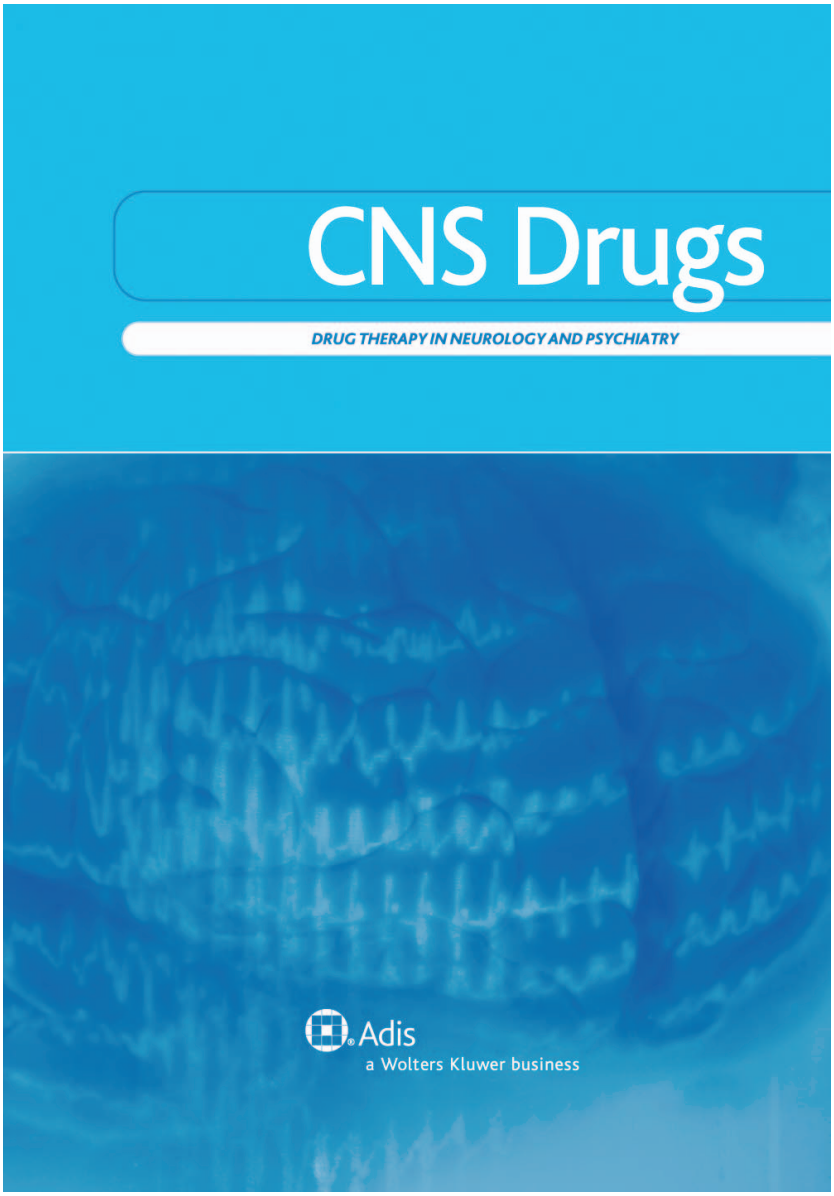

ORIGINAL RESEARCH ARTICLE

CNS Drugs 2010; 24 (5): 431-442
1172-7047/10/0005-0431/$49.95/0

Predictive Factors of Discontinuation and Switch of Cholinesterase Inhibitors in Community-Dwelling Patients with Alzheimer's Disease

A 2-Year Prospective, Multicentre, Cohort Study

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Abstract

Background: The efficacy of cholinesterase inhibitors (ChEIs), especially over the long term, is still under discussion. There is a lack of data concerning the optimal drug treatment duration and the reasons for discontinuation, particularly outside the clinical trial setting.

Objective: To identify predictive factors of discontinuation and switch of ChEIs in a real-world setting.

Methods: A multicentre cohort study of 686 patients with mild-to-moderate ambulatory Alzheimer's disease who were diagnosed in 16 Alzheimer's disease expert centres in 2000–2 and who were assessed twice yearly for 2 years. The main outcome measure was ChEI discontinuation and switch (analysed using Cox survival analyses).

Results: After 2 years, of the 611 subjects treated with a ChEI at baseline, 100 subjects had switched or discontinued ChEI therapy (incidence rate 12.7 [95% CI 10.2, 15.2] per 100 person-years). The incidences of switching and discontinuation were 9.2 (95% CI 7.0, 11.3) and 3.6 (95% CI 2.3, 4.8) per 100 person-years, respectively. In the multivariate analysis, predictive factors for switching were an ineffective ChEI dose (adjusted hazard ratio [HR_a] = 6.91, 95% CI 3.08, 15.49), rapid cognitive decline (HR_a = 4.10, 95% CI 1.85, 9.05), hospitalization unrelated to Alzheimer's disease (HR_a = 2.33, 95% CI 1.07, 5.09) and anxiety (HR_a = 2.08, 95% CI 1.16, 3.73). Predictive factors of discontinuation

were: hospitalization related ($HR_a = 9.14$, 95% CI 2.69, 31.07) or unrelated ($HR_a = 4.23$, 95% CI 1.54, 11.59) to Alzheimer's disease, use of an anticholinergic drug ($HR_a = 4.26$, 95% CI 1.46, 12.45) and weight loss ($HR_a = 3.77$, 95% CI 1.15, 12.33).

Conclusions: This study highlights four types of predictors of switch or discontinuation, reflecting disease progression, reconsideration of ChEI benefits, adverse drug reactions to ChEIs and inappropriate concurrent use of anticholinergic drugs. Attention should be paid to anticholinergic agents and prescribers should be given better information about these drugs.

Background

Cholinesterase inhibitors (ChEIs) are considered first-line symptomatic drugs for cognitive impairment in mild to moderate Alzheimer's disease. The efficacy of ChEIs remains controversial because randomized controlled trials (RCTs) have reported only modest improvements in cognitive and functional decline and have failed to demonstrate benefits for psychological and behavioural disturbances.[1] Most of these trials were of short duration and the rare long-term trials have reported conflicting results,[2-5] raising concerns over long-term sustained benefits and optimal duration of use. The question of ChEI discontinuation remains highly debated, with no clear guidelines describing how long ChEIs should be taken or when treatment should be stopped.[6] This is partly due to the difficulties in defining what should be considered a clinically relevant response,[7] since Alzheimer's disease is a progressive disorder and its evolution varies greatly between individuals.[8] Moreover, the selection bias commonly observed in RCTs is particularly evident in Alzheimer's disease.[9] Most observational studies deal with effectiveness and safety, and there are insufficient data in the real-life setting regarding patterns of long-term ChEI use. Only a few studies, conducted over short-term periods, have investigated the factors associated with ChEI discontinuation. Moreover, they were mostly based on pharmacy claims data and provided no clinical data (e.g. cognitive, functional impairment).[10-14] The aim of this study was to determine the predictive factors of switch and discontinuation of ChEIs in a cohort of ambulatory Alzheimer's disease patients followed for 2 years.

Methods

The multicentre REAL.FR (Réseau sur la maladie d'Alzheimer Français) cohort was set up to study the natural history of Alzheimer's disease and its management. A detailed protocol of the study has been published elsewhere.[15] The study was approved by the Institutional Review Board of each participating university. Briefly, REAL.FR was carried out in a network of 16 French university hospitals. Ambulatory community-dwelling Alzheimer's disease patients (n = 686) were enrolled between 2000 and 2002 and followed-up for 2 years. Inclusion criteria were Alzheimer's disease (according to DSM-IV and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease and Related Association criteria[16,17]) with a Mini Mental State Examination (MMSE)[18] score between 10 and 26. Furthermore, patients had to be under the care of an informal caregiver. At inclusion and every 6 months, patients underwent a standardized comprehensive assessment involving the following tests: MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS cog),[19] Clinical Dementia Rating (CDR),[20] Activities of Daily Living (ADL),[21] Neuropsychiatric Inventory (NPI)[22] and Mini Nutritional Assessment (MNA).[23] Drug exposure was determined from caregiver reports and, when possible, prescriptions brought to the consultation. Drug intake was recorded according to the Anatomical Therapeutic Chemical (ATC)

classification. The caregiver-patient relationship and level of caregiver burden, assessed using the Zarit Burden Interview,[24] were recorded. Socioeconomic status (based on household income, coded as a categorical variable) and level of education (coded as the highest degree obtained) were collected from informal caregivers, as well as the occurrence of hospitalizations and institutionalizations. All data, except for clinical assessments, were collected from informal caregivers during inpatient visits at the memory clinic.

Contact procedures were planned in the case of a missed visit. Patients were systematically contacted and offered another appointment date. If the patient could not be contacted, the general practitioner or the second informal caregiver was contacted. Institutionalization and hospitalization were systematically investigated with the general practitioner when dropouts occurred. If the missed visit was not rescheduled, the next visit was scheduled as initially planned.[25]

Switching was defined as a temporary or definitive switch from the baseline ChEI (donepezil, rivastigmine or galantamine) to another ChEI, and discontinuation as a temporary or definitive discontinuation of the baseline ChEI. The time to the event, based on the caregiver's report, was calculated from the inclusion date. Daily doses of rivastigmine <6 mg, galantamine <16 mg and donepezil <5 mg were considered ineffective. Concurrent use of anticholinergic drugs and ChEIs was defined as reported use of both types of drugs at the same visit. We defined anticholinergic drugs according to Goodman and Gilman's pharmacology textbook[26] and *La Revue Prescrire*.[27] Drugs considered as anticholinergic are presented in table I. Benzodiazepines were defined as ATC classes N05BA and N05CD (benzodiazepine derivatives), N05CF01 and N05CF02 (benzodiazepine analogues such as zolpidem and zopiclone), N03AE01 (clonazepam) and M03BX07 (tetrazepam). Antipsychotic drugs were defined as ATC class N05A. A history of depression was defined by a score ≥4 on the NPI depression subscale or use of antidepressants (ATC class N06A) at the previous visit. Hospitalizations for behavioural or psychological disturbances, malnutrition, increased cognitive impairment, anorexia, agitation, aggressiveness, anxiety or running away were considered to be related to Alzheimer's disease, as opposed to those for traumatology, non-Alzheimer's disease-related surgery (e.g. cataract, hip replacement due to arthrosis), infections, arthrosis or pain. Rapid cognitive decline was defined by MMSE score, and considered as a loss of ≥4 MMSE points in the 6 previous months.[28]

The present analysis was conducted among the patients treated with ChEIs at the end of the baseline visit. Baseline characteristics were described using mean values ± standard deviation (SD) and proportions for quantitative and qualitative variables, respectively. Two separate survival analyses were performed to identify predictive factors of (i) switch and (ii) discontinuation of the baseline ChEI, using relative hazard ratios (HRs) and 95% confidence intervals (CIs). Patients were followed up until the first occurrence of the event, or until the censor date (disenrolment, death, final endpoint). For time-dependent variables (ADL score, MMSE score, loss of 4 points on the MMSE score, weight loss, hospitalization, drug use, ineffective dose of ChEI, NPI subscores, Zarit Burden score in three categories [little or no burden: ≤20, mild to moderate: 20–40, moderate to severe: >40], depression [considered as NPI depression subscale score ≥4 or use of an antidepressant], malnutrition based on MNA score ≤23.5), survival analyses were based on the measure collected during the visit preceding the event, except for hospitalization, which was considered regardless of the period when it occurred. A backward stepwise Cox proportional hazards model was used, with adjustment for the centre (non-proportionality stratification[29]) and the variables considered to be potential confounders. Tests based on interaction with time were used to assert the proportional hazards assumption for time-constant variables (centre, age and sex of the patient, level of education, income, medical histories, co-morbidities, length of time since diagnosis, duration of ChEI use, age and sex of the caregiver, caregiver status and living arrangements). Statistical interactions were verified. P-values were based on two-sided tests and considered statistically significant if $p < 0.05$. All analyses

Table I. Drugs possessing anticholinergic properties

ATC class	Drugs	ATC subclass	
A02	Drugs for acid-related disorders	A02BX03	*Drugs for peptic ulcer and gastro-oesophageal reflux disease*: pirenzepine
A03	Drugs for functional gastrointestinal disorders	A03AA	*Drugs for functional bowel disorders*: synthetic anticholinergics, esters with tertiary amino group
		A03AB	*Drugs for functional bowel disorders*: synthetic anticholinergics, quaternary ammonium compounds
		A03BA	*Belladonna and derivatives*: belladonna alkaloids, tertiary amines
		A03BB	*Belladonna and derivatives*: belladonna alkaloids; semisynthetic, quaternary ammonium compounds
		A03CA	*Antispasmodics in combination with psycholeptics*: synthetic anticholinergic agents in combination with psycholeptics
		A03CB	*Antispasmodics in combination with psycholeptics*: belladonna and derivatives in combination with psycholeptics
		A03DA	*Antispasmodics in combination with analgesics*: synthetic anticholinergic agents in combination with analgesics
		A03DB	*Antispasmodics in combination with analgesics*: belladonna and derivatives in combination with analgesics
A04	Antiemetics and antinauseants	A04AD05	Metopimazine
C01	Cardiac therapy	C01BA03	*Antiarrhythmics class Ia*: disopyramide
D04	Antipruritics	D04AA10	Promethazine
G04	Urologicals	G04BD	*Other urologicals, including antispasmodics*: urinary antispasmodics
N02	Analgesics	N02BG06	*Other analgesics and antipyretics*: nefopam
N04	Antiparkinson drugs	N04A	Anticholinergic agents in Parkinson's disease
N05	Psycholeptics	N05AA01	Chlorpromazine
N05	Psycholeptics	N05CM05	*Hypnotics and derivatives*: scopolamine
N05	Psycholeptics	N05BB01	*Anxiolytics*: hydroxyzine
		N05AA02	Levomepromazine
		N05AA06	Cyamemazine
		N05AB02	Fluphenazine
		N05AB03	Perphenazine
		N05AC02	Thioridazine
		N05AC04	Pipotiazine
		N05AG02	Pimozide
		N05AH01	Loxapine
		N05AH02	Clozapine
N06	Psychoanaleptics	N06AA02	Imipramine
		N06AA03	Imipramine oxide
		N06AA04	Clomipramine
		N06AA06	Trimipramine
		N06AA09	Amitriptyline
		N06AA12	Doxepin
		N06AA16	Dosulepin
		N06AA17	Amoxapine
		N06AA21	Maprotiline

Continued next page

Table I. Contd

ATC class	Drugs	ATC subclass	
R01	Nasal preparations	R01AX03	*Decongestants and other nasal preparations for topical use*: ipratropium bromide
R03	Drugs for obstructive airway diseases	R03BB	*Other drugs for obstructive airway diseases, inhalants*: anticholinergics
R06	Antihistamines for systemic use	R06AA02	Diphenhydramine
		R06AA08	Carbinoxamine
		R06AB01	Brompheniramine
		R06AB02	Dexchlorpheniramine
		R06AB04	Chlorphenamine
		R06AD01	Alimemazine
		R06AD07	Mequitazine
		R06AD08	Oxomemazine
		R06AE01	Buclizine
		R06AX02	Cyproheptadine
S01	Ophthalmologicals	S01FA	*Mydriatics and cycloplegics*: anticholinergics

ATC = Anatomical Therapeutic Chemical.

were performed using SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Of the 686 patients recruited, 611 were treated with a ChEI at baseline. 234 subjects (38.3%) had dropped out by the 2-year follow-up period and a further 51 did not attend the 2-year visit (figure 1). Baseline characteristics are summarized in table II. The 611 patients treated with a ChEI at baseline were mostly (82.3%) recruited from geriatric departments, had a mean ± SD age of 77.6 ± 6.8 years, and were mostly (70.2%) women. They had been diagnosed with Alzheimer's disease for a median of 9 months (mean ± SD age at diagnosis 76.5 ± 7.0 years), and many were still moderately cognitively impaired. Fifty-five percent were completely independent for ADL. According to the NPI, 87.1% had at least one behavioural disturbance. Although all patients had an identified informal caregiver, 26.4% lived alone at home. The level of healthcare support remained low, with 17.7% receiving nursing care at home, 43.2% homehelp and 1.7% using daycare facilities.

At baseline, 80 subjects (13.1%) were prescribed a ChEI during the first visit, whereas 531 had already been prescribed a ChEI for a median of 6 months (interquartile range [1–14]). 433 subjects (70.9%) were treated with donepezil, 163 (26.7%) with rivastigmine and 15 (2.4%) with galantamine. The proportion of patients untreated with a ChEI was 2.5% (13/518), 3.4% (15/447), 3.9% (15/380) and 4.3% (14/323) from the second (V2) to the fifth (V5) visit, respectively. At baseline, 91.8% of the treated subjects were considered to be treated with an effective dose and this percentage increased at the second visit and then remained stable (95.5% [483/506], 94.7% [409/432], 94.5% [346/366] and 95.5% [296/310] from V1 to V5, respectively). Use of at least one drug with anticholinergic properties was reported by 37 (6.1%), 35 (6.8%), 33 (7.4%), 29 (7.6%) and 29 (9.0%) subjects at V1 to V5, respectively, accounting for 6.1% (37/609), 6.5% (33/505), 7.4% (32/432), 7.4% (27/365) and 9.1% (28/309), respectively, of subjects treated with ChEIs and 0% (no untreated patient at baseline), 15.4% (2/13), 6.7% (1/15), 13.3% (2/15) and 7.1% (1/14), respectively, of untreated subjects. The main anticholinergic drugs used were hydroxyzine and urinary antispasmodics (which accounted for around 50% of the ChEI-anticholinergic combination), followed by anticholinergic antipsychotics, non-selective monoamine reuptake inhibitors and anticholinergic drugs for functional bowel disorders.

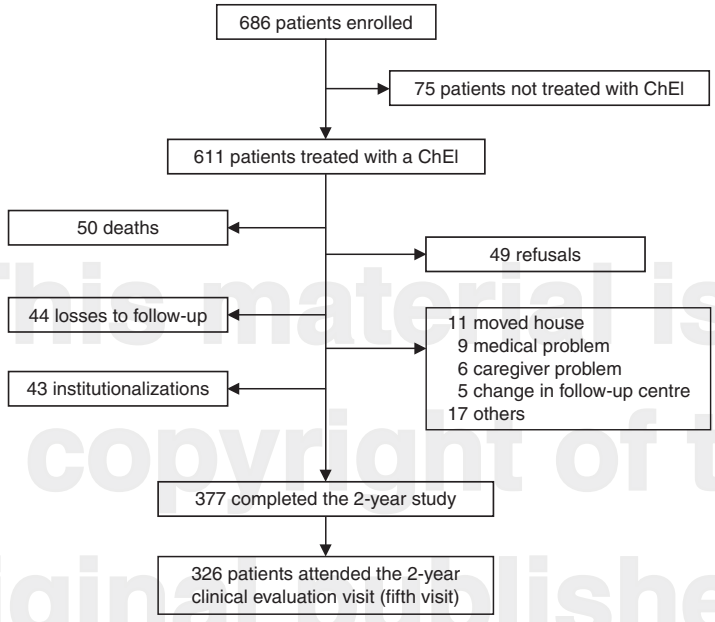

Fig. 1. Flow chart of the population studied in the REAL.FR study during the 2 years of follow-up. **ChEI** = cholinesterase inhibitor.

After 2 years of follow-up, 100 subjects had either switched or discontinued ChEI therapy at a median time of 8.5 months (261 days), representing an incidence rate of 12.7 per 100 person-years (95% CI 10.2, 15.2). Specifically, 72 patients had switched to another ChEI, at a median time of 10 months (298 days), representing a rate of 9.2 per 100 person-years (95% CI 7.0, 11.3). The most frequent switches observed were from donepezil to galantamine (34.7%, n = 25/72) and from donepezil to rivastigmine (31.9%, n = 23/72). After adjustment, several independent factors remained associated with switching to a different ChEI (table III): an ineffective ChEI dose (HR_a = 6.91, 95% CI 3.08, 15.49), rapid cognitive decline (HR_a = 4.10, 95% CI 1.85, 9.05), hospitalization unrelated to Alzheimer's disease (HR_a = 2.33, 95% CI 1.07, 5.09) and an anxiety score ≥4 points on the NPI (HR_a = 2.08, 95% CI 1.16, 3.73). Thirty discontinuations occurred at a median time of 5 months (150 days), representing a rate of 3.6 per 100 person-years (95% CI 2.3, 4.8). Use of an anticholinergic drug was an independent predictor of ChEI discontinuation (HR_a = 4.26, 95% CI 1.46, 12.45), as were Alzheimer's disease-related (HR_a = 9.14, 95% CI 2.69, 31.07) and non-Alzheimer's disease-related hospitalization (HR_a = 4.23, 95% CI 1.54, 11.59) and weight loss ≥4% of weight at previous visit (HR_a = 3.77, 95% CI 1.15, 12.33).

Discussion

In this observational study, the combined incidence rate of ChEI switch or discontinuation was 12.7 per 100 person-years (9.2 for switching and 3.6 for discontinuation). In RCTs, between 8% and 25% of patients discontinue ChEI use.[30] Outside of the clinical trial setting, discontinuation rates appear to be higher. Previous studies assessing ChEI persistency have mainly been based on pharmacy claims. It is difficult to compare the results of these studies because of differences in study design. The low discontinuation and switch rates observed in our study are in accordance with those from a study reporting a high rate of patients treated over the long term[10] and support the lower discontinuation rate observed among patients visiting their physician office frequently.[14] Nevertheless, in pharmacy claims

Table II. Demographic and clinical characteristics of patients treated with a cholinesterase inhibitor (ChEI) at the end of the baseline visit in the REAL.FR cohort study (n = 611)

Age (y, mean ± SD)	77.6 ± 6.8
Sex (%)	
female	70.2
Length of time since diagnosis (mo, median [interquartile range])	9 [4–20]
Level of education (%)	
technical/high school certificate or higher	20.6
early secondary education	22.7
primary school certificate	35.6
elementary or illiterate	21.1
Monthly household income [€ (%)]	
>2287	28.5
1500–2287	24.3
<1500	47.2
Caregiver status and living arrangements (%)	
spouse	54.8
child (non-cohabiting)	20.9
child (cohabiting)	15.2
other	9.0
Caregiver sex (%)	
female	60.0
Zarit Burden score (median [interquartile range])	19 [9–32]
MMSE score (mean ± SD)	20.1 ± 4.2
ADAS-cog score (mean ± SD)	17.7 ± 8.0
Total ADL score (out of 6, mean ± SD)	5.5 ± 0.9
CDR score (%)	
0.5	34.7
1	42.3
≥2	23.0
NPI score (median [interquartile range])	10 [3–21]
No. of co-morbidities (%)	
0	27.9
1	37.4
≥2	34.6
No. of medications other than ChEI (mean ± SD)	3.4 ± 2.3
Anticholinergic drug use (%)	6.1
Benzodiazepine use (%)	16.9
Antipsychotic drug use (%)	6.4
MNA score ≤23.5 (%)	31.9
Medical assistance[a] (%)	67.3
Non-medical assistance[b] (%)	49.2

a Outpatient clinics, nurse home visits, speech therapist, physiotherapist, doctor.

b Home help, day centre, night-time assistance, daytime assistance, meals on wheels, personal alarm.

ADAS-cog = Alzheimer Disease Assessment Scale-cognitive subscale; **ADL** = Activities of Daily Living; **CDR** = Clinical Dementia Rating; **MMSE** = Mini Mental Status Examination; **MNA** = Mini Nutritional Assessment; **NPI** = Neuropsychiatric Inventory.

studies, discontinuation rates observed over 1 year are generally higher than ours.[12-14,31] Our outcome, based on ChEI use assessed by caregivers rather than dispensings used in pharmacy claims, may explain the low discontinuation and switch rates found. Indeed, caregivers may have been reluctant to report ChEI discontinuation in this study. Moreover, drug dispensing data are known to overestimate drug use in chronic diseases.[32] Also, incidence rates could have been underestimated, as ChEIs could have been initiated before baseline. Caregivers are usually responsible for patients' drug intakes, and the presence of a defined caregiver may therefore explain the low rates of discontinuation in our study. This hypothesis may also support the lower risk of discontinuation observed among subjects in assisted-living facilities.[11] Variations in prescribing practices and healthcare systems could also account for the differences in discontinuation and switch rates seen in our study compared with previous research: France has the highest prevalence of ChEI use in Europe.[33] Lastly, we cannot reject a potential attrition bias if subjects who drop out respond less well to ChEI therapy than those remaining in the study, although it has been shown that ChEI-treated patients at baseline are at a decreased risk of dropping out.[25]

What are the factors leading to the discontinuation of ChEIs? The summaries of product characteristics mention that ChEIs should be prescribed until clinical benefit can no longer be demonstrated but the literature is sparse on the definition of such a response.[7] Furthermore, there are discrepancies between recommendations.[34,35] Factors associated with ChEI switch or discontinuation have rarely been studied in longitudinal studies of patients with dementia, and it is difficult to compare previous results with those of the present study because of methodological differences. We identified only retrospective pharmacy claim studies investigating ChEI persistency, with considerable variations in definitions, and little adjustment for clinical data. This study highlights the different predictors of ChEI switch or discontinuation, which are related to patient (cognitive decline, anxiety, weight loss), environment (hospitalizations) and drug factors. As patient-related factors and Alzheimer's disease-related hospitalization may reflect the progression of Alzheimer's disease, these were expected to be predictive of events. Rapid cognitive decline was linked to switching and may reflect the evolution of Alzheimer's disease despite ChEI use, suggesting the decision to switch to another ChEI may be made in the hope of a better therapeutic response. Anxiety may reflect a psychological disturbance related to Alzheimer's disease. One could imagine that anxious Alzheimer's disease patients may be assisted by anxious caregivers, who may pressurize the physician to prescribe a different ChEI. Weight loss could be considered either as an indicator of progression of Alzheimer's disease or a gastrointestinal adverse drug reaction to ChEIs. As weight loss was found to be predictive of discontinuation rather than switching, one could imagine that it may rather reflect worsening of Alzheimer's disease.

As expected, Alzheimer's disease-related hospitalization was predictive of discontinuation and, in fact, was the strongest predictor. During a hospitalization for worsening of Alzheimer's disease, the question of ChEI effectiveness arises. A drug holiday may be undertaken to assess the real benefit of ChEI use; in other cases the medication may be permanently stopped. Hospitalization unrelated to Alzheimer's disease predicted both switching and discontinuation. While the main cause for hospitalization was not directly linked to deterioration of Alzheimer's disease, a new co-morbidity, or a drug-drug interaction may explain a switch to another ChEI. Hospitalization may also bring about a reconsideration of the risk-benefit balance of ChEI treatment. Our results contrast with those of a study reporting a lower risk of discontinuation in hospitalized patients.[14] This discrepancy could be explained by differences in healthcare access, the length of follow-up period or residual confounding.

An ineffective dose was found to be predictive of switching, in accordance with the findings of another study in which prescribers were also specialists in Alzheimer's disease.[36] In our study, an ineffective dose of ChEI was prescribed in 8.2% (50/611), 4.6% (23/506), 5.3% (23/432), 5.5%

(20/366) and 4.5% (14/310) of subjects from V1 to V5, respectively. Among specialists, an inability to prescribe an effective dose of ChEI may reflect adverse drug reactions rather than insufficient knowledge.

Use of anticholinergic drugs was predictive of discontinuation. The physician's knowledge of this inappropriate combination or the lack of effectiveness of the ChEI may be two possible explanations for this result. A considerable variety of drugs have anticholinergic properties. While some are intentionally prescribed for these properties, many others have undesirable anticholinergic effects and are prescribed for other properties. Given the polypharmacy often observed in the elderly, the likelihood of being prescribed an anticholinergic drug is not negligible. Adverse reactions to anticholinergic drugs are well documented and include delirium, agitation, cognitive impairment and decreased functional performance, and behavioural disturbances.[37,38] Use of anticholinergic drugs is considered inappropriate in the elderly.[39] Pharmacodynamic interactions between ChEIs and anticholinergic medications are of particular importance[40] because their concurrent use may counteract the modest effects of ChEIs in patients with Alzheimer's disease, thereby compromising their efficacy, which is costly for both the patient and the health insurance system. Use of anticholinergic drugs should therefore be restricted to situations where there is no available alternative. In our study, the prevalence of concurrent anticholinergic use was estimated to be around 6–9%, which is of consequence in a cohort managed by specialists probably already aware of the need to limit such combinations. Although direct comparisons are difficult because of variations in settings and definitions of anticholinergic drugs and concurrent use, these rates appear to be lower than those reported in North America (varying between 20.7 and 35.4%[10,41,42]), but are similar to those observed in a Swedish population-based study.[43]

Our study did not find that benzodiazepine or antipsychotic drug use were predictive factors of ChEI discontinuation or switch, in contrast to suggestions made in other studies.[11,14]

Several limitations in our study should be discussed. Selection bias could have occurred

Table III. Cox multivariate models stratified by centre: adjusted hazard ratios (HR_a) for characteristics associated with a switch of cholinesterase inhibitor (ChEI) [n = 58/518] or discontinuation of ChEI (n = 29/591)

Switch[a]	HR_a	95% CI	p-Value	Discontinuation[b]	HR_a	95% CI	p-Value
Ineffective ChEI dose	6.91	3.08, 15.49	<0.001	Hospitalization related to Alzheimer's disease	9.14	2.69, 31.07	<0.001
Loss of ≥4 points on the MMSE score	4.10	1.85, 9.05	<0.001	Use of anticholinergic drug	4.26	1.46, 12.45	0.008
Hospitalization unrelated to Alzheimer's disease	2.33	1.07, 5.09	0.034	Hospitalization unrelated to Alzheimer's disease	4.23	1.54, 11.59	0.005
NPI anxiety score ≥4	2.08	1.16, 3.73	0.014	Weight loss ≥4%	3.77	1.15, 12.33	0.028
				NPI sleep disturbances ≥4	2.55	0.99, 6.56	0.053

a The model initially included the following variables: number of co-morbidities, patient sex, patient age, household income, duration of ChEI use, hospitalization related to Alzheimer's disease, MMSE score, caregiver status and living arrangements, ADL limitations (≥1 vs 0), delusion score ≥4 on NPI scale, agitation score ≥4 on NPI scale, appetite abnormalities score ≥4 on NPI scale, Zarit Burden score (little or no burden: ≤20; mild to moderate: 20–40; moderate to severe: >40), depression (NPI depression subscale score ≥4 or use of an antidepressant), malnutrition based on MNA score (≤23.5 vs >23.5).

b The model initially included the following variables: patient sex, patient age, household income, duration of ChEI use, ineffective ChEI dose, MMSE score, loss of ≥4 points on the MMSE score, caregiver status and living arrangements, ADL limitations (≥1 vs 0), apathy score ≥4 on NPI scale, Zarit Burden score (little or no burden: ≤20; mild to moderate: 20–40; moderate to severe: >40), depression, antipsychotic drug use.

ADL = Activities of Daily Living; **MMSE** = Mini Mental Status Examination; **MNA** = Mini Nutritional Assessment; **NPI** = Neuropsychiatric Inventory.

because recruitment was via specialized centres. However, in France, only specialists can initiate ChEI use. This study was conducted among ambulatory subjects only, which may limit the generalizability of the results, although patients with mild-to-moderate dementia are rarely institutionalized in France. Institutionalization during follow-up was a potential cause of dropout. However, 45% of the patients who were institutionalized during the study were still followed up after institutionalization. Also, we studied ChEI prescriptions reported by caregivers, rather than dispensing data or patient adherence, and medication compliance was not assessed in this study. Our study was not conducted with a 'new user design': as ChEIs were often introduced before inclusion in our study, we did not assess the incidence of events since ChEI initiation, possibly leading to the selection of a group of good responders, an overestimation of ChEI tolerability and an underestimation of switch or discontinuation rates. Because memantine was not available until 2003 in France, its use was too rare to be taken into account in this study. Use of other drugs (especially anticholinergic drugs) may have been under-reported compared with reports to administrative databases. Our list of anticholinergic drugs may not have been exhaustive and we assessed the number of anticholinergic drugs rather than the anticholinergic burden. However, there is no consensus for any list or scale. Lastly, because of the limited number of patients treated with anticholinergic drugs, we could not take into account CNS penetration.

Nevertheless, this large real-life cohort study of patients with Alzheimer's disease followed over a long period was based on clinical data, ensuring a standardized diagnosis of Alzheimer's disease and adjustment for numerous confounding factors. The study prospectively determined several factors that appear to be predictive of ChEI switch or discontinuation, reflecting progression of Alzheimer's disease and ongoing reconsideration of the benefits of and/or intolerance to ChEI therapy. It also highlighted the extent to which use of anticholinergic drugs could affect ChEI use in patients with Alzheimer's disease.

Conclusions

In this study, four predictors of ChEI switch or discontinuation were identified, reflecting disease progression, reconsideration of ChEI benefits, development and/or reassessment of adverse drug reactions to ChEIs and inappropriate concurrent use of anticholinergic drugs. Optimizing medication prescription in patients with Alzheimer's disease remains a challenge. So far, apart from memantine, ChEIs represent the only available approved medications and patients must receive the optimum benefit from these medications. The independent effects of anticholinergic drugs on ChEI discontinuation should be given greater consideration and indicate a need for more care and caution when prescribing these agents.

Acknowledgements

REAL.FR was supported by a grant from the Clinical Research Hospital Program from the French Ministry of Health (PHRC N° 98-47N, PHRC N° 0101001). This funding organization was not involved in the design and conduct of the study, collection of data, management, analysis, interpretation of data and preparation or review and approval of the manuscript.

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The authors have no conflicts of interest that are directly relevant to the contents of this study.

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