Changes in the use of psychotropic drugs during the course of Alzheimer's disease: a large-scale longitudinal study of French medical records

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Potential Conflicts of Interest
Stéphane Epelbaum has received honoraria as a speaker or consultant for ELI-LILLY, GE Healthcare, Astellas pharma, ROCHE and BIOGEN. Béranger Lekens and Laurène Gantzer are employees of Cegedim. The other authors have nothing to report.

Abstract

INTRODUCTION: We aim to understand how patients with Alzheimer's Disease (AD) are treated by identifying in a longitudinal fashion the late-life changes in patient's medical history that precede and follow the AD diagnosis.

METHODS: We use prescription history of 34,782 patients followed between 1996 and 2019 by French general practitioners. We compare patients with an AD diagnosis, patients with mild cognitive impairment (MCI), and patients free of mental disorders. We use a generalized mixed-effects model to study the longitudinal changes in the prescription of eight drug types for a period encompassing 15 years before diagnosis and 10 years after.

RESULTS: In the decades preceding diagnosis, we evidence that future AD patients are treated significantly more than MCI patients for most psychotropic drugs and that most studied drugs are increasingly more prescribed with age. At time of diagnosis, psychotropic drugs but benzodiazepines show a significant increase in prescription, while other drugs are significantly less prescribed. In the 10 years following diagnosis, nearly all categories of drugs are less and less prescribed including antidementia drugs.

DISCUSSION: Pre-clinical changes between future AD patients and MCI patients may indicate that subtle cognitive changes are recognized and treated as psychiatric symptoms. The disclosure of AD diagnosis drastically changes patients' care with the top priority given to the management of psychiatric symptoms. The decrease of all prescriptions in the late stages may reflect treatment discontinuation and simplification of therapeutic procedures. Such a study provides therefore new insights into the medical practices in the treatment of AD.

Alzheimer's disease; medical records; longitudinal analysis; prescriptions; management practices; patient care; mild cognitive impairment; individual matching; risk factors; co-morbidities

1 Introduction

Clinical trials against Alzheimer's disease have failed repeatedly over the last decades. As a matter of fact, only four symptomatic drugs are on the market in Europe and the USA. And yet, these drugs have been delisted in France since 2018 for their "lack of efficacy".

Caring of patients without curative therapeutic options represents a major challenge for caregivers and creates a unique situation compared to other therapeutic areas. This difficulty is further increased by the characteristics of this very slowly progressing disease, with no clearly identified starting point and whose effects on cognition and behavior partially overlap with those of natural ageing.

In the preclinical stage, caregivers have to treat multiple and diffuse cognitive and behavioral symptoms without a reliable prognostic tool to anticipate the possible onset of the disease. At the time of diagnosis, the absence of treatment makes it difficult to disclose the diagnosis and requires considering variable familial and social contexts. And as the disease progresses, caregivers must deal with the aggravation of the handicap that often coincides with the appearance or aggravation of multiple co-morbidities.

Most epidemiological or real-life studies focus on the identification of risk factors[1–4] without targeting specific disease stages, often leaving aside the preclinical stage that is characteristic to AD and its comparison with the post-diagnosis stage. Other studies aim to highlight possible social, cultural or medical factors affecting the diagnosis or the treatment of AD with antidementia drugs in primary care[5–8]. We believe it is also important and urgent to study how patients developing AD are treated across all disease stages from the preclinical to the latest stages.

To do so, we exploit a large longitudinal database of medical records to understand how the drug prescription changes as the disease manifests and progresses in the patients' lives. The aim of this longitudinal analysis of medical prescriptions is to understand the medical practices in the management of patients developing AD, to provide an objective basis for the evaluation of future public health policies or to show how patients' care could be deeply modified if disease modifying drugs were to be marketed in the coming years.

2 Materials and method

2.1 Materials

We used standardized electronic medical record files from the health improvement network (THIN) of GERSDATA, a Cegedim health data company. Cegedim is a company developing and commercializing healthcare management software. We used the data coming from an observatory of 2,000 general practitioners among 25,000 health practitioners using Cegedim products in France. These practitioners have been selected to be representative of the global practitioner cohort in terms of sex, age and geographic locations. Patients data is anonymized at

source since 1994 and is compliant with the European general data protection regulations (GDPR). We used the prescriptions made by these practitioners, which are all paired with a corresponding prescription diagnosis. Data used in this study covers the period 1996-2019.

We defined three cohorts from the THIN database using the following criteria:

- AD group: all patients diagnosed with Alzheimer's disease dementia with international classification of diseases 10th edition (ICD10) codes F00 or G30, who have been followed for at least 2 years before this first diagnosis and were diagnosed at 50 years old or later.
- MCI group: all patients diagnosed with a memory impairment (ICD10 codes F06.7 or R41) that is not explained by any of the following conditions: dementia (F00-F03), mental retardation (F70–F79), disorders of psychological development (F80–F89), inflammatory diseases of the central nervous system (G00–G09), systemic atrophies primarily affecting the central nervous system (G10–G13), extrapyramidal and movement disorders (G20–G26), other degenerative diseases of the nervous system (G30–G32), demyelinating diseases of the central nervous system (G35–G37), epilepsy (G40-G42), and cerebrovascular disorders (G45-G46).
- CN group: patients with no ICD10 diagnosis of category F (Mental and behavioral disorders) or G (Diseases of the nervous system).

The AD group was then matched with each of the control groups (CN and MCI). For each individual in the AD group, we randomly selected an individual from each control group with the same sex, and the same age at the first and last visit in the database (plus or minus one year). We identified 34,782 patients in the THIN database which characteristics are described in Table 1.

We selected the following treatment categories with their ATC codes based on a literature review of AD risk factors and co-morbidities:

- glucose lowering treatments (A10A, A10B)
- tension reducing treatments (C02, C03, C07, C08, C09)
- anti-inflammatory and antirheumatic treatments (M01)
- antipsychotic treatments (N05A)
- benzodiazepine (N05BA, N05CD, N05CF)
- antidepressant (N06A)
- antidementia drugs (N06D)
- herpes treatments (J05AB01, J05AB09, J05AB11)

We divided each patient's follow-up period in 6 months periods and measured if a patient had a prescription for each treatment category at least once within each period.

2.2 Methods

We modeled the evolution of the prescription pattern with time, with time 0 corresponding to the time of diagnosis for the AD group. The cohorts being individually matched, for an individual

of each control group time 0 corresponds to the age of AD diagnosis of the matched individual in the AD group.

We studied the prescription pattern by performing two group comparisons: AD vs. MCI and AD vs. CN. For each comparison, we considered the log-odds of being treated with a category of drugs in the two groups for each 6-month period of the total follow-up period of 25 years. We modeled the change of these log-odds with time using a generalized mixed effect model with logit as link function and the outcome being the presence of a prescription for each patient at each 6-month period. In the AD group, the model assumed a different linear change before and after diagnosis; both linear functions had a fixed intercept and slope, and a random intercept was added for each patient. In the other groups, the model assumed a single linear function with a fixed intercept and slope and a random intercept (see Supplementary Materials for details).

We then tested whether slopes and intercepts were statistically different in the pre-diagnosis period between both groups. We also tested the change in slope and intercept between the pre-diagnosis and post-diagnosis period within the AD population. We used Wald tests corrected for multiple comparisons using the Bonferroni method with a significance threshold of 5%.

3 Results

Estimates of the coefficients of the mixed-effects model are reported in Table 2 for the comparison between AD and MCI and in Supplementary Table S1 for the comparison between AD and CN. The estimated typical changes of drug prescription in time are plotted in Figure 1.

Comparing AD with MCI patients, we evidenced that in the 15-year period preceding diagnosis,

- future AD patients were treated significantly more than MCI patients for anti-depressant (odd-ratio (OR) multiplied by 3.18), antipsychotic (x 3.17) and already anti dementia drugs (x 4.17), and significantly less for anti-inflammatory/anti-rheumatic (x 0.62) and tension reducing (x 0.82) drugs,
- all studied drugs but anti-inflammatory/anti-rheumatic drugs and anti-herpetic were more and more prescribed with age, and the odd-ratio increased significantly more in the future AD patients than in the MCI patients or controls (OR for anti-depressant is increased by 26% each year for AD patients, and only by 9% for MCI patients). Prescription of anti-inflammatory/anti-rheumatic drugs decreased more in the AD group than in the MCI or control group.

At the time of diagnosis, the prescription of all types of drugs but anti-herpetic showed a significant change with an expected increase in dementia drugs (OR multiplied by 7.64) but also in antipsychotic (x 3.03) and antidepressant (x 1.92). By contrast, other drugs showed a significant decrease in prescription: benzodiazepine, glucose lowering, tension reducing, and even anti-inflammatory/anti-rheumatic drugs that were already less prescribed in these patients than in the MCI groups before the diagnosis.

In the 10 years following diagnosis,

- prescriptions of anti-dementia (OR x 0.76 per year), antidepressant (OR x 0.86 per year), and benzodiazepine (OR x 0.93 per year) strongly decreased, while benzodiazepines remained stable (OR x 1.03 per year). After 5 years, frequency of prescription of these drugs came back at the same level they had before diagnosis.
- tension reducing (OR x 0,88 per year) and glucose lowering (OR x 0,94 per year) drugs were also less and less prescribed as the disease progresses, whereas they tended to be more prescribed in the years preceding the diagnosis.

4 Discussion

In this large sample of the general population seen in general practitioner offices in the last 25 years in France we evidenced different prescription practices in patients with AD diagnosis as compared to patients with stable MCI and normal cognition. This longitudinal case-control study also allows us to give complementary insights into risk-factors for AD and the possibility to design automatic methods to identify patients at-risk to develop dementia in the clinical routine.

4.1 Management practices

This analysis showed a steady increase in the prescription of most neurological drugs with age at least ten years before the diagnosis of the disease. This result seems surprising, especially for anti-dementia drugs. It could be explained by certain medical practices that tend to delay as much as possible the disclosure of the diagnosis of AD to the patient. For instance, the average reported MMSE in a subsample of 705 patients was 20.5 (standard deviation 4.8) in the 5 to 2 years prior to AD diagnosis which is lower than that usually used for inclusion in today's clinical trials with "disease modifying drugs".

This explanation is all the more credible since the time of diagnosis was associated with radical changes in the patient's care. The management of psychiatric symptoms becomes predominant (with the notable exception of benzodiazepines), and the treatment of other co-morbidities (such as diabetes, hypertension or inflammatory/rhumatologic diseases) becomes second priority. The spectacular increase in psychotropic prescription in AD patients at time of diagnosis is expected for antidementia drugs, but is much more surprising for antipsychotics which use is advised against by French and European healthcare authorities since 2008 [9]. This is probably due to the fact that the THIN aggregates data from the last 25 years and it will be a particularly useful tool to monitor this practice, which can be impacted by public health policies [10], in the coming years.

In the years following diagnosis, all treatments were less and less prescribed, either because of a probable lack of perceived efficacy of the treatments, because of side effects or both. This decrease in almost all drug categories probably reflects the gradual changes induced by the

autonomy loss over the course of AD. The general practitioners tend to simplify the therapeutic procedures as much as possible for these patients, especially in institutions [11]. The decrease in antidementia drugs probably relates to the limited magnitude of effect [12,13] which can sometimes be disappointing for patients and their care giver, and lead to treatment discontinuation. This decreasing slope of prescription after AD diagnosis seems opposed to the findings of a recent observational study of prescription changes following nursing home admission [14]. However, our study does not indicate if patients were institutionalized or not which explains part of the discrepancy. One should also note that despite this gradual post-diagnosis prescription decrease, the frequency of psychotropic drugs remained higher in AD patients than in the two control groups as already reported [15].

4.2 Relation with known risk factors and co-morbidities of AD

The most dramatic differences were evidenced for psychotropic drugs. There was a gradual increase in the prescription of antidepressant, antipsychotic, and antidementia drugs in the 15 years preceding diagnosis. Interestingly, the probability of being treated by one of these drugs was already superior to that of CN 15 years before diagnosis while it was inferior to that of MCI until 10 to 5 years before AD diagnosis and superior afterwards. As in any case-control study we can only hypothesize about such findings. Some authors have proposed that differences evidenced 15 years before AD diagnosis are indeed directional in the sense that it is hardly plausible that AD is already clinically relevant at this point to justify a psychotropic treatment [16]. However, our prescription probability curves are really reminiscent of those described by Amieva et al. [17] showing a cognitive decline up to 16 years before the diagnosis of dementia in highly educated individuals in the PAQUID cohort. This could indicate that subtle changes, related to AD brain lesions occurring up to 30 years before diagnosis [18] would be recognized as psychiatric symptoms and treated as such. An argument in favor of this hypothesis is the prescription probability curve of antidementia drugs compared to that of the CN group. We see that the two curves diverge around 8 years before the diagnosis. This implies that the general practitioners detect subtle cognitive changes in some patients, years before they later decline to the point of AD dementia. This pre-AD diagnosis period of 5 to 10 years exactly matches the duration of the prodromal phase of the disease estimated recently in a large, multicohort study by Vermunt et al. [19]. This means that it is in fact possible to diagnose AD much earlier which would help in secondary prevention trials. Nowadays, the frequency of patients with early stage AD diagnosis in France is quite low for many reasons, including the low referral by general practitioners to memory clinic specialists [20].

We studied anti-herpetic treatment prescription as a proxy of infection by herpes simplex virus type 1 (HSV-1) [21]. HSV-1 is indeed a neurotropic virus that is highly prevalent in the aged population. Both genomic and proteomic studies revealed an HSV-1 enrichment in AD brains. Epidemiological data have repeatedly confirmed the link between HSV-1 and AD (e.g. [22]). In vitro

and in vivo, HSV-1 favors Aß production as well as increased phosphorylation of Tau in neurons [23–25].

We did not evidence in this study any difference between patients who at some point received an AD diagnosis compared to the CN or MCI groups that would support these claims. Importantly, the frequency of anti-herpetic drugs is low in our three groups which could mean that many patients with recurring herpetic manifestations auto-medicate in the French Healthcare system. Such auto-medication is not accounted for in this study and might explain this lack of evidence.

Midlife vascular risk factors [26], have been identified as dementia risk factors. In our study, AD patients were more frequently treated with tension reducing drugs prior to diagnosis as compared to CN but less than MCI. This can be easily explained as MCI patients are probably affected by vascular neurocognitive disorders instead of AD.

Anti-inflammatory and antirheumatic drugs were more frequently prescribed in AD patients before diagnosis as compared to the prescription frequency in the CN group but less than in the MCI group. The relationship between systemic inflammation and AD has been explored thoroughly in the last two decades [27] and recent findings support a role for peripheral inflammation as early as the prodromal stage of AD and dementia with Lewy Bodies [28]. Our finding suggests that this inflammation might be earlier still, thus concurring with another recent study showing that neuroinflammation predates amyloid deposition in the brain of patients with prodromal AD [29]. At the time of diagnosis, the prescription frequency of this type of drugs fell below that of stable MCI and CN groups and continues to decrease afterwards. This is probably due to the rate of adverse events with non-steroidal anti-inflammatory (NSAID) drugs [30] especially in patients with cognitive decline who may experience treatment observance difficulties. Finally, the fact that the efficacy of aspirin, steroid and NSAIDs (traditional NSAIDs and selective cyclooxygenase-2 inhibitors) is not proven and thus not recommended for the treatment of AD [31] probably accounts for the findings after AD diagnosis in our study.

4.3 Strengths and limitations of the study

The use of a large sample of patients, representative of the general population in France assessed with the same standardized electronic clinical records software, is the main strength of our study. Another strength lies in the use of three groups rather than two. In most populational studies a group of patients with AD is compared with a control group[22,32,33]. Such a dichotomy does not consider the complexity of AD. Prior to dementia, stages of preclinical and prodromal AD (or MCI due to AD) have been described [34–36]. These stages may be difficult to diagnose. Roughly 50% of patients with MCI have a genuine AD process [37]. Using a stable MCI control group allowed us to distinguish “chronic conditions affecting cognition” (such as lasting psychiatric conditions like anxiety of recurring depression, learning disability, traumatic brain injuries) from neurodegenerative disorders leading to dementia. Finally, the long period of

follow-up is particularly well suited for the study of such a chronic disease as AD spans decades of life [19].

As in all large scale populational studies, the diagnosis of AD remains however based mostly on its classical, mostly clinical criteria and have not systematically been validated in expert memory clinics with up-to-date biomarkers. However, the relative lack of precision of data is likely to be compensated by the large sample size which allows to draw general conclusions. Finally, the retrospective case control studies do not permit to draw causality inferences from their findings. As previously discussed, the over prescription of antidepressant in the AD group 15 years before diagnosis could be the cause or consequence (and maybe even both) of AD later in life. Only intervention studies and the longitudinal follow-up of patients for decades may inform on the directionality of the observed associations.

5 Conclusion

Longitudinal study of large databases of medical records provides new insights into medical practices in a given country, in real life and over long periods of time. It provides here for the first time a snapshot of medical practices for the management of Alzheimer's disease in France over the period 1996-2019. In particular, we have been able to highlight the profound changes in the care of patients more than ten years before the diagnosis of Alzheimer's disease, and the impact of the disclosure of this diagnosis on the care of patients, not only for neurological and psychiatric disorders, but also for other co-morbidities.

This type of study therefore seems essential to inform policy makers, in particular in the public health domain, about medical practices to help them define effective health policies, and in turn to study the consequences of these health policies on medical practices. It is interesting to note that the data used for this study correspond to the period of implementation in France of the Alzheimer's plan (2008-2012) and the neurodegenerative diseases plan (2014-2019). The study presented here will therefore provide an interesting basis of comparison for analyzing possible changes in medical practices after the delisting of acetylcholinesterase inhibitors in France on August 1, 2018.

Therefore, such large standardized routinely sustained databases will certainly prove to be very valuable tools to design, implement and evaluate public health policies in the future.

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Figure legend

Figure 1: Longitudinal changes in the probability of being treated for one of the eight considered drugs for a typical patient developing AD (red), with mild cognitive impairments (yellow) and without known mental health problems (green)

Tables

Table 1 Cohort description. Data are mean (standard deviation). Significant differences between the 2 matched cohorts for each matching are indicated in the CN and MCI columns. Significant differences between the AD group matched with the MCI group, and the AD group matched with the CN group are indicated in the AD column of the AD-MCI matching. * = significant at the 0.05 level; ** = significant at the 0.01 level; *** = significant at the 0.001 level (two-sided t-test with Bonferroni correction for multiple comparison)

	AD-CN matching		AD-MCI matching	
	AD	CN	AD	MCI
Number of patients	11067	11067	10750	10750
Age group (%) 21-50 51-75 >75	 1.0 52.8 46.2	 0.9 51.0 48.1	 2.6 *** 53.5 43.9 *	 2.5 52.0 45.6
Gender (%) Male Female	 39.5 60.5	 39.5 60.5	 37.1 ** 62.9	 37.1 62.9
Number of visits / patient	54.43 (49.49)	31.06 (33.53) ***	63.80 (58.38) ***	56.33 (55.27) ***
Number of days between 2 visits	101.85 (164.41)	223.24 (321.61) ***	100.44 (163.98)	115.72 (210.60) ***
Follow-up interval in years	6.86 (4.47)	6.64 (4.32) **	8.44 (5.58) ***	8.00 (5.83) ***

Table 2 Estimated coefficients of the mixed-effects model for the AD vs MCI analysis. Data are odd ratios, ratio of odd-ratios, annual rate of change in odd-ratios and ratios thereof (Standard deviations) * = significant at the 0.05 level; ** = significant at the 0.01 level; *** = significant at the 0.001 level (Bonferroni correction for multiple comparison was applied). AD: Alzheimer's disease, MCI: mild cognitive impairment

	Odd-ratios			**Annual rate of change in odd-ratios**		
	Odd-ratio for MCI patients at 80 yrs old	**ratio of AD to MCI odd-ratios just before diagnosis**	**ratio of AD pre-diagnosis to post-diagnosis odd-ratio**	**annual rate of change in odd-ratio for MCI patients**	**ratio of annual rate of change of AD to MCI patients before diagnosis**	**ratio of annual rate of change of AD pre-diagnosis to post-diagnosis**
Anti herpetic	1.19e-04 (1.9e-08)***	0.827 (0.09)	0.746 (0.079)	1.01 (0.0075)	0.985 (0.013)	0.979 (0.036)
Anti inflammatory and antirheumatic	0.156 (0.032)***	0.621 (0.013)***	0.581 (0.011)***	0.932 (0.0016)***	0.982 (0.0031)***	0.987 (0.0093)
Antidepressant	0.0361 (0.0017)***	3.18 (0.53)***	1.92 (0.11)***	1.09 (0.0031)***	1.16 (0.0062)***	0.688 (0.0042)***
Antipsychotic	1.3e-04 (2.2e-08)***	3.17 (1)***	3.03 (0.47)***	1.03 (0.0071)**	1.15 (0.014)***	0.87 (0.011)***
Benzodiazepine	0.0878 (0.01)***	0.984 (0.05)	0.894 (0.025)**	1 (0.0023)	1.02 (0.0039)***	0.919 (0.0074)***
Dementia drugs	0.0625 (0.0051)***	4.17 (0.73)***	7.64 (1.6)***	1.01 (0.0025)***	1.51 (0.013)***	0.499 (0.0022)***
Glucose lowering	3.26e-05 (1.4e-09)***	1.23 (0.2)	0.776 (0.037)***	1.17 (0.0064)***	1.04 (0.0085)***	0.776 (0.0098)***
Tension reducing	1.43 (2.7)**	0.825 (0.039)*	0.833 (0.019)***	1.15 (0.0029)***	1.03 (0.0039)***	0.75 (0.0046)***