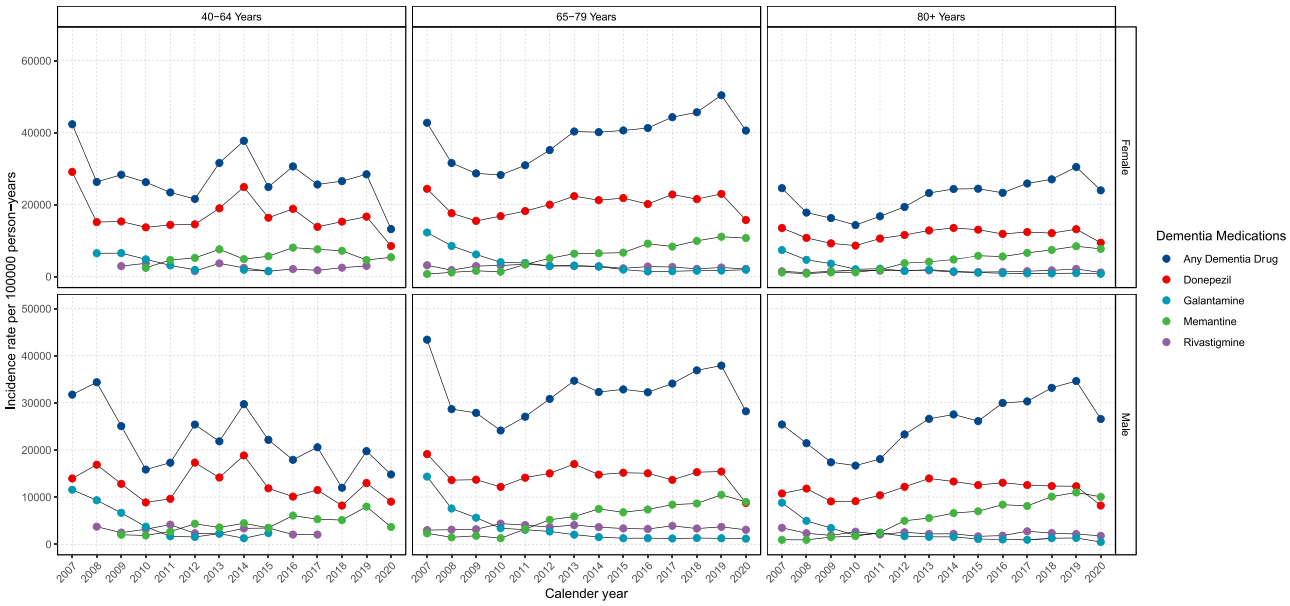

Figure 2. Incidence rate per 100,000 persons-year of ADD prescriptions per age and sex in the Clinical Practice Research Datalink (CPRD-GOLD).

(13,764–15,227)). During the study period, the overall ADDs prescription decreased in all age strata except for patients aged ≥65 to 79 years from 2013 onwards where it remained stable. The most frequently prescribed ADDs in all age strata were rivastigmine and donepezil. Memantine was frequently prescribed among the youngest (≥40 to 64 years old) and the oldest (≥80 years old). Men and women had similar ADD prescriptions (IR per 10^5 PY (95%CI) of 20,453 (20,155–20,753) and IR of 20,254 (20,038–20,472), respectively). Donepezil, memantine and rivastigmine were the most frequently prescribed antidementia drugs in both sexes.

In the Netherlands, the majority of the IR per 10^5 PY prescriptions of memantine, rivastigmine and galantamine were prescribed to subjects ≥65 years old, especially in those between ≥65 and 79 years old (IR (95% CI) of 10,702 (10,058–11,376)) compared with those ≥80 (IR (95% CI) of 4,864 (4,538–5,206)). Men had higher IR of ADD prescriptions compared with women (IR per 10^5 PY (95% CI) of 7,571 (7,083–8,086) versus IR of 6,352 (5,998–6,722)). For both sexes, a decreasing trend in the IR of ADD prescriptions was observed, which was more pronounced in women, with no relevant differences between drugs.

Discussion

A large heterogeneity in the IR of ADDs was observed with common features in all three countries. First, an overall treatment gap, with only 37% in the UK, 38% in Spain and nearly 12% in the Netherlands of dementia patients receiving an ADD prescription during the study period. Second, a greater prescription of ADDs in patients aged ≥65 to 79 years compared with older patients, and at lastly, a

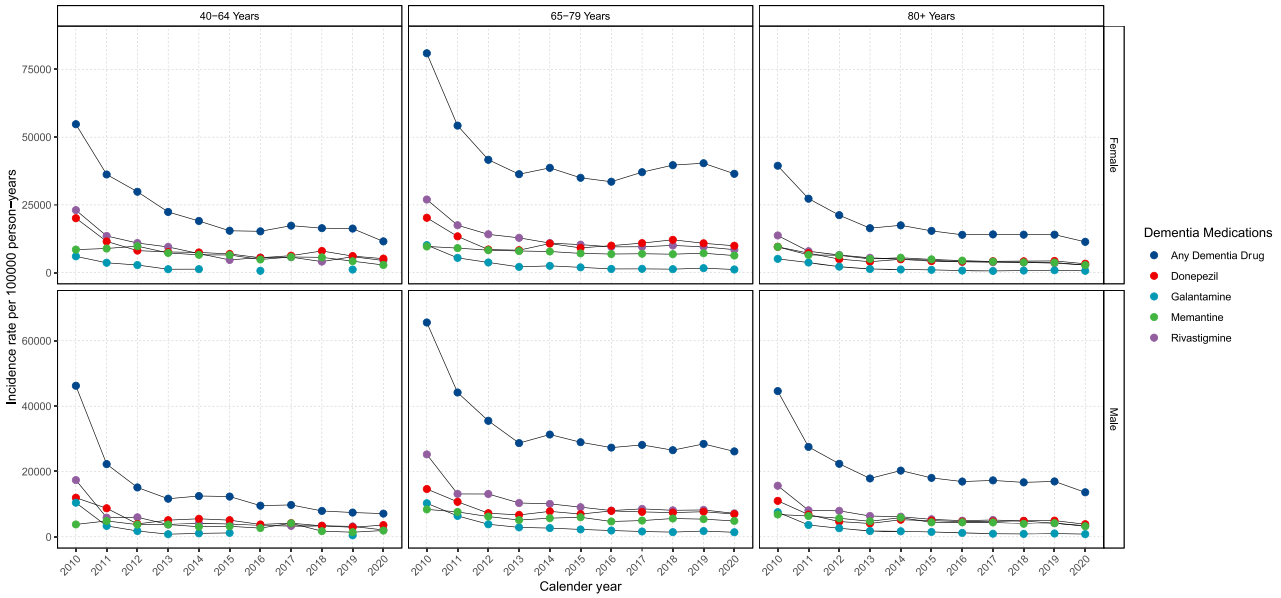

Figure 3. Incidence rate per 100,000 persons-year of ADD prescriptions per age and sex in the Information System for Research in Primary Care (SIDIAP).

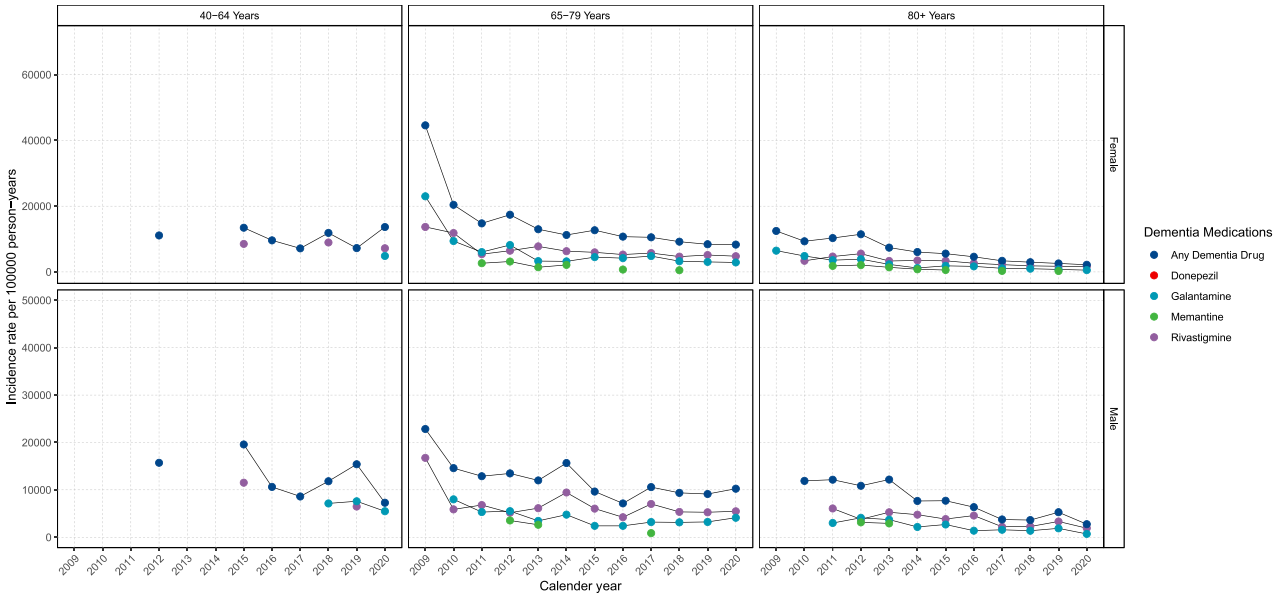

Figure 4. Incidence rate per 100,000 persons-year of ADD prescriptions per age and sex in the Integrated Primary Care Information (IPCI).

possible gender inequity in the access of these drugs; similar incidence rates of the ADDs were observed in men and women in Spain, higher in men in the UK and in the Netherlands, despite having a larger proportion of women with a dementia diagnosis in all three countries.

Individually, donepezil, memantine and rivastigmine were the most frequently prescribed ADDs in the UK and Spain, while rivastigmine was the most frequent initiated drug in the Netherlands. Memantine was the only ADD with an increasing trend until the end of the study period in the UK.

The treatment gap in the management of dementia has been previously observed [7, 8, 10, 31, 32]; in the UK, between 2005 and 2015, only 29% of patients with dementia had a prescription of an anti-dementia treatment [10]. In Spain, higher proportions (70.4%) were observed among patients from the Registry of Dementias of Girona (ReDeGi) between 2007 and 2014 [32]. In the Netherlands, the use of ADDs remained low (0.8 to 14.4%) among nursing home residents [33]. Methodological differences make comparison difficult; however, the low proportion of incident users of anti-dementia treatment reported in this study suggests an

important treatment hesitancy in the prescription of these drugs, in spite of the dementia guidelines [15, 16].

In the UK, the increasing trend observed is in line with government policies implemented in the country and changes in the NICE recommendations in 2009 [34] which widened treatment initiation to patients with mild dementia. The opposite is seen in the Netherlands, where a decreasing trend is observed despite having a National Dementia Strategy implemented since 2004 [35] which could be due to a reluctance to prescribe ADDs given its limited efficacy, as reflected in the current Dutch dementia guidelines [36]. In Spain, national dementia strategies were not implemented until 2019 [37] which prevent us from seeing their effect on the use of these drugs.

Overall, we observe a great national and an international variability in the incident prescriptions of ADDs which was also reported by specific care experts and explained by differences in the access to dementia care [38]. Our results support these findings with longitudinal data; the heterogeneity observed suggests that the current dementia strategies in each country are insufficient and outline the need for further consensus regarding the management of dementia.

The trends observed in all three countries need to be put into context and interpreted with caution; patients with dementia could contribute to the denominator during the whole period after the first diagnosis of dementia until the first ADD prescription. This definition reflects better the real use the ADDs, where patients do not always start treatment when diagnosed with dementia but obscures the IR of these drugs among incident dementia patients. Consequently, a sensitivity analysis was performed censoring the population 1 year after the diagnosis of dementia (Appendices 3–5). While trends in CPRD-GOLD (UK) and in IPCI (the Netherlands) remained similar although attenuated, the opposite was observed for SIDIAP (Spain); the IR of ADDs among incident dementia patients decreased until 2013 and later tended to increase up to 2019. These results suggest that, in Spain, newly diagnosed dementia patients might have a greater access to ADDs than the overall dementia patients.

A greater IR of ADDs among patients ≥65 to 79 years old has been previously observed [6, 7, 13, 32] and suggests a tendency to use these medications in early phases of the disease. The high IR observed in subjects aged ≥40 to 64 years old in the UK could be due to the low number of incident users of ADDs (N = 236) in this age stratum and the short follow-up of these patients, forbidding us from drawing any conclusion.

We found that women were more frequently diagnosed with dementia and had a higher proportion of ADD prescribed in all the countries (Table 1) which is in line with what has already been reported [6, 7, 13]. However, we found a higher IR of ADDs in men in the UK and in the Netherlands and a similar IR compared with women in Spain. The shorter follow-up of men compared with women in our study (88,155.30 persons-year in men versus 166,074.56 person-years in women from 2010 to 2020 in Spain, 61,013.32 person-years in men versus 104,732.13 person-years in women from 2007 to 2020 in the UK and 11,801.32 in men versus 18,904.91 in women in the Netherlands) could have contributed to the increased incidence observed. An explanation could be that men receive an ADD prescription earlier than women (triggering the censoring of these patients), whose treatment initiation could be delayed, raising concerns about a possible gender inequity in the access to these drugs that should be explored in future studies.

The considerable variability in the incident prescription of antidementia drugs may also stem from a lack of studies directly comparing these medications in real-world scenarios. The current dementia guidelines primarily rely on evidence from randomised controlled trials that compared these drugs with placebo [39]. However, the strict inclusion criteria of such trials render their findings challenging to apply to real-world dementia patients. The absence of studies comparing the effectiveness and cost-effectiveness might contribute to the observed heterogeneity in drug usage. Conducting further research to assess the relative effectiveness and cost-effectiveness of antidementia drugs in real-world population, with particular attention to potential gender disparities, could assist healthcare authorities in prioritising their use.

Strengths and limitations

The main strength of this study is the large, multinational, population-based data included, which enables us to easily extrapolate our findings. Furthermore, the new-user design allowed us to explore the real-world clinical management and variations of the incident prescriptions of ADDs in the UK, Spain and the Netherlands. To our knowledge, this is also the first study of the trend and incident use of ADDs in the Dutch population. However, this study has also some limitations; our estimates are based on the dementia population for which the ADDs are currently approved and therefore other indications (off-label) were not captured but are expected to be minimal. Second, the data analysed were gathered from routinely collected electronic healthcare records which can be affected by under-registration or misclassification of events, including dementia diagnosis. Finally, our results are based on prescribed medication and not on actual drug intake, which would lead to an overestimation of our IR.

Conclusions

Treatment of dementia remains suboptimal and highly heterogeneous. Further consensus on the pharmacological management of patients living with dementia is urgently needed.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: KV and MM work for a research group who, in the past 3 years, received unconditional research grants from Chiesi, UCB, Amgen, J&J and the EMA, none of which relate to the content of this work. EB, DN, BR, TDS and CR do not have any conflict of interest. DPA's department has received grant/s from Amgen, Chiesi-Taylor, Lilly, Janssen, Novartis and UCB Biopharma. His research group has received consultancy fees from Astra Zeneca and UCB Biopharma. Amgen, Astellas, Janssen, Synapse Management Partners and UCB Biopharma have funded or supported training programmes organised by DPA's department.

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Data availability: In accordance with current European and national law, the data used in this study are only available for the researchers participating in this study. Thus, we are not allowed to distribute or make publicly available the data to other parties. However, researchers from public institutions can request data from SIDIAP if they comply with certain requirements. Further information is available online (https://sidiap.org/index.php/en/solicituds-en) or by contacting SIDIAP (sidiap@idiapjgol.org).

References

1. GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 2022; 7: e105–25.
2. Day GS, Scarmeas N, Dubinsky R *et al.* Aducanumab use in symptomatic Alzheimer disease evidence in focus: a report of the AAN Guidelines Subcommittee. Neurology 2022; 98: 619–31.
3. van Dyck CH, Swanson CJ, Aisen P *et al.* Lecanemab in early Alzheimer's disease. N Engl J Med 2023; 388: 9–21.
4. Sims JR, Zimmer JA, Evans CD *et al.* Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 2023; 330: 512–27.
5. Miculas DC, Negru PA, Bungau SG, Behl T, Hassan SSU, Tit DM. Pharmacotherapy evolution in Alzheimer's disease: current framework and relevant directions. Cells 2022; 12: 131.
6. François M, Sicsic J, Elbaz A, Pelletier FN. Trends in drug prescription rates for dementia: an observational population-based study in France, 2006-2014. Drugs Aging 2017; 34: 711–21.
7. De Hoyos-Alonso MC, Tapias-Merino E, Meseguer Barros CM, Sánchez-Martínez M, Otero A. Consumption trends for specific drugs used to treat dementia in the region of Madrid (Spain) from 2002 to 2012. Neurologia 2015; 30: 416–24 English, Spanish.
8. Villanueva G, López de Argumedo M, Elizondo I. Dementia drug consumption in the Basque Country between 2006 and 2011. Neurologia 2016; 31: 613–9 English, Spanish.
9. Hoffmann F, van den Bussche H, Glaeske G, Kaduszkiewicz H. Eight-year prescription trends of memantine and cholinesterase inhibitors among persons 65 years and older in Germany. Int Clin Psychopharmacol 2010; 25: 29–36.
10. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Health 2017; 2: e149–56.
11. Lu ZK, Xiong X, Wang X, Wu J. Gender disparities in anti-dementia medication use among older adults: health equity considerations and management of Alzheimer's disease and related dementias. Front Pharmacol 2021; 12: 706762.
12. Jelenc M, Korošec A, Lovrečič M. Trends in prescription of drugs for the treatment of dementia in Slovenia in the period from 2008 to 2018. Revija za zdravstvene vede [Internet] 2020; 7: 19–30.
13. Ippoliti I, Ancidoni A, Da Cas R, Pierantozzi A, Vanacore N, Trotta F. Anti-dementia drugs: a descriptive study of the prescription pattern in Italy. Neurol Sci 20231–9; 44: 1587–95.
14. Olazarán J, Carnero-Pardo C, Fortea J *et al.* Prevalence of treated patients with Alzheimer's disease: current trends and COVID-19 impact. Alzheimers Res Ther 2023; 15: 130.
15. National Institute for Health and Care Excellence (UK). Dementia: Assessment, Management and Support for People Living with Dementia and their Carers. London: National Institute for Health and Care Excellence (NICE), 2018.
16. Manzano MS, Fortea J, Villarejo A, Sanchez del Valle R. Guías diagnósticas y terapéuticas de la Sociedad Española de Neurología 2018. 5. Guía oficial de práctica clínica en demencias. Sociedad Española de Neurología. https://www.sen.es/pdf/guias/Guia_Demencias_2018.pdf (accessed 4 october 2023).
17. Zaidi AS, Peterson GM, Bereznicki LRE, Curtain CM, Salahudeen M. Outcomes of medication misadventure among people with cognitive impairment or dementia: a systematic review and meta-analysis. Ann Pharmacother 2021; 55: 530–42.
18. Saraon SK, Bernick C, Wint D, McConnell E. Screening for adverse drug reactions in dementia patients on cholinesterase inhibitor therapy. J Am Geriatr Soc 2020; 68: 216–8.
19. Tan CC, Yu JT, Wang HF *et al.* Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2014; 41: 615–31.
20. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ. Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: a network meta-analysis. Cochrane Database Syst Rev 2021; 2021: CD013306.
21. Livingston G, Sommerlad A, Orgeta V *et al.* Dementia prevention, intervention, and care. Lancet 2017; 390: 2673–734.
22. San-Juan-Rodriguez A, Zhang Y, He M, Hernandez I. Association of anti-dementia therapies with time to skilled nursing facility admission and cardiovascular events among elderly adults with Alzheimer disease. JAMA Netw Open 2019; 2: e190213.

23. Walsh S, King E, Brayne C. France removes state funding for dementia drugs. BMJ 2019; 367: l6930.
24. Vohra N, Hadi MA, Khanal S, Kurmi OP, Paudyal V. Impact of deprivation, dementia prevalence and regional demography on prescribing of antidementia drugs in England: a time trend analysis. Br J Clin Pharmacol 2021; 87: 3747–55.
25. Recalde M, Rodríguez C, Burn E *et al.* Data resource profile: the information system for research in primary care (SIDIAP). Int J Epidemiol 2022; 51: e324–36.
26. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010; 69: 4–14.
27. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010; 60: e128–36.
28. de Ridder MAJ, de Wilde M, de Ben C *et al.* Data resource profile: the Integrated Primary Care Information (IPCI) database, The Netherlands. Int J Epidemiol 2022; 51: e314–23.
29. Voss EA, Makadia R, Matcho A *et al.* Feasibility and utility of applications of the common data model to multiple, disparate observational health databases. J Am Med Inform Assoc 2015; 22: 553–64.
30. IncidencePrevalence: estimate incidence and prevalence using the OMOP common data model. https://cran.r-project.org/web/packages/IncidencePrevalence/index.html. (accessed 4 October 2023).
31. Villar-Fernández I, Bjerrum L, Feja C, Rabanaque MJ. Variability in the prescription of cholinesterase inhibitors and memantine. Dement Geriatr Cogn Disord 2009; 28: 373–9.
32. Calvó-Perxas L, Turró-Garriga O, Vilalta-Franch J *et al.* Trends in the prescription and long-term utilization of antidementia drugs among patients with Alzheimer's disease in Spain: a cohort study using the registry of dementias of Girona. Drugs Aging 2017; 34: 303–10.
33. Du J, Janus S, Voorthuis B *et al.* Time trends in psychotropic drug prescriptions in Dutch nursing home residents with dementia between 2003 and 2018. Int J Geriatr Psychiatry 2022; 37: 1–10.
34. Mukadam N, Livingston G, Rantell K, Rickman S. Diagnostic rates and treatment of dementia before and after launch of a national dementia policy: an observational study using English national databases. BMJ Open 2014; 4: e004119.
35. Ministry of Health Welfare and Sport. National Dementia Strategy 2021-2030 Internet, 2020. Available at: file://diskstation/Usuaris/creyes/Downloads/National+Dementia+Strategy+2021+-+2030%20(1).pdf (accessed 1 September 2023).
36. Netherlands Huisartsen Genootschap. NHS-Richtlijnen. Dementie, 2020. https://richtlijnen.nhg.org/standaarden/dementie#volledige-tekst-richtlijnen-beleid; (accessed 4 October 2023).
37. Ministerio de sanidad consumo y bienestar social. Sanidad 2019. Plan integral de Alzheimer y otras demencias (2019–2023). [accessed on the 01/09/2023]. Available at: https://www.sanidad.gob.es/profesionales/saludPublica/docs/Plan_Integral_Alhzeimer_Octubre_2019.pdf (accessed 1 September 2023).
38. Schmachtenberg T, Monsees J, Thyrian JR. Structures for the care of people with dementia: a European comparison. BMC Health Serv Res 2022; 22: 1372.
39. Versijpt J. Effectiveness and cost-effectiveness of the pharmacological treatment of Alzheimer's disease and vascular dementia. J Alzheimers Dis 2014; 42: S19–25.

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