

Use of drug treatments for Alzheimer's disease in France: a study on a national level based on the National Alzheimer's Data Bank (Banque Nationale Alzheimer)^{†‡}

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ABSTRACT

Purpose To examine the way in which specific drug treatments for Alzheimer's disease are used and whether their use complies with clinical practice guidelines issued by the French National Authority for Health in patients with Alzheimer's disease.

Methods We analysed a cross-section of the French National Alzheimer's databank (BNA). Participants were individuals who consulted centres contributing to the BNA in 2010 and diagnosed with Alzheimer's disease and with at least one Mini Mental State Examination (MMSE) score recorded during the course of the year.

Results Of 191 919 consultations recorded in the database, 29.9% involved a diagnosis of Alzheimer's disease, and 26 809 patients had completed at least one MMSE. In 76.9% of cases, treatment was given with an anti-Alzheimer's drug. Monotherapy with an acetylcholinesterase inhibitor was prescribed for 48.3% of patients, monotherapy with memantine in 14.2% and dual therapy in 14.4% of cases. Treatment given did not comply with the guidelines in 20.7% of cases. Prescriptions not complying with the guidelines were associated with a lower mean MMSE score (13.6 vs. 18.0; $p < 0.00001$) and more cases of treatment with antidepressants (29.2% vs. 22.8%; $p < 0.00001$), anxiolytics (14.7% vs. 12.3%; $p < 0.00001$) and antipsychotics (8.7% vs. 4.9%; $p < 0.00001$).

Conclusion Four of five prescriptions for treatment with anti-Alzheimer's drugs complied with the specific drug treatment chapter of the 2008 French clinical guidelines. Prescriptions not complying with the guidelines for acetylcholinesterase inhibitors and memantine were usually issued in situations involving advanced-stage Alzheimer's disease. The BNA can provide precise information on medical practice in Alzheimer's disease and related disorders. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—Alzheimer's disease; drug use guidelines; memantine; cholinesterase inhibitors; observational study; data bank; pharmacoepidemiology

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INTRODUCTION

The various agencies worldwide responsible for marketing authorisations and for monitoring medicinal products currently allow to use two different classes of treatment for Alzheimer's disease (AD): acetylcholinesterase inhibitors and NMDA glutamate receptor antagonists. In France, these drugs are initially prescribed by a specialist (neurologist, geriatrician or psychiatrist) and are fully covered by national health insurance. The aim of treatment is not to achieve a cure but to assist

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[†]K.T., F.L.D., C.P. and P.R. conceived and designed the study. K.T., F.L.D., C.P., P.F., S.S. and P.R. analyzed the data. K.T. and J.Q. carried out the statistics. K.T. and P.R. prepared the manuscript. K.T. is guarantor.

[‡]All the data presented in the article have been anonymised. Anonymisation has been done under the conditions of the Commission Nationale de l'Informatique et des libertés (CNIL), which is responsible in France for data protection and data use with respect to the human identity, the human rights, privacy and liberties.

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in controlling the symptoms. The symptomatic efficacy of drug treatments for AD has been demonstrated in numerous randomised trials.^{1–4} Nevertheless, their effectiveness in relation to cognition is modest, and there have been few assessments of their effect over time.^{1,5} In addition, psychotropic drugs can also be useful to control behavioural and psychological symptoms of the disease.⁶ However, pharmacological treatment options, such as antipsychotics, antidepressants and anticonvulsants, need careful consideration of the benefits and limitations of each drug class. This is most particularly important for antipsychotics with widely reported side effects.⁷

In 2008, the French National Authority for Health (HAS) issued professional guidelines on the diagnosis and management of AD and related disorders.⁸ These guidelines were disseminated to prescribers by HAS Web site and several French medical associations. The application of these guidelines in practice has not yet been studied. We report here on data from the French National Alzheimer's Bank (BNA) relating to prescriptions for drugs for AD and their compliance with HAS guidelines.

METHODS

Database and population

One of the measures of the Alzheimer French National Plan 2008–2012 provides for the setting up of a nationwide system for collecting activity data and for epidemiological surveillance related to AD.^{9,10} It records data within a system specific to France, based on specialist consultations for patients with memory disorders: memory centres (CMs); memory resource and research centres (CMRRs) and private specialists (PSs).

Every time a patient visits a centre, the physician completes a patient file specifically designed for AD and related disorders [CIMA (Corpus minimum d'information Alzheimer) or minimum data set on AD], which can be filled in online using a fully Web-based application. One of the items included in the CIMA relates to the use of pharmacological treatments.

Records have been done under the conditions of the Commission Nationale Informatique et libertés (CNIL), responsible in France for data protection and use with respect to the human identity and the human rights. Each centre has its own access code, enabling it to query the national database at any time and also access its own consolidated and anonymised data.

Patients included in the cross-sectional study attended appointments at CMs, CMRRs and PSs contributing to the development of the BNA during the course of 2010 (extraction from the database, 21 March 2011). The only criterion for inclusion in this study was a

diagnosis of AD recorded in the CIMA. Patients with any other diagnosis (mixed dementia in particular) were not included. Patients taking part in medical research were also excluded because we considered that this situation could lead to other medical care than that in current clinical practice. The analysis was conducted only in centres, where the rate of zero Mini Mental State Examination (MMSE) scores did not exceed 10%. We considered that above this percentage the risk of bias was too high. As patients who attended several appointments during the year could have several CIMAs, we extracted data from the database so that each patient appears only once, keeping only the last MMSE recorded.

Recommendations

With regard to the pharmacological treatment of AD, HAS issued three guidelines:⁸

- (1) Regardless of age and the stage of the disease at the time of diagnosis (apart from the very severe stage: MMSE < 2), specific treatment should be considered, taking account of the risk-benefit ratio for the patient.
- (2) Possible prescriptions: mild stage (MMSE > 20): a cholinesterase inhibitor (donepezil, galantamine or rivastigmine); moderate stage (10 < MMSE < 20): a cholinesterase inhibitor or a glutamate receptor antagonist (memantine); and severe stage (MMSE 10): a glutamate receptor antagonist (memantine).
- (3) No arguments to support dual therapy at present.

Analysis

Anti-Alzheimer's treatments used were described according to their pharmaceutical class: acetylcholinesterase inhibitors and glutamate receptor antagonists. To measure deviations from the HAS guidelines, two types of indicator were used:

- (1) With regard to patients prescribed treatment not complying with the HAS guidelines: these include (i) the prescription of an acetylcholinesterase inhibitor although the MMSE score was less than 10; (ii) the prescription of an NMDA receptor antagonist although the MMSE score was above 20; and (iii) the prescription of dual therapy regardless of MMSE score. Patients not receiving any treatment for AD were considered as complying with the guidelines on account of possible individual contraindications.
- (2) Use of dual therapy: an acetylcholinesterase inhibitor prescribed in conjunction with an NMDA receptor antagonist and related to all patients (subgroup of the first indicator).

Frequency prescription of psychotropic agents (hypnotics, anxiolytics, antidepressants and antipsychotics) and the prescribing of psychotropic drugs are also recorded.

Categorical variables were analysed using the χ^2 test, and continuous variables, using an analysis of variance. These analyses were carried out using SPSS v11.0.1, with an alpha risk of 5%.

RESULTS

Twenty-seven CMRRs, 236 CMs and 30 PSs were contributing to the BNA. In 2010, 191 919 consultations were conducted and recorded (Figure 1). Of these, 57 333 involved a diagnosis of AD, that is, 29.9% of all consultations. A total of 2953 appointments, that is, 5.2% of the total, involved inclusions in a medical research protocols. The MMSE score was recorded for 64.9% of the remaining 53 831 appointments, that is, 34 950 appointments for which the MMSE was completed. These 34 950 appointments involved 26 809 patients, giving an average of 1.3 appointments per person (range, 1–7). The mean age was 81.3 years (± 7.6 years), and women accounted for 70.6% of the population (Table 1).

Almost three quarters of the patients attended an appointment in a CM (73.2% of patients) and 24.9% in a CMRR, and 1.9% saw a PS. The mean MMSE score was 17.1 (± 6.2). Distribution by MMSE class according to the limits set by HAS in its guidelines was as follows: 32.6% of patients with an MMSE score

Table 1. Main characteristics of the population included in the analysis ($n = 26\,809$)

Mean age	81.3 years (± 7.6)
Women	70.6% (18 917 patients)
Mean MMSE score	17.1 (± 6.2)
MMSE score class	
MMSE >20 (mild)	32.6% (8733 patients)
10 < MMSE \leq 20 (moderate)	51.8% (13 898 patients)
MMSE <10 (severe)	15.6% (4178 patients)
Psychotropic prescriptions	
Antidepressants	24.1% (6459 patients)
Anxiolytics	12.8% (3439 patients)
Antipsychotics	5.7% (1517 patients)
Hypnotics	5.3% (1408 patients)
Centre types	
Memory centres	73.2% (19 628 patients)
Memory resource and research centres	24.9% (6676 patients)
Private specialists	1.9% (505 patients)

of more than 20 (8733 patients), 51.8% with an MMSE score of between 10 and 20 (13 898 patients) and 15.6% with an MMSE score of 10 or less (4178 patients) (Table 1). The mean MMSE score was the same for patients attending all three types of consultation (CMs: 17.1, CMRRs: 17 and PSs: 17.7; $p = 0.057$). Age differed with 81.7 for CMs as compared with 80 years for CMRRs and PSs ($p < 10^{-5}$). There were more female patients in CMs (71.3%) than in CMRRs (68.7%) and PSs (64.8%) ($p < 10^{-5}$). Table 2 summarises the prescription frequency of the different pharmacological treatments according to the MMSE.

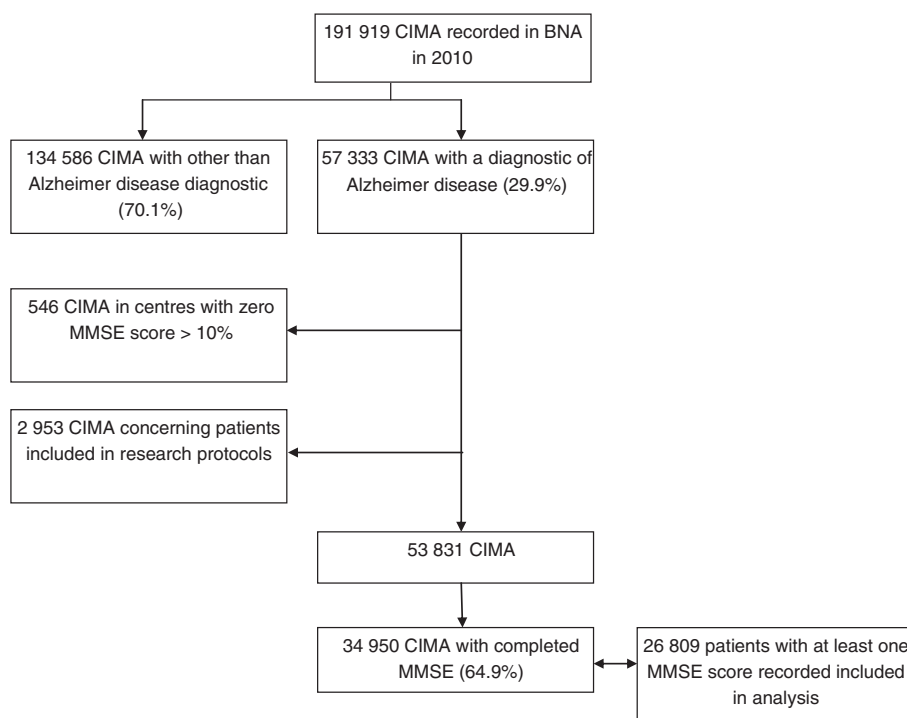


Figure 1. CIMA and patients included in the BNA analysis. CIMA (Corpus minimum d'information Alzheimer) = minimum data set submitted at the BNA at each patient appointment

Table 2. Prescription frequency according to the MMSE score

	MMSE ≤ 10 (n = 4178)	10 < MMSE ≤ 20 (n = 13 898)	MMSE > 20 (n = 8733)	Total (n = 26 809)	Significance
AChE	51.2% (2138)	63.2% (8783)	67.3% (5881)	62.7% (16802)	<10 ⁻⁵
AChE monotherapy	25.8% (1076)	46.7% (6497)	61.5% (5375)	48.3% (12948)	<10 ⁻⁵
Memantine	52.2% (2179)	31.4% (4364)	12.8% (1118)	28.6% (7661)	<10 ⁻⁵
Memantine monotherapy	26.7% (1117)	15.0% (2078)	7.0% (612)	14.2% (3807)	<10 ⁻⁵
AChE and memantine Dual therapy	25.4% (1062)	16.4% (2286)	5.8% (506)	14.4% (3854)	<10 ⁻⁵
Antidepressant	25.3% (1059)	24.3% (3377)	23.2% (2023)	24.1% (6459)	0.018
Anxiolytic	17.8% (742)	12.7% (1763)	10.7% (934)	12.8% (3439)	<10 ⁻⁵
Antipsychotic	11.4% (475)	5.9% (814)	2.6% (228)	5.7% (1517)	<10 ⁻⁵
Hypnotic	6.1% (256)	5.3% (742)	4.7% (410)	5.3% (1408)	0.002

AChE, acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine).

Use of drug treatments for AD

Treatment with an anti-Alzheimer's drug was prescribed for 76.9% of patients (Figure 2). There was no difference between male and female patients in terms

of whether they received treatment (77% for women compared with 76.7% for men; $p=0.61$). There was no age difference (81.3 years for patients who received treatment compared with 81.7 years for those who did not; $p=0.225$). The mean MMSE score was lower in

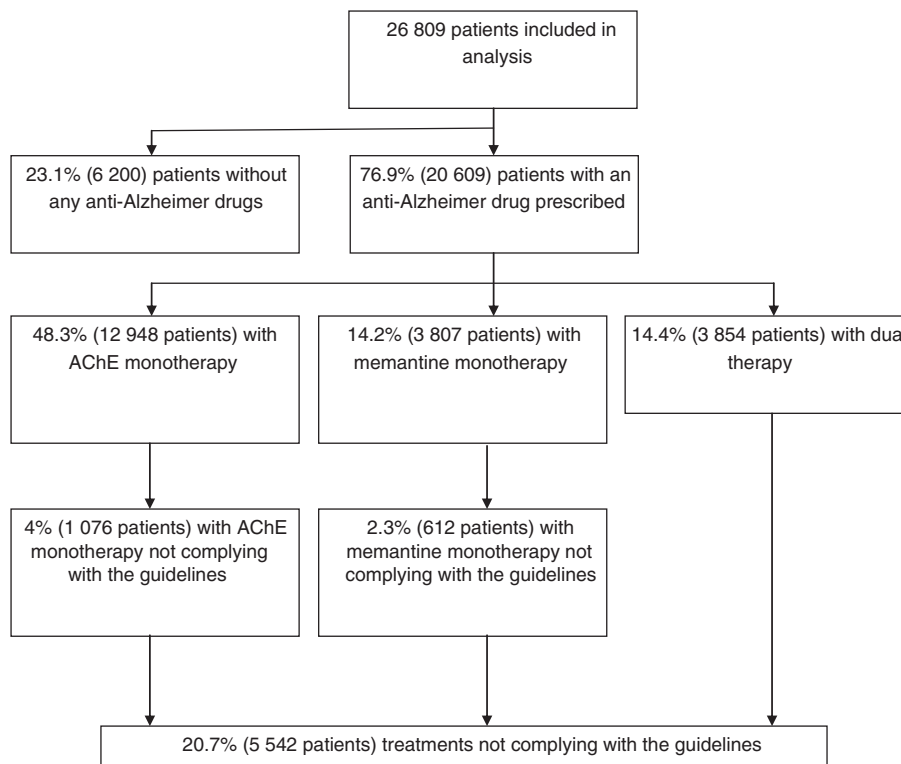


Figure 2. Drug treatments for Alzheimer's disease modalities. AChE = acetylcholinesterase inhibitors (donepezil, rivastigmine and galantamine)

the group of patients who received treatment (16.9) compared with those who did not (17.4; $p < 10^{-5}$).

Acetylcholinesterase inhibitors were prescribed for 62.7% of patients (16 802 patients), more frequently than NMDA receptor antagonists, which were administered in 28.6% of cases (7661). An acetylcholinesterase inhibitor was prescribed as monotherapy for 48.3% of patients (12 948). In relation to patients receiving a specific anti-Alzheimer's drug, monotherapy with acetylcholinesterase inhibitors accounted for 62.8% of all forms of treatment (12 948 of 20 609). Monotherapy with an NMDA receptor antagonist was prescribed for 14.2% of patients in the entire population (3807 cases) and represented 18.5% of all forms of treatment. The level at which anti-Alzheimer's treatment was prescribed was significantly lower for patients attending CMRRs than for those attending CMs and PSs (70.4% of patients attending CMRRs vs. 78.9% of patients attending CMs and 83% of patients attending PSs, $p < 10^{-5}$) (Table 3).

Dual therapy

In 14.4% of cases (3854 patients), combined treatment with an acetylcholinesterase inhibitor and memantine was prescribed. This form of treatment accounted for 18.7% of patients receiving anti-Alzheimer's treatment of any type. Dual therapy was prescribed more frequently in men than in women (15.4% vs. 14%; $p = 0.02$) and in slightly younger patients (80.5 years vs. 81.4 years; $p < 10^{-5}$). There was an upward trend for prescriptions for dual therapy for lower MMSE scores (Table 2) according to the HAS classification. The frequency of the dual therapy for patients with an MMSE score of 10 or less (25.4%) was higher than the frequency for dual therapy prescription for patients with an MMSE score of > 20 (5.8 %).

Dual therapy was prescribed for 14.3% of patients in CMs and for 13.8% of cases in CMRRs, whereas the PSs taking part prescribed dual therapy for 24.8% of patients ($p < 10^{-5}$) (Table 3). If patients attending appointments with PSs are disregarded, there is no significant difference between CMs and CMRRs ($p = 0.26$).

Treatments not complying with the guidelines

Medication not complying with the guidelines was prescribed in 20.7% of cases, essentially involving 3854 cases of dual therapy (14.4% of patients). Furthermore, monotherapy with an acetylcholinesterase inhibitor was prescribed in 1076 cases, although the MMSE score was 10 or lower (i.e., 4% of all patients and 8.3% of cases of acetylcholinesterase inhibitor monotherapy) and 612 cases of memantine monotherapy, although the MMSE score was more than 20 (i.e., 2.3% of patients and 16.1% of cases of memantine monotherapy). Patients prescribed treatment not complying with the guidelines were slightly younger and more frequently men than women (80.9 years vs. 81.4 years and 21.7% men compared with 20.2% women; $p < 10^{-5}$ and $p = 0.008$). The mean MMSE score of patients whose prescription did not comply with the guidelines was lower than that of patients whose prescription complied (13.6 vs. 18.0; $p < 10^{-5}$). Most treatments not complying with the guidelines were reported in patients with an MMSE score of 10 or lower: 51.2% of cases that could be analysed compared with 16.4% for the intermediate group (between 10 and 20) and 12.8% of cases that could be analysed in the group with an MMSE score of more than 20 ($p < 10^{-5}$). If patients consulting PSs are disregarded, there is no significant difference between CMs and CMRRs (20.6% of cases at CMs did not comply with the guidelines versus 20.1% at CMRRs; $p = 0.31$) (Table 3).

Psychotropic treatments

Antidepressants were the most widely prescribed class of psychotropic agents (24.1% of the 26 809 patients) (Table 1). Some psychotropic agents were prescribed more for patients who had a specific anti-Alzheimer's treatment. This was the case for antidepressants (26.1% of patients on an anti-Alzheimer's treatment compared with 17.5% for patients not receiving specific treatment, $p < 10^{-5}$) (Figure 3). When dual therapy was administered, a psychotropic agent was coprescribed more frequently except for hypnotic agents (4.7% for the dual therapy group vs. 5.3%; $p = 0.11$) (Figure 3b).

Table 3. Treatments modalities of CM, CMRR and PS

	CMs (236 centres, 19 628 patients)	CMRRs (27 centres, 6676 patients)	PSs (30 centres, 505 patients)	Global p and p for CMRR vs. CM
Anti-Alzheimer drugs	78.9% (15 492)	70.4% (4698)	83% (419)	$p < 10^{-5}$ / $p < 10^{-5}$
Dual therapy	14.3% (2810)	13.8% (919)	24.8% (125)	$p < 10^{-5}$ / $p = 0.26$
Treatment not complying with the guidelines	20.6% (4053)	20.1% (1340)	29.5% (149)	$p < 10^{-5}$ / $p = 0.31$

CMs, memory centres; CMMRs, memory resource and research centres; PSs, private specialists.

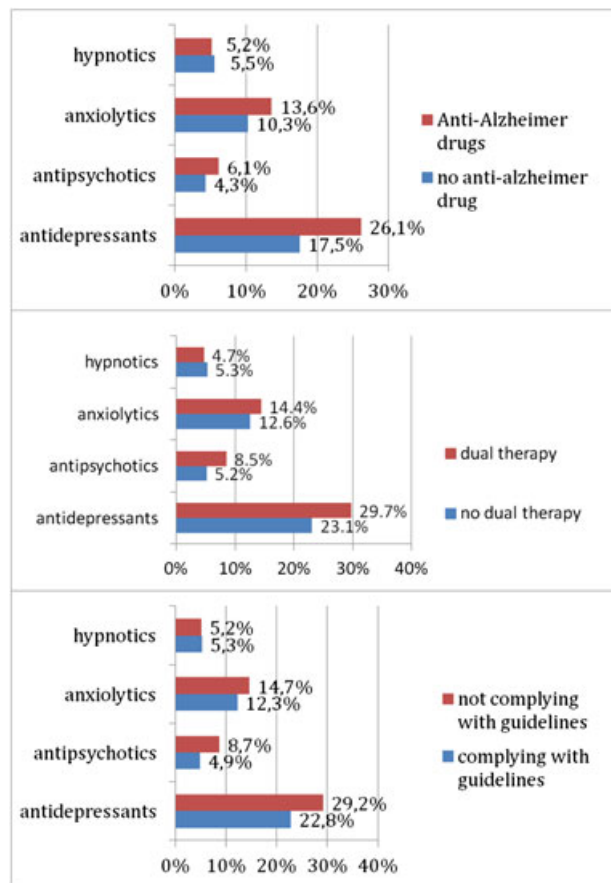


Figure 3. (a) Psychotropic coprescriptions according to the use of an anti-Alzheimer treatment. (b) Psychotropic coprescriptions according to the use of a dual anti-Alzheimer therapy. (c) Psychotropic coprescriptions according to the use of a treatment not complying with the guidelines. Significances: (a) hypnotics $p=0.25$; anxiolytics $p < 10^{-5}$; antipsychotics $p < 10^{-5}$; antidepressants $p < 10^{-5}$. (b) hypnotics $p=0.11$; anxiolytics $p=0.02$; antipsychotics $p < 10^{-5}$; antidepressants $p < 10^{-5}$. (c) hypnotics $p=0.94$; anxiolytics $p < 10^{-5}$; antipsychotics $p < 10^{-5}$; antidepressants $p < 10^{-5}$.

A psychotropic agent was coprescribed more frequently when the treatment prescribed did not comply with the guidelines, except for hypnotic agents (5.2% for the group not complying with the guidelines vs. 5.3%; $p=0.94$) (Figure 3c).

DISCUSSION

Principal findings

Good practice guidelines are drawn up to help the doctor and/or the patient to reach the correct health-related decision in a particular clinical context.¹¹ This study suggests that in France approximately 80% of patients with AD consulting in BNA-related centres receive treatment complying with the HAS guidelines. It shows that a combination of two classes of drugs is used in 14% of cases. Prescriptions for acetylcholinesterase

inhibitor monotherapy not complying with the guidelines, in other words, for patients in whom the condition is too advanced, stand at 4% and those for glutamine antagonists at 2.3% for patients in whom the condition is not sufficiently advanced. Prescriptions not complying with the guidelines are associated with a lower mean MMSE score (13.6 vs. 18.0; $p < 10^{-5}$). This study also shows that antidepressants are prescribed for 24.1% of patients with AD and that antidepressants, anxiolytics and antipsychotic agents are prescribed more often when the anti-Alzheimer's treatment does not comply with the guidelines.

Comparison with other studies

In this study, treatment for AD was prescribed for 76.9% of the population. In a parliamentary report issued in 2005, it was estimated that one Alzheimer's patient in three received specific treatment.¹² However, this estimate related to the population of patients with AD as a whole; it included people who had not yet been diagnosed and were outside the care system. According to the Thalès panel,¹³ 64.5% of patients diagnosed with AD were treated with anti-Alzheimer's drugs. In the BNA, our estimate is higher than that given in the Thalès study, but our data relate to a different population as 98.1% of the appointments were conducted at specialist centres (CMs and CMRRs).

Acetylcholinesterase inhibitors were prescribed as monotherapy in 62.8% of patients receiving an anti-Alzheimer's drug, more than for the NMDA receptor antagonist, which was administered as a monotherapy in 18.5% of cases. These proportions of use of anti-Alzheimer's drugs are comparable with existing data.^{12,14} We do not have any information on the type of acetylcholinesterase inhibitor used, but this did not affect the measurement of deviations from the guidelines because the latter deal with pharmacotherapeutic classes. Treatment with dual therapy, which was one of the areas of deviation from the guidelines, involved 14.4% of cases and 18.7% of cases involving treatment. Thus, memantine was prescribed in combination in almost one in two cases. These same proportions were reported for the prescription of memantine in combination with an acetylcholinesterase inhibitor in a French study published in 2008 in which over 5000 patients were treated with memantine.¹⁵ Although some circumstantial evidence was found on tolerability and benefits in practice for dual therapy or efficacy of acetylcholinesterase inhibitors for the more severe stages of the disease,¹⁶⁻¹⁸ these points have not been officially demonstrated.¹⁹

Interpretation and unanswered questions

Deviations were reported for 20.7% of patients, mainly relating to use of dual therapy. The MMSE score appears to be closely linked to prescriptions not complying with the guidelines and the lower the MMSE score, the more frequent the prescription for treatments not complying with the guidelines. Thus, if we consider the MMSE score as a marker of the stage of advancement, it appears that prescriptions deviating from the guidelines are issued mainly to deal with patients in whom disease progresses despite pharmacological treatment. The information available to us to explain these deviations was limited, but it can be assumed that irrespective of the MMSE score, the patients concerned were experiencing more functional problems, as suggested by a recent study.²⁰ The MMSE score is of course necessary but is not enough to serve as a treatment guide.²¹ Some groups have been able to propose other criteria to help to evaluate the therapeutic measures taken by suggesting measuring the improvement in the patient's behaviour²² or assessing the attainment of pragmatic objectives identified at the start of treatment.²³

More psychotropic agents were prescribed in association with treatments not complying with the guidelines (exception of hypnotics). It can be assumed that a clinical exacerbation may be manifested by psychiatric symptoms that are not adequately controlled either by anti-Alzheimer's drugs or by nonpharmacological measures, which leads to the use of psychotropic agents. Nevertheless, the use of psychotropic agents and antipsychotics in particular has demonstrated moderate benefits and may be accompanied by potentially serious side effects.^{6,24,25}

Patients from CMRRs were prescribed anti-Alzheimer drugs less frequently than were patients from CMs (70.4% and 78.9%). One possible explanation for this result is that as a resource and research centres CMRRs provide more alternative strategies to the patients (e.g., non-drugs-based alternative care techniques, therapeutic clinical trials).

The extent to which treatment not complying with the guidelines was prescribed did not vary significantly between CMs and CMRRs (20.6% for CMs and 20.1% for CMRRs). This finding supports the hypothesis that the use of less codified treatments links to the patient's condition, as the patient's mean MMSE scores were identical in both types of centre.

There are very little variations in the guidelines on a European level. No organisations recommend combination therapy. The National Institute of Health and Clinical Excellence recently reviewed its guidelines to include memantine, which was not previously included, and has extended indications for cholinesterase inhibitors in mild and moderate stages.²⁶ The European Federation of

Neurology Societies states that memantine should be considered alone in moderate and severe stage, and cholinesterase inhibitors can be considered at the time of diagnosis and could be clinically useful for moderate, mild and severe stages, as suggested by a recent article.^{27,28}

Strengths and limitations of the study

As far as we are aware, this is the largest study conducted on this subject.

There are also some limitations. First, at the time of the study, the BNA was not an exhaustive record of the consultation in France. As the BNA only started to function on October 2009, not all CMs were actively participating in 2010, and, in addition, independent specialists were underrepresented. Furthermore, the BNA does not include patients out of the care system.¹⁰

We kept the recording of the last MMSE carried out during the year and thus favoured representation of more serious cases. Nevertheless, this bias was limited by the low mean number of MMSEs carried out during the year, the figure of which was 1.3. We did not have any data relating to the patient's history, in particular, how long the disease had been present and the patient's clinical and paraclinical characteristics or nonpharmacological treatments. We were not able to evaluate whether any prescriptions not complying with the recommendations were justified by a particular medical context. As it was a cross-sectional study with no longitudinal data available at the time of the study, it was impossible to perform analysis concerning the duration of the prescription or the rate of discontinuation. Finally, we studied compliance with the guidelines at time point *t*, 2 years after their introduction. As the BNA did not exist before the 2010, changes to prescribing practice before and after guidelines introduction—and therefore their effectiveness—are not part of this study.

CONCLUSION

The use of anti-Alzheimer's drugs outside of guidelines for the treatment of Alzheimer's patients appears in this study to involve an extension of the indication, which is true in most cases of off-label use of medicinal products.²⁹ This type of prescription is common and generally occurs in situations involving advanced stages of AD. The aim of the BNA is to increase the level of information available to doctors, to parties involved in research and to the regulatory health authorities. It is now able to provide information on practice within the profession and may subsequently provide longitudinal data.

CONFLICT OF INTEREST

KT was an employee of Merck Serono and Glaxo-SmithKline, but worked on unrelated therapeutic areas (oncology and thrombosis). PR received grant to his institution from Janssen and payments for lectures from Eisai and Lundbeck.

KEY POINTS

- Efficacy of drug treatments for AD is modest, and specific guidelines were developed to define the use of the two classes of drugs.
- About 20% of the prescriptions are not complying with the French national guidelines. Association of the two classes of drug treatments for AD was the principal modality of prescription not complying with the guidelines. Prescriptions not complying with the guidelines for both classes of drugs for AD were usually issued in situations involving more severe stage AD.

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