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RESEARCH ARTICLE

Prescription patterns of antidementives in a high income country: A pharmacoepidemiologic study

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Abstract

Introduction: Dementia is a leading and growing cause of morbidity and mortality. The aim of this study was to investigate real-world prescription patterns of antidementive medication in one of the largest cohorts published thus far to optimize use in this growing population.

Methods: Prescription claims from 2005 to 2016 were provided by Austrian sickness funds, covering 98% of the population of Austria. Patients treated with at least one of the four approved antidementive drugs (ADDs) were included. Prescription prevalence was calculated for 2014 and 2015, and prescription patterns were traced on an individual level during the entire study period.

Results: A total of 127,896 patients were treated with an ADD between 2005 and 2016. The prevalence was 0.93% in 2014 and 1% in 2015. The median age at initiation of treatment was 82.3 years, and 65% were female. Initial therapy was a cholinesterase inhibitor (ChEI) in 80% and memantine in 20%. The median duration of therapy was 13.3 months. Eighteen percent of patients switched medication: two thirds to receive memantine, and one third to a different cholinesterase inhibitor. More than 26% discontinued treatment early.

Conclusion: We find that discontinuation of ADDs is more frequent than switching; memantine is a common starting drug and age at the start of treatment is rather high in this population. Interpretation should be cautious, but the data may suggest that treatment guidelines are followed inconsistently. Appropriate provision of the available options should be emphasized to optimize cognitive survival, comorbidity, quality of life, and health care expenditures.

KEYWORDS

Alzheimer's disease, cholinesterase inhibitors, dementia, epidemiology, memantine, pharmacoepidemiology, prescription patterns

1 | INTRODUCTION

Dementia is a leading cause of global morbidity and mortality and its prevalence is expected to rise dramatically in the next decades.[1]

Despite intensive effort in drug development, there are still only two classes of evidence-based medication available to slow the progress of dementia, cholinesterase inhibitors (ChEIs), and the *N*-methyl-D-aspartate (NMDA) antagonist memantine.[2] Increasing emphasis lies on the appropriate provision of these existing effective therapeutic strategies.[3,4] These antidementive drugs (ADDs) are approved only for Alzheimer's dementia (AD) and overlap cases, but are frequently prescribed off-label in other types of dementia.[5] Whereas ChEIs are approved for the treatment of early and middle stages of dementia, memantine is approved for the treatment of more advanced cases in middle and late stages and therefore considered a second-line therapy. Switching therapy between different ADDs is currently recommended when one ADD is not tolerated or when the disease progresses. This progress is naturally hard to assess in a per se progressive disorder, and the decision is ultimately up to the treating physician.[6] Ambiguous effects are reported for combination therapy; therefore guidelines do not recommend a routine use.[7,8] However, discontinuation of ADDs in late stages of dementia was shown to be detrimental compared to continuing with any ADD.[9] Moreover, use of ADDs in people with dementia was reported to reduce the risk of ischemic stroke and death.[10]

Nationwide prescription registries may be used to monitor quality of care for people with dementia,[11] and recent studies investigating prescription patterns in different countries were beneficial in adding knowledge of treatment in this challenging patient group.[12-14]

We analyzed the national Austrian prescription database to assess prescription patterns of ADDs with an unbiased approach. We aimed to assess their use and provide insights that could help optimizing the provision of ADDs.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the existing literature using common online sources (eg, PubMed, Scopus). We identified studies that applied similar methods or aimed to answer similar questions; however, they were of much smaller size or scope and restricted to a small subpopulation. These relevant studies were cited appropriately.
2. Interpretation: Our findings suggest that the start of dementia treatment in a high income country happens relatively late and that treatment is more frequently discontinued than switched to a different agent. This may suggest that treatment guidelines are followed inconsistently, and that consequently improvement in adherence could have large effects on quality of life and health care expenditures.
3. Future directions: The reported data suggest targets for structured interventions in dementia care on a large scale. Furthermore, we expect similar studies from other countries and health care systems to contrast our findings.

2 | METHODS

2.1 | Study design

This pharmacoepidemiology study is a retrospective analysis of a longitudinal cohort including 98% of all insured persons in Austria[15] covered by 13 Austrian social security institutions. The data set described here was extracted through prescription records in the period of January 2005 through June 2016. Patients who have been prescribed one ADD, that is, donepezil, galantamine, rivastigmine, or memantine, were included in this study.

Local authorities regulate these prescriptions relatively strictly: the diagnosis of dementia must be made by a specialized physician, follow-ups must be scheduled after reaching the target dose, and the disease must be monitored with clinical scores at least twice per year. Furthermore, proof of disease severity must be obtained before initiation of treatment (ie, documentation of a certain score on the Mini-Mental State Examination (MMSE): ChEIs $\leq$24 but $\geq$10 to initiate and discontinue <10; memantine $\leq$14 to initiate and discontinue <3). Combination therapy was defined as the concurrent prescription of ChEIs and memantine and is currently not reimbursed by the sickness funds.[16] This regulation was not changed since memantine was first approved.

The date of the first and the last prescription of one or multiple ADDs during the observation period were recorded. In addition, sex, date of birth, and, if applicable, date of death were stored. The study was approved by the ethical committee of the Medical University of Vienna (EK 2049/2016).

2.2 | Prescription prevalence

For technical and governance reasons, simultaneous availability of data from all 13 insurance providers was available only for the years 2014 and 2015. These years were subsequently chosen for the calculation of prescription prevalence numbers.

2.3 | Prescription demographics and pathways

Data were entered into each database prospectively beginning with a certain date, usually the 1st of January of a given year. As a consequence, people who were previously treated with an ADD were recorded as starting their treatment on that date. Because we could not assess prior treatment or duration of treatment in these patients, they were defined as patients with unclear prior therapy status. They were included in prescription prevalence analysis but excluded from further analysis of prescription pathways.

A medication switch was defined as a consecutive prescription of different ADDs in the same patient during the observation period.

Early discontinuation was defined as living for at least 1 year after the last prescription was received. A patient who received their last medication on the 1st of January 2014 and died on the 1st of June 2015 was included, whereas a patient who died in August 2014 was not. Patients who discontinued later than June 2015 were not included in this analysis because the remaining follow-up duration was too short.

2.4 | Statistical analysis

Categorical variables are shown as percentages; continuous variables are presented as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normal data. Prescription prevalence for a given year was calculated by recording patients that were alive in that year and prescribed an antidementive at least once, that is, including single prescriptions, between the start of the observation and the last day of that year, representing patients alive and ever treated with an antidementive in that year. Period prevalence was calculated using publicly available data on the population size in Austria.[17] Calculations were performed using R (Version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria.)

3 | RESULTS

A total of 127,896 individual patients insured with one of 13 Austrian sickness funds were treated with an ADD between 2005 and 2016. Sixty-five percent of the patients were female and the median age at the start of treatment was 82.3 years (interquartile range [IQR] 76.8–86.7).

3.1 | Prescription prevalence

Here we identified all patients that were ever treated with an ADD and were alive in the years 2014 and 2015.

In 2014, the prevalence of use of antidementive medication was 0.93% (78,743 patients, 66.7% female). In 2015, the prevalence was 1% (84,916 patients, 66.5% female). The period prevalence for 2014 and 2015 increased with age and peaked in the group aged 80–89 years with 112 of 1000 insured persons in 2014 and 118 of 1000 in 2015, respectively. Women were more frequently treated than men (Figure 1).

3.2 | Prescription demographics and pathways

We identified 22,943 patients (17.9%) with unclear prior therapy status. These patients were of similar age and sex as patients who initiated antidementive therapy during the observation period (data shown in Supplemental Table S1).

Consequently, 105,043 patients who initiated antidementive therapy in the study period were analyzed regarding their prescription trajectory. The first prescribed therapy was a ChEI in 79.8% (39% donepezil, 33.6% rivastigmine, and 7.3% galantamine), memantine in 19.8%, and a combination therapy of ChEI and memantine in 0.3% of cases (Table 1). Sixty-five percent were female. The median age at the start of treatment was 82.3 years (IQR 76.8–86.6); it was lowest in patients in whom a combination therapy was initiated and highest in those who initiated memantine. The overall median duration of therapy in months was 13.3 (IQR 2.7–31.4). The median duration of treatment differed significantly between the treatment options, with the longest duration recorded for the very rare primary combination therapy followed by galantamine, and the shortest for memantine (Table 1). A total of 14,814 patients (14.1%) received only one prescription, that is, they obtained only one pack of antidementive medication.

A total of 18,886 patients (18%) switched from one to another ADD or added another ADD as a combination therapy (Table 1 and Figure 2A). Switching occurred most often when the initial therapy was a combination of memantine and ChEI, and least often in memantine. All patients who were treated initially with a combination therapy switched treatment, mostly to a monotherapy with memantine (81.2%). A switch from one ChEI to another occurred least frequently in rivastigmine (18.3% of all patients initially treated), followed by donepezil (21.1%) and galantamine (26.2%, Figure 2B). The median time until switch was 7.7 months (IQR 1.2–20). Times until switching differed between initial agents (rivastigmine 7.2 months, donepezil 7.7, galantamine 9.7, memantine 7.8, primary combination 3.8). After switching, 39.4% were treated with memantine, 36% were treated with a different ChEI, 18.3% with a combination of memantine and a ChEI, and 6% were treated with two ChEIs (Figure 2B). The amount of patients erroneously adding a ChEI to an existing ChEI therapy decreased with duration of this study (from 308 cases in 2012 to 103 in 2016). Those who switched were younger (median 80.9 vs 82.6 years, $P < 0.001$) and were treated for a longer period than those who did not switch (median 31.6 vs 10.3 months, $P < 0.001$).

Early discontinuation, defined as outliving the date of the last subscription by at least 1 year, occurred in 27,481 patients (26.2%, Figure 2A). The most frequently discontinued therapy was a ChEI (27.3% of all ChEI users discontinued making up 74% of all discontinuations) and there was no meaningful difference between the different ChEIs. Initial therapy with memantine was discontinued in 26.6% of all users (18% of all discontinuations). When therapy was switched to memantine, it was later discontinued in 17% of users (6% of all discontinuations). Of all discontinuations, 9898 (36%) were single prescriptions, that is , only one pack of medication was obtained. Characteristics and starting drug of patients receiving a single prescription did not differ meaningfully between initiated medications (38% donepezil, 36% rivastigmine, 36% galantamine, and 32% memantine).

4 | DISCUSSION

Despite intensive effort in drug development in dementia, still only two classes of evidence-based medication are available. Emphasis should be placed on appropriate provision of sparse available options, even more so as beneficial pleiotropic effects of treatment with ADDs

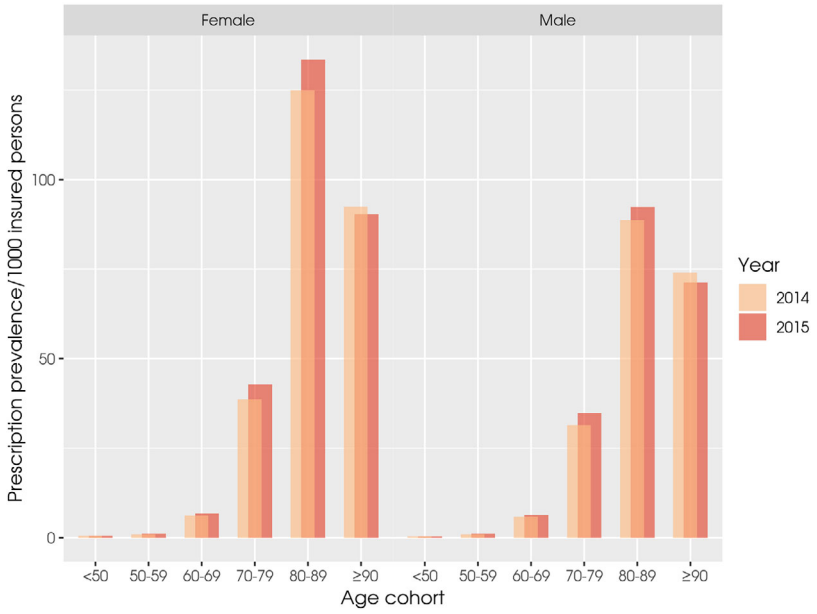

FIGURE 1 Prescription prevalence per age cohort by sex. Prescription prevalence of antidementive medication per 1000 injured persons in the Austrian population during the years 2014 and 2015. The graph is stratified by age cohorts and sex, showing female patients on the left and male patients on the right.

TABLE 1 Demographics at start of first antidementive therapy

Medication prescribed	Patients, n (%)	Female, n (%)	Age in years (median [IQR])	Duration of therapy in months (median [IQR])	Switched, n (%)	Discontinued, n (%)
Overall	105,043 (100)	68,562 (65.3)	82.25 [76.77, 86.62]	13.30 [2.67, 31.43]	18,864 (18.0)	27,481 (26.2)
Donepezil	41,012 (39)	26,778 (65.3)	81.68 [76.31, 86.04]	14.00 [2.83, 32.33]	8664 (21.1)	10,563 (25.8)
Rivastigmine	35,247 (33.6)	22,176 (62.9)	81.87 [76.37, 86.28]	12.80 [2.40, 30.80]	6442 (18.3)	9234 (26.2)
Galantamine	7712 (7.3)	5123 (66.4)	81.56 [76.35, 85.81]	18.78 [4.90, 39.80]	2021 (26.2)	2155 (27.9)
Memantine	20,795 (19.8)	14,305 (68.8)	84.27 [79.16, 88.33]	11.17 [2.27, 26.97]	1460 (7.0)	5444 (26.2)
Combination	277 (0.3)	180 (65.0)	80.67 [73.73, 85.87]	19.13 [4.20, 57.87]	277 (100.0)	85 (30.7)

were reported previously.[10] Given the growing population of dementia patients, optimized use of ADDs can lead to significant public health implications.

For the first time, claims data of Austrian health insurance registries were used to investigate prescription prevalence and prescription pathways of ADDs, amounting to one of the largest cohorts ever studied for this question.

The average prescription prevalence for the evaluated years was 0.97%, or 81,830 patients. We recorded the highest prevalence in patients aged 80–89 years, and as expected, female patients were more frequently affected. Due to the lack of robust national epidemiological studies, we emphasize the value of this real-world data in the context of a country with strict prescription regulations. The most recent national dementia prevalence estimates 100,000 to 150,000.[18] When taking into account that the estimation of prescription data tends to highly underestimate the prevalence of chronic conditions,[19] recent prevalence estimates seem rather low in the light of prescription prevalence found here

The most common first-prescribed medication was a ChEI in 80% of the cases, and donepezil was the most frequent starting drug, closely followed by rivastigmine and galantamine. Accordingly, 20% of patients were treated initially with memantine and only a minor part started with a combination therapy. The median age at the start of first antidementive treatment was 82.3 years, and patients treated initially with memantine were the oldest in our cohort. The median duration of therapy was 13.3 months in this cohort. Comparison and interpretation of these data are difficult, because similar studies were conducted in other regions, that is, with sometimes substantial differences in health care systems, and in smaller cohorts. Data from other European countries and Japan suggest that the population identified here displays reasonable similar characteristics with respect to demographic factors and treatment patterns.[14,20-22] However, the fact that memantine was a common starting drug and that age at the start of treatment was higher than reported elsewhere could support the notion that in this population, therapy is initiated comparatively late in the course of the disease.

A therapy switch occurred in 18% of the patients, and of those 60% switched to memantine (Figure 2), which is in line with contemporary guidelines.[2] One third of the switchers switched to another ChEI, most frequently when treated with galantamine. When memantine was the first initiated therapy, switches occurred least often, as expected because there is no other therapy approved for later stages of the disease. Patients who switched were almost 2 years younger at the start of first antidementive therapy than non-switching patients, and they were subsequently treated for a longer period of time. This could

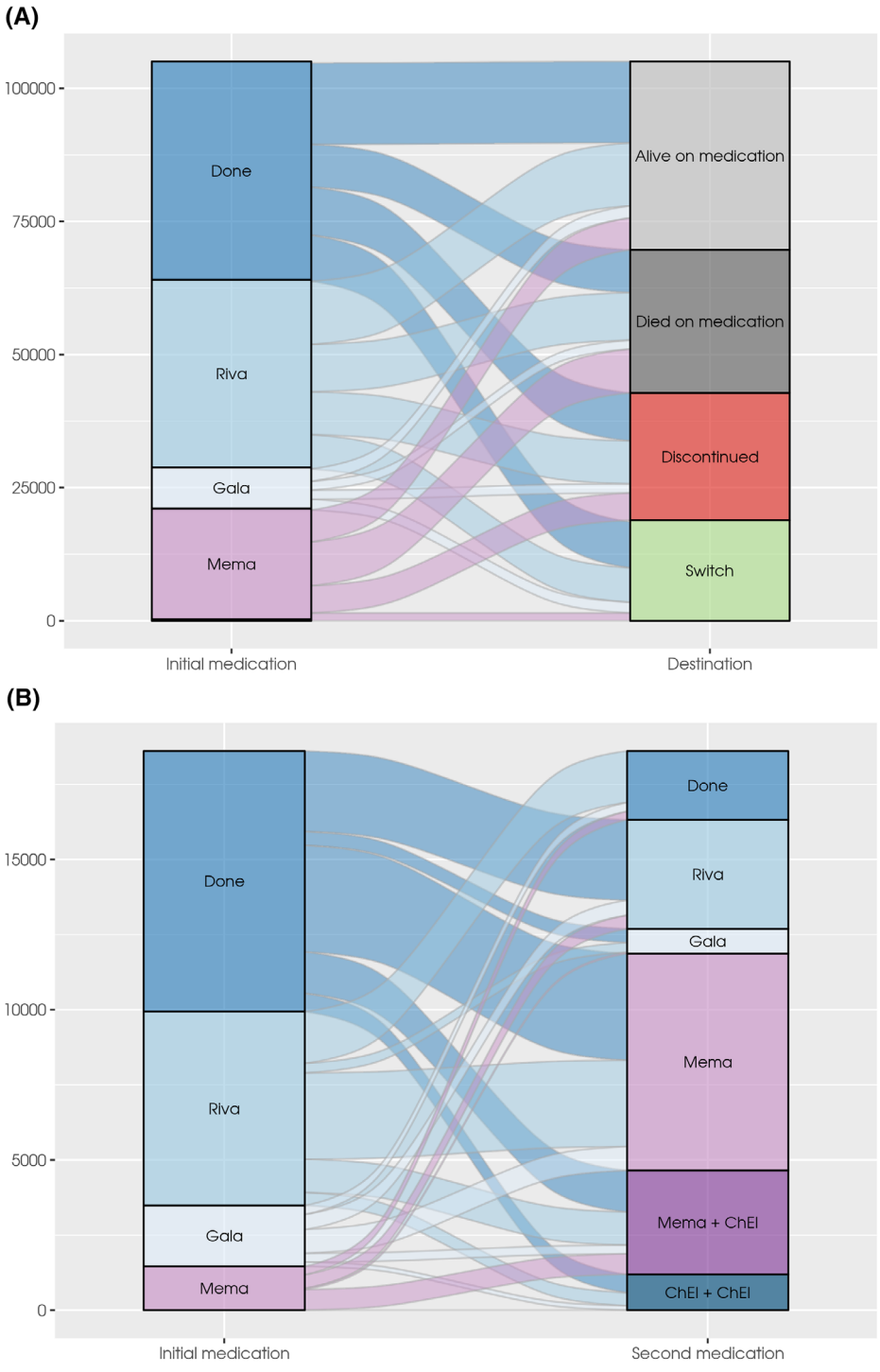

FIGURE 2 2 (A) Medication pathways in patients treated with antidementives. (B) Medication switches in patients treated with antidementives. Sankey plot of disease pathways and changes in medication in patients treated with different antidementive drugs (ADDs). Please note that a small portion of patients with an initial combination of two ADDs (<0.1%) are not shown for clarity. (A) Initially recorded ADD on the left side and status at end of follow-up on the right side. (B) Initially recorded ADD on the left side and second medication recorded after switching on the right side. ChEI, cholinesterase inhibitor; Done, donepezil; Gala, galantamine; Mema, memantine; Riva, rivastigmine.

indicate a more engaged access to treatment in this patient group, perhaps owing to their younger age.

On the other hand, early discontinuation of therapy was recorded in 26% of the patients. Reports suggest a favourable outcome for continuing any antidementive treatment, even in advanced stages in which therapy effectiveness is hard to establish.[9] Keeping this in sight, the fact that almost one fourth of patients discontinued their medication well before their death, and again almost one fourth of ChEI users discontinued their therapy early without switching to another ADD, could be interpreted as a sign that guidelines are followed too inconsistently,

especially because 36% of all discontinuations received only one prescription, suggesting that common adverse effects did not play a major role in the decision to discontinue. We cannot assess the patients' cognitive or functional states at the time of discontinuation, yet it seems likely that at least a proportion of these patients could have been switched before discontinuation.

Although this study is limited by several factors, because we observed prescription pathways without access to clinical data, we believe that this real-world data of Austria gives a reasonable insight into treatment pathways of a high-income country with a tightly regulated prescription practice.

As such, these data must be interpreted with caution; nevertheless the here-reported treatment pathways suggest a late-in-life or late-in-disease start of antidementive treatment. This could be the consequence of a prevalent but misguided sentiment among prescribers that current ADDs are neither clinically nor economically effective. Given the magnitude of the disease, this can have large effects on quality of life and the health care system as a whole.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

RW, TS, and ES devised the protocol. BR performed the initial data acquisition. RW and TS performed the statistical analysis. RW and ES interpreted the data and prepared the manuscript. FS, HC, SS, TP, and SK provided feedback and major contribution to the manuscript and performed additional analysis. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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