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RESEARCH ARTICLE

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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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 patients' medical history that precede and follow 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 15 years before diagnosis and 10 years after.

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

Discussion: Pre-diagnosis differences 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, priority being 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. This study therefore provides new insights into the medical practices for management of AD.

KEYWORDS
Alzheimer's disease, comorbidities, individual matching, longitudinal analysis, management practices, medical records, mild cognitive impairment, patient care, prescriptions, risk factors

1 | INTRODUCTION

With 35.6 million people living with dementia worldwide in 2010[1], dementia is a major public health issue. It is in an important economic burden for society, with an estimated annual cost of €32,507 per person living with dementia in Europe.[2] Alzheimer's disease (AD) is the main cause of dementia, representing 60% to 80% of cases.[3]

AD is very slow and progressive, with no clearly identified starting point, and its effects on cognition and behavior partially overlap with those of natural aging. As a result, general practitioners struggle to diagnose AD with certainty at an early stage[4] and do not refer at-risk patients to memory clinic specialists[5], resulting in a late diagnosis. When AD is identified, general practitioners also tend to delay as much as possible its disclosure to the patient.[6,7] Disclosure of diagnosis is made especially difficult by the lack of curative therapeutic options. Clinical trials evaluating drugs against AD have failed repeatedly over the last decades, and only four symptomatic drugs are currently on the market in Europe and the United States. And yet, these drugs have been delisted in France since 2018 for their "lack of efficacy."

Late diagnosis, delayed disclosure, and lack of treatment make management of AD unique compared to other therapeutic areas. The management of AD-related but non-diagnosed symptoms can be challenging. At the same time, caregivers must often handle the appearance or aggravation of multiple comorbidities. Combined with the economic burden AD represents, these issues call for efficient public health policies, which need to be informed by a good understanding of current medical practices. We propose to study these medical practices using the proxy of prescriptions by general practitioners.

Most epidemiological studies performed on clinical routine data focus on the identification of risk factors[8–11] without targeting specific disease stages, often leaving aside the pre-diagnosis stage that is characteristic of 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.[12–15] We believe it is also important and urgent to study how patients developing AD are treated across all disease stages, from the earliest to the latest.

To do so, we exploit a large longitudinal database of medical records to understand how prescription practices change 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, and to show how patients' care could be deeply modified if disease-modifying drugs were to be marketed in the coming years.

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed for articles studying prescription practice for Alzheimer's disease (AD) using medical records. Identified articles focus on a specific comorbidity or on anti-dementia treatment solely. None consider patients' medical history in a longitudinal fashion.
2. **Interpretation**: This study provides for the first time a snapshot of medical practices for the management of AD in a typical European country over the period 1996 to 2019, based on the analysis of a longitudinal databases of medical records from a representative panel of general practitioners.
3. **Future directions**: This study shows that such longitudinal analyses of real-world data are essential to inform health policy makers about medical practices and to help them define effective health policies. It could provide an interesting basis of comparison for analyzing the consequences on medical practices of health policies, such as the delisting of acetylcholinesterase inhibitors in France in August 2018, or of potential future disease-modifying drugs.

2 | MATERIALS AND METHODS

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 health-care management software. We used the data coming from an observation of 2000 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 are anonymized at source since 1994 and are 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 to 2019.

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

- AD group: all patients diagnosed with AD dementia with international classification of diseases 10th edition (ICD-10) 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 (mild cognitive impairment) group: all patients diagnosed with a memory impairment (ICD-10 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

TABLE 1 Cohort description

	AD–CN matching		AD–MCI matching	
	AD	CN	AD	MCI
Number of patients	11067	11067	10750	10750
Age group (%)				
21–50	1.0	0.9	2.6 ***	2.5
51–75	52.8	51.0	53.5	52.0
>75	46.2	48.1	43.9 *	45.6
Sex (%)				
Male	39.5	39.5	37.1 **	37.1
Female	60.5	60.5	62.9	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 two 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) ***

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; MCI, mild cognitive impairment.
Notes: Data are mean (standard deviation). Significant differences between the two 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).

system (G30–G32), demyelinating diseases of the central nervous system (G35–G37), epilepsy (G40–G42), and cerebrovascular disorders (G45–G46). Note that these patients therefore never have an AD diagnosis in the database.

- CN (cognitively normal) group: patients with no ICD-10 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 1 year). We identified 34,782 patients in the THIN database, whose characteristics are described in Table 1.

We studied prescriptions as a proxy of comorbidities and patient care. The Anatomical Therapeutic Chemical (ATC) Classification System was used to identify prescribed drugs. We selected the following drug categories with their ATC codes based on a literature review of AD risk factors and comorbidities:

- Glucose-lowering drugs (A10A: insulins and analogues, A10B: blood glucose lowering drugs, excluding insulins)
- Blood pressure–reducing drugs (C02: antihypertensives, C03: diuretics, C07: beta-blocking agents, C08: calcium channel blockers, C09: agents acting on the renin–angiotensin system)
- Anti-inflammatory and antirheumatic drugs (M01: anti-inflammatory and antirheumatic products)
- Antipsychotic drugs (N05A: antipsychotics)
- Benzodiazepine (N05BA: anxiolitics—benzodiazepine derivatives, N05CD: hypnotics and sedatives—benzodiazepine derivatives, N05CF: hypnotics and sedatives—benzodiazepine related drugs)
- Antidepressants (N06A: antidepressants)
- Antidementia drugs (N06D: anti-dementia drugs)
- Antiherpetic drugs (J05AB01: aciclovir, J05AB09: famciclovir, J05AB11: valaciclovir)

We divided each patient's follow-up period (from first to last visit) in 6-month periods and measured if a patient had a prescription for each drug category at least once within each period.

2.2 | Methods

2.2.1 | Longitudinal analysis

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 versus MCI and AD versus 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 supporting information for details).

TABLE 2 Estimated coefficients of the mixed-effects model for the AD versus MCI analysis

	OR			Annual rate of change in OR		
	OR for MCI patients at 80 years old	Ratio of AD to MCI ORs just before diagnosis	Ratio of AD pre-diagnosis to post-diagnosis OR	Annual rate of change in OR 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
Antiherpetic	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)
Antidepressants	0.0361 (0.0017)***	3.18 (0.53)***	1.92 (0.11)***	1.09 (0.0031)***	1.16 (0.0062)***	0.688 (0.0042)***
Antipsychotics	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)***
Antidementia	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)***
Blood pressure–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)***

Abbreviations: AD, Alzheimer's disease, MCI, mild cognitive impairment; OR, odds ratio.
Notes: Data are OR, ratio of OR, annual rate of change in OR 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).

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%.

2.2.2 | Complementary analysis for the AD group

We performed a complementary analysis for the drug categories having a different prescription pattern in the AD group and CN group. This complementary analysis was performed on the AD group matched with the CN group for AD patients with at least one prescription from the drug category. The proportion of AD patients with no prescription in the AD group is also given. We computed the longest consecutive use, as the longest period of consecutive prescriptions, considering that each prescription was valid for a year (2 prescription 1 year apart therefore correspond to 2 years of consecutive use). We computed the time interval between the first prescription and AD diagnosis in each group (negative if the first prescription was after AD diagnosis), as well as the proportion of patients having their first prescription before AD diagnosis. We considered that we could only know the date of first prescription for patients with no prescription from the studied drug category during their first year of follow-up, so only these patients were considered for this computation. Last, to study multiple therapy, we computed for each visit the number of drugs from distinct groups prescribed in the studied drug category, keeping the highest number for each patient. As a general rule, level 3 ATC codes were considered distinct groups. Additional rules, depending on drug categories, are described in supporting information. Note that multiple therapy analysis was not applied to benzodiazepines, which only included one chemical subgroup.

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 Table S1 in supporting information for the comparison between AD and CN. The estimated typical changes of drug prescription in time are plotted in Figure 1.

Differences in prescription patterns can first be observed in the pre-diagnosis phase, that is, comparing patients of the AD group before their diagnosis to the two control groups. Future AD patients were treated significantly more than MCI patients with antidepressants (odds ratio [OR] multiplied by 3.18), antipsychotic drugs (x 3.17), and antidementia drugs (x 4.17), and significantly less for anti-inflammatory/antirheumatic (x 0.62) and blood pressure–reducing (x 0.82) drugs. All studied drugs except anti-inflammatory/antirheumatic drugs and antiherpetics were more frequently prescribed with age in all groups, and the OR increased significantly more in the future AD patients than in the MCI or CN patients (OR for antidepressants is increased by 26% each year for future AD patients, and only by 9% for MCI patients). Prescription of anti-inflammatory/antirheumatic drugs decreased more in the AD group than in the MCI or CN group.

At the time of diagnosis, the prescription of all types of drugs but antiherpetics showed a significant change with an expected increase in dementia drugs (OR multiplied by 7.64) but also in antipsychotic drugs (x 3.03) and antidepressants (x 1.92). By contrast, other drugs showed a significant decrease in prescription: benzodiazepines, glucose-lowering, blood pressure–reducing, and even anti-inflammatory/antirheumatic drugs that were already less prescribed in future AD patients than in the MCI groups in the pre-diagnosis phase.

In the 10 years after diagnosis, prescriptions of anti-dementia drugs and antidepressant drugs strongly decreased (Figure 1), reaching their pre-diagnosis level 5 years after diagnosis. Blood pressure–reducing

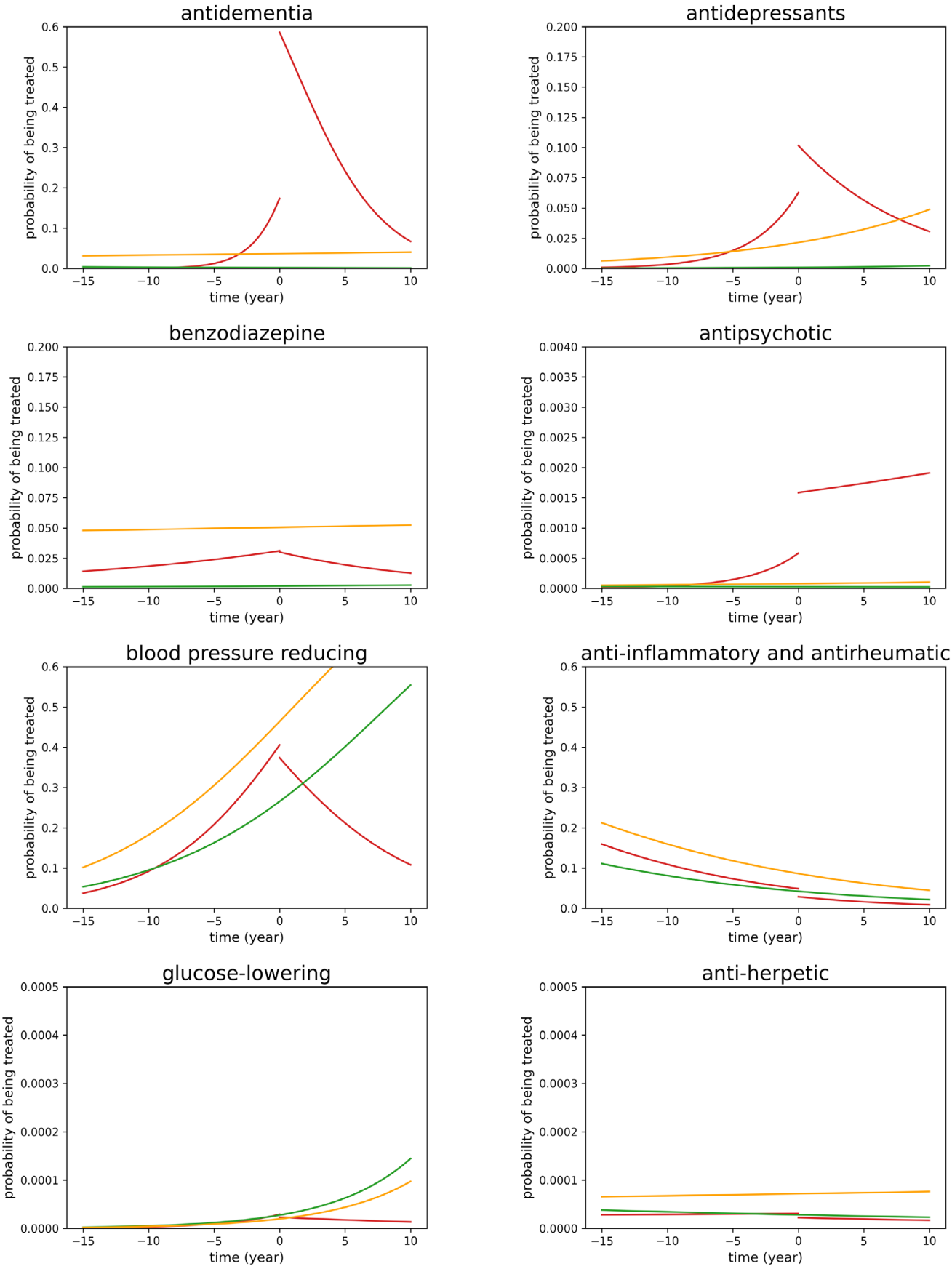

FIGURE 1 Longitudinal changes in the probability of being treated for one of the eight considered drugs for a typical patient developing Alzheimer's disease (red), with mild cognitive impairments (yellow), and without known mental health problems (green)

TABLE 3 Complementary analysis among subjects of the AD group with at least one prescription of the studied drug category

	Proportion of AD patients with at least one prescription	Longest consecutive use mean (SD)	Time from first prescription to AD diagnosis mean (SD)	Proportion of first prescriptions before AD diagnosis	Proportion of patients being prescribed the given number of drugs on the same visit		
					1	2	3 or more
Anti-inflammatory and antirheumatic	48.86%	2.21 (2.02)	3.48 (3.80)	83.54%	99.60%	0.40%	0.00%
Antidepressants	49.77%	2.94 (2.37)	1.39 (2.93)	61.19%	93.59%	6.32%	0.09%
Antipsychotics	21.39%	1.84 (1.40)	-0.22 (2.57)	32.65%	94.45%	5.10%	0.45%
Benzodiazepine	48.24%	3.18 (2.88)	1.92 (3.67)	64.76%	NA	NA	NA
Antidementia	67.55%	2.65 (1.95)	0.47 (1.79)	28.77%	81.86%	18.14%	0.00%
Glucose-lowering	14.18%	5.06 (3.67)	2.36 (3.76)	71.57%	53.07%	30.94%	16.00%
Blood pressure–reducing	64.57%	5.33 (3.92)	2.33 (3.41)	71.81%	34.82%	32.92%	32.26%

Abbreviations: AD, Alzheimer's disease; SD, standard deviation.

and glucose-lowering drugs were also less and less prescribed as the disease progressed (Figure 1), whereas they tended to be more prescribed in the years preceding the diagnosis. The change in slope induced by AD diagnosis was significant for most drug categories, except for antiherpetic drugs (ratio of 0.98) and anti-inflammatory and antirheumatic (ratio of 0.99) drugs, for which the rate of change in OR was not significantly different before and after AD diagnosis.

Table 3 describes, for each drug category and in the AD group, the proportion of patients with at least one prescription; the length of consecutive use; time from first prescription to AD diagnosis; proportion of first prescriptions before AD diagnosis; and proportion of patients being prescribed one, two, or at least three drugs for the same category at the same visit. Antipsychotic drugs have the shortest consecutive prescription time, 1.84 years on average, and are prescribed the latest, on average 0.22 years after AD diagnosis. Anti-inflammatory and antirheumatic drugs are prescribed the earliest, on average 3.48 years before AD diagnosis. Blood pressure–reducing and glucose-lowering drugs are mostly prescribed before AD diagnosis (for 71.81% and 71.57% of patients, respectively) and for long periods of time (5.33 and 5.06 years on average, respectively). Multiple therapy is only observed in large proportion for these prescriptions (in 65.18% of patients for blood pressure–reducing drugs and in 46.97% of patients for glucose-lowering drugs).

4 | DISCUSSION

In this large sample of the general population seen in general practitioner offices in the last 25 years in France, we discovered different prescription practices in patients with AD diagnosis compared to patients with stable MCI and normal cognition. This longitudinal case-control study also allows us to give complementary insights into risk factors and comorbidities for AD. The identification of prescription patterns characteristic of AD several years before diagnosis can facilitate further research aiming to identify patients at-risk to develop dementia in clinical routine.

4.1 | Management practices

This analysis showed a steady increase in the prescription of most neurological drugs with age at least 10 years before the diagnosis of the disease. This result seems surprising, especially for antidementia drugs because systematic reviews show no benefit in prescribing them at such an early stage.[16] It could be explained by the inability of general practitioners to diagnose AD with certainty at an early stage[4], the tendency to delay as much as possible the disclosure of the diagnosis of AD to the patient,[6,7] and the low referral by general practitioners to memory clinic specialists.[5] Several studies have also identified issues regarding the use of ICD-10 for dementia diagnosis, because of the ambiguous phrasing of the corresponding labels[17], leading to a lower rate of diagnosis compared to other diagnosis criteria.[18] In our study, the average reported Mini-Mental State Examination score in a subsample of 705 patients was 20.5 (standard deviation 4.8) in the 2 to 5 years prior to AD diagnosis. It is lower than the cutoff usually used for inclusion in today's clinical trials with "disease-modifying drugs," ranging from 22[19] to 25.[20]

At the time of diagnosis, radical changes in the patient's care were observed. The management of psychiatric symptoms becomes predominant (with the notable exception of benzodiazepines), and the treatment of other comorbidities (such as diabetes, hypertension, or inflammatory/rheumatologic diseases) becomes second priority. The increase in psychotropic prescription in AD patients at time of diagnosis is expected for antidementia drugs, but is much more surprising for antipsychotics—as use of these has been advised against by French and European health-care authorities since 2008.[21] This is probably because 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 [22], in the coming years.

In the years after diagnosis, all drugs were less and less prescribed, either because of a probable lack of perceived efficacy of the drugs, 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. General practitioners tend to simplify the

therapeutic procedures as much as possible for these patients, especially in institutions.[23] The decrease in antidementia drugs probably relates to the limited magnitude of effect,[24,25] which can sometimes be disappointing for patients and their care givers, and leads to treatment discontinuation. This decreasing slope of prescription after AD diagnosis seems opposed to the findings of a recent observational study of prescription changes after nursing home admission.[26] However, our study does not indicate if patients were institutionalized or not, which explains part of the discrepancy. 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.[27]

4.2 | Relation with known risk factors and comorbidities of AD

The most dramatic differences were seen for psychotropic drugs. There was a gradual increase in the prescription of antidepressants, antipsychotic drugs, 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. It was inferior to that of MCI until 10 to 5 years before AD diagnosis and superior afterward. 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, as it is hardly plausible that AD is already clinically relevant at this point to justify a psychotropic treatment.[28] However, our prescription probability curves are reminiscent of those described by Amieva et al.[29] 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,[30] would be recognized as psychiatric symptoms and treated as such. De Oliveira et al.[31] also show that neuropsychiatric symptoms are more common as impairment increases, leading to an increase in antipsychotic drugs. In our study, antipsychotic drugs are prescribed less frequently (in only 21.39% of AD patients) and later in the disease process (0.22 years after AD diagnosis on average) than other psychotropic drugs, and for short periods of time (1.84 years on average), following recommendations by the French health authorities to keep the treatment duration as brief as possible and to prefer non-drug alternatives.[32] In comparison, antidepressant drugs were prescribed frequently (to 49.77% of AD patients) and early (before AD diagnosis for 61.19% of patients).

Another argument suggesting early symptoms is the prescription probability curve of antidementia drugs compared to that of the CN group. We see that the two curves diverge ≈8 years before the diagnosis. Table 3 also shows that 28.77% of first antidementia drug prescriptions happen before AD diagnosis in the AD group. 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.[33] This early detection of subtle cognitive changes by general practitioners means that it is possible to diagnose AD much earlier, which would help in secondary prevention trials.

We studied antiherpetic drug prescription as a proxy of infection by herpes simplex virus type 1 (HSV-1).[34] 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., Tzeng et al.[35]). In vitro and in vivo, HSV-1 favors amyloid beta production as well as increased phosphorylation of tau in neurons.[36–38]

We did not find, 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 antiherpetic drugs is low in our three groups. It could mean that many patients with recurring herpetic manifestations auto-medicate in the French health-care system. Such auto-medication is not accounted for in this study and might explain this lack of evidence.

Midlife vascular risk factors[39] have been identified as dementia risk factors. In our study, blood pressure–reducing drugs were prescribed before AD diagnosis in 71.81% of cases, and for long periods of time (5.33 years on average). AD patients were more frequently treated with blood pressure–reducing drugs prior to diagnosis compared to CN but less than MCI. MCI patients are probably affected by vascular neurocognitive disorders instead of AD.

Glucose-lowering drugs were also prescribed for long periods of time (5.06 years on average), starting before AD diagnosis in 71.57% of cases. As for blood pressure–reducing drugs, prescriptions were less frequent after AD diagnosis, which may reflect simplification of therapeutic procedures. Kidney failure was reported for 2.47% of AD patients, which is significantly higher than for CN subjects (1.90%, $P = .004$). Given that chronic kidney disease can lead to improved glucose levels[40], the decrease in glucose-lowering drugs after AD diagnosis might also be explained by a worsening in renal function.

Anti-inflammatory and antirheumatic drugs were more frequently prescribed in AD patients before diagnosis compared to the prescription frequency in the CN group but less than in the MCI group. They were prescribed before AD diagnosis for 83.54% of AD patients, on average 3.48 years before diagnosis, which is the earliest in all studied categories. The relationship between systemic inflammation and AD has been explored thoroughly in the last two decades.[41] Recent findings support a role for peripheral inflammation as early as the prodromal stage of AD and dementia with Lewy bodies.[42] Our finding suggests that this inflammation might be earlier still. It concurs with another recent study showing that neuroinflammation predates amyloid deposition in the brain of patients with prodromal AD.[43] At the time of diagnosis, the prescription frequency of this type of drug fell below that of stable MCI and CN groups and continues to decrease afterward. This is probably due to the rate of adverse events with nonsteroidal anti-inflammatory (NSAID) drugs,[44] especially in patients with cognitive decline who may experience treatment observance difficulties. Finally, the fact that the efficacy of aspirin, steroids, and NSAIDs (traditional NSAIDs and selective cyclooxygenase-2 inhibitors) is not proven and thus not recommended for the treatment of AD [45] probably accounts for the findings after AD diagnosis in our study.

Multiple therapy was mostly observed for blood pressure–reducing and glucose-lowering drugs. This is expected, as associations of different pharmaceutical classes are frequently recommended in these two diseases.

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 population studies, a group of patients with AD is compared to a control group.[35,46,47] 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.[48–50] These stages may be difficult to diagnose. Roughly 50% of patients with MCI have a genuine AD process.[51] 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, or 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.[33]

As in all large-scale populational studies, the diagnosis of AD remains, however, based mostly on its classical, mostly clinical criteria and has 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 us to draw general conclusions. Finally, the retrospective case control studies do not permit us to draw causality inferences from their findings. As previously discussed, the overprescription of antidepressants 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.

Because of its longitudinal nature, our model does not allow us to study the effect of the date of the visits, which can impact results in two ways. First, the health of the general population improves with time: several studies[52,53] have shown that AD prevalence at a given age decreases, and that cognition of the elderly is better today than it was 10 years ago.[54] Second, management practices are impacted by public health polices and recommendations that evolve with time. Another study, using a different statistical model, could allow us to study these effects and study the impact of public health policies to make further recommendations.

5 | CONCLUSION

This longitudinal study of a large database of medical records provides new insights into medical practices in France for the management of AD, in clinical routine and over a long period of time (1996–2019). In particular, we have been able to highlight the profound changes in the care of patients more than 10 years before the diagnosis of AD, 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 comorbidities. The insights we provide are essential to inform policy makers about current medical practices to help them define effective health policies, and in turn to study the consequences of these health policies on medical practices.

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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.

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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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