Persistent use of Analgesic Medications in Mild-to-Moderate Alzheimer's Disease.

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Key words: analgesics, persistent pain, Alzheimer's disease, dementia

Abstract

Background and Objectives: Previous studies have reported a lower use of analgesics in patients with Alzheimer's disease (AD) than in non-AD elderly. To date, no study has focused on persistent analgesic use in patients with mild to moderate AD.

Methods: The REAL.FR cohort study enrolled community-dwelling patients with mild to moderate AD. Persistent analgesic use was defined as the consumption of at least one analgesic drug during two consecutive visits (6 months). Associated factors were identified in a nested case-control study.

Results: In REAL.FR, 595 patients were present during at least two consecutive visits (mean age= 77.5 ± 6.8 years, MMSE=20.1 ± 4.2). Prevalence of persistent analgesic use was 13.1% (95%CI=[10.4-15.9]). The incidence of persistent analgesic use was 5.9/100 patient-years (95%CI=[5.2-6.6]).

Women (adjusted Odds Ratio OR=3.1, 95%CI=[1.2-8.2]), patients with musculoskeletal disorders (OR=3.4, 95%CI=[1.6-7.3]) and patients treated with numerous medications (OR=3.0, 95%CI=[1.5-85.8]) were more likely to use analgesics persistently. Statistically significant associations were found with disease duration and disease progression but not with AD severity at baseline.

Conclusions: Our results suggest a low use of analgesics in AD patients, which could vary with AD progression.

1. Introduction

Patients with Alzheimer's disease (AD) could experience a dysfunction in pain since AD is a neurodegenerative disease that can affect cerebral areas involved in pain perception. In various settings, studies have reported a lower analgesic use in cognitively impaired patients than in non-cognitively impaired elderly.[1-19] Most of these studies included various dementia aetiologies despite differences may exist in pain perception according to the dementia's cause.[20, 21]

Few studies have focused on acute analgesic use in patients with an ascertained AD diagnosis.[1-3, 14] One study reported a lower use of analgesics in AD patients than in non-AD patients (33% vs. 64% among those having a painful condition).[1] Two studies focused on specific drug classes, finding a lower use of non-steroidal anti-inflammatory drugs (NSAIDs) (5% vs. 39%)[14] and a lower overall use of opioids (3.6% vs. 4.6%), but an increased use in strong opioids (0.95% vs. 0.76%) in AD patients than in non-AD elderly.[3] The fourth study found a similar acute use of analgesics between AD and non-AD patients (2.9 ± 1.1 vs. 3.0 ± 1.3 equivalent mg paracetamol).[2]

Persistent pain or its inadequate treatment is associated with numerous adverse outcomes in the elderly (e.g. falls, functional impairment, depression, etc.) and may be distressing for caregivers.[22] To date, only one study has investigated persistent analgesic use in AD patients.[2] In this cohort of nursing home residents with a very severe cognitive impairment, the use of analgesics by two months of longer was lower in AD than in non-AD patients (24 ± 4 vs. 40 ± 5 equivalent mg paracetamol).

To our knowledge, no study of persistent analgesic use in mild-to-moderate AD has been published. Studying persistent analgesic use since the early stages of AD is of particular importance for three reasons: first, these patients do not usually live in institutions and thus are not taken care of like nursing home residents; second, psychological consequences of

persistent pain may worsen AD's signs or speed up AD's progression; last, AD's progression may influence pain experience and thus the need for analgesics.

Thus, we aimed to study the course of persistent analgesic use in a cohort of community-dwelling patients with mild to moderate AD. In particular, we estimated the incidence and prevalence of persistent analgesic consumption and identified the factors associated with incident persistent analgesic use.

2. Subjects and methods

2.1 Setting and participants

The "Réseau sur la maladie d'Alzheimer Français" (REAL.FR) cohort study has been described in detail elsewhere.[23] Briefly, the study aimed to assess the natural course of AD, and it consisted of patients recruited in the 16 expert centres of the French AD's Network (hospital gerontology, neurology or psychiatry units) between 2000 and 2002. The patients had to meet the DSM-IV[24] and NINCDS-ADRDA[25] criteria for dementia of Alzheimer's type at mild-to-moderate stage (MMSE score between 10 and 26). The patients were living in the community at the time of enrolment and looked after by an informal caregiver. The included patients were followed up for 4 years. Local ethical committees and the Institutional Review Boards of each participating university approved REAL.FR.

2.2 Data collection

The data were prospectively collected during standardised examinations every 6 months after baseline assessment. On these occasions, examination was carried out by clinical investigators (gerontologists, neurologists or psychiatrists). In particular, the examination assessed: cognitive status (MMSE,[26] ADAS-Cog[27]), dementia severity (clinical dementia rating (CDR)[28]), functional status (activities and instrumental activities of daily living (ADL, IADL)[29]), and behavioural and psychological symptoms of dementia (Neuro-Psychiatric Inventory (NPI)[30]). The caregiver reported at each examination the drugs currently used by

the patient (AD pharmacological treatment as well as any other drugs, including over-the-counter (OTC) drugs), documented with prescriptions when possible.

2.3 Key variables

Persistent analgesic use was defined by the consumption of ≥ 1 analgesic drug for at least 2 consecutive visits (suggesting at least 6-month duration of use).[31] Analgesics were defined by their anatomical, therapeutic and chemical classification (ATC) code:[32] N02A (opioid analgesics), N02B (non-opioid analgesics) or M01A (non-steroidal anti-inflammatory drugs and anti-rheumatic drugs). For every report of aspirin intake, we retrospectively checked the drug's indication and dosage in patients' records in order to rule out any use for cardiovascular protection.

2.4 Analysis

The present analysis was restricted to those subjects who had attended at least 2 consecutive visits (595 out of the 686 patients initially included in REAL.FR). We computed 95% confidence intervals (95%CI) with binomial exact limits for prevalence and incidence estimates.

To study factors associated with analgesic use in this AD cohort, we conducted a nested case-control study.[33] Incident persistent analgesic users were classified as cases. The date of the consecutive visits where cases started using analgesics persistently was recorded as the index date. Each case was randomly matched for index date to four controls (who did not report persistent analgesic use at the index date).

We used a conditional logistic regression model matched for index date and adjusted for age to analyze associated factors. Variables considered in initial models were measured at baseline and the ones significant in univariate analyses ($p<0.2$): sex, age, level of education, living arrangements (living alone or not), number of drugs received at baseline (apart from

antidementia and analgesic drugs), current or history of incapacitating osteoarthritis, body mass index (BMI), and centre type (geriatric centre vs. neurologic or psychiatric centres). We explored two dimensions of AD: 1- AD's severity, assessed by baseline CDR, baseline MMSE score, index date CDR, index date MMSE score; 2- AD's progression, assessed by the variation in MMSE score since baseline and since the last visit, and the duration since first AD signs.

Baseline characteristics were measured at the time of the patients' inclusion in the REAL.FR study. We checked that there was no collinearity between our selected variables inspecting the correlation matrix for continuous variables and not including two variables with Spearman correlation coefficients > 0.7 as a rule of thumb and inspecting contingency tables for categorical or dichotomous variables.

We used a backward method, controlling for confounders and collinearity at each step, to select variables with a 5% significant threshold. Additionally, interactions between the final selected variables were tested. Statistical analyses were performed with SAS© software version 9.1 (SAS institute, Cary, NC, USA).

3. Results

Characteristics of the 595 patients included at baseline are shown in Table 1. The majority of enrolled patients were females (77%) and the mean age was 77.5 ± 6.8 years. At baseline, AD had evolved for 3.3 ± 2.2 years on average, with a mean MMSE of 20.1 ± 4.2. Most of the patients were autonomous in the activities of daily living at baseline (75% had an ADL score ≥ 5.5). The mean duration of follow-up was 29 months and 206 patients (34.6%) attended the 4-year visit.

3.1 Prevalence and incidence of persistent analgesic use

Overall, 152 patients reported using analgesics at least once throughout the study with 78 considered as persistent users. Prevalence of acute use (i.e. use of analgesic at any visit) was

25.6% (95%CI=[23.1-29.2]). Prevalence of persistent analgesic use was 13.1% (95%CI=[10.4-15.9]). Prevalence rates of acute analgesic and persistent analgesic use are shown in Table 2. During follow up, prevalence of acute use showed a non-significant increasing trend (test for trend, p=0.12), while persistent use remained steady over time (ranging from 6.4% to 8.5%).

Within the 4 year-study period, 77 patients started to use analgesics persistently, thus indicating a shift in patients using analgesics. The incidence of persistent analgesic use was 5.9/100 patient-years (95%CI=[5.2-6.6]).

Among the incident persistent analgesic users, 50 patients (64.9%) started using one analgesic compound, while 19 (24.7%), 7 (9.1%) and 1 (1.3%) patients reported the simultaneous use of 2, 3 and 4 analgesic compounds, respectively. Analgesic drug classes used are shown in Table 3. The most common analgesic used alone or in combination was acetaminophen. Opioid drugs consisted mainly of tramadol and dextropropoxyphen. Three patients used other opioids (extented release morphine sulfate in 2 patients and transdermal fentanyl in 1 patient).

3.2 Factors associated with the start of persistent analgesic use

The nested case-control study included 269 patients (Table 4). Compared to the subjects not included in the nested case-control study, the ones included only differed for sex with fewer men (24% vs. 33%, p=0.015).

Compared to controls, cases were more frequently women, had a lower education level, a higher BMI, a smaller recent decrease in MMSE score (not statistically significant), were taking more medications and reported more frequently incapacitating osteoarthritis.

The results of the multivariate analysis are shown in Table 5. Women, patients with osteoarthritis were more likely to use analgesics persistently. The risk also increased with every other medication used.

We found statistically significant associations between persistent analgesic use and AD duration and recent change in MMSE, but not with MMSE score at baseline or at the index date. Patients with longer AD duration since diagnosis were significantly less likely to be treated with persistent analgesics. Patients who did not experience a worsening in cognitive functions (i.e. an increase in MMSE score between 2 visits) were more likely to use analgesics than patients whose MMSE did not change or decreased. In our study 32 cases (49%) and 67 controls (26%) were found to have an increase in MMSE at index date (on average 2.2 points, SD=1.2).

4. Discussion

Overall, we estimated the prevalence of persistent analgesic use at 13%. Our study lacked a control group but we can compare our findings with the literature. A French postal survey assessed persistent pain prevalence (defined as a daily pain complaint of any intensity that persisted for at least 3 months) in 2004.[34] It reported a prevalence of 20% in the general population and 52% in people aged 75 years and older.[34] Despite different methods, our 13% analgesic use figure contrasts with persistent pain prevalence found in previous work, but this gap concurs with the lower analgesic use found in severe AD patients than in non-AD elderly.[2]

Two main hypotheses may explain this low use of analgesics. 1.) AD patients experience as much pain as non-AD people but receive fewer analgesics for many reasons: [35] (i) AD patients, especially apathetic patients, rarely complain about pain, (ii) clinical staff do not adequately recognize pain or (iii) physicians avoid prescribing more drugs to AD patients fearing adverse drug reactions which are prevalent in frail older people ; [36] or 2.) AD patients have a different experience of pain from non-AD people as indicated by neuropathology and psycho-physic studies.[20,39-44]

Evidence supports the two hypotheses and suggests that due to modifications in pain processing, AD patients experience persistent pain differently,[20,39-44] but that they also receive fewer analgesics than their non-AD counterparts.[38] Since the elderly without dementia also usually receive suboptimal pain treatment,[36, 37] one can wonder about the quality of pain control in AD.

Our study is the first to examine the factors associated with persistent analgesic use in such a large number of patients with an ascertained diagnosis for AD. As expected, females, patients taking more drugs and those with incapacitating osteoarthritis were more likely to start using analgesics.[38, 39]

The likelihood to start using analgesics persistently was not associated with AD severity (i.e. MMSE score at baseline or at the index date) in our study . This result concurs with previous findings.[2] Conversely, persistent analgesic use was associated with two proxies for the progression of AD within patients: a recent improvement in cognitive functions (i.e. increase in MMSE score since the last visit) was associated with the start of persistent analgesic use; whereas, a duration of AD longer than 5 years was associated with a decreased probability to start persistent analgesic use. These results indicate that the apparent lack of association between persistent analgesic use and AD severity in cross-sectional surveys (i.e. inter-patients) might actually exist within patients when we looked at AD progression. Indeed, the more the disease progressed, the less likely were the patients to start using analgesics on a persistent basis.

Our work had some limitations. First, the measure of analgesic use suffers from some limitations as the REAL.FR study was not designed for that purpose. The measure relied on caregivers' memory and willingness and we may have missed some analgesics taken on an "as-needed" basis, however unlikely to constitute persistent use. A comparison of patient interviews and claims data to assess drug use in the elderly showed a fair agreement between

the two sources in France.[40] Also, we were unsure whether patients actually consumed the analgesics, even if we asked caregivers about any drug use, not only about prescribed drugs. We excluded adjuvant analgesics (e.g. gabapentin, amitriptyline, etc.) because these drugs were seldom used (11 patients at baseline) and not to treat pain. Second, we assumed a maintained exposure to analgesics during the 2 visits to define persistent use, but we were unable to check this assumption. Third, we observed an important attrition which could lead to under-representing the frailest patients (who may have died, had a major AD progression, or entered a nursing home). Attrition, however, matched what is usually reported in AD studies.[41] Last, study patients, recruited in expert AD centres, may not be representative of all AD patients.

5. Conclusion

Our results suggest a lower prevalence of persistent analgesic use in mild to moderate AD patients as compared to what has been reported in the elderly without dementia. We showed that persistent analgesic use was decreased during AD progression. Further longitudinal studies are required to better understand pain physiopathology according to MMSE evolution. Until then, we should carefully screen AD patients for painful symptoms to adequately recognize and treat pain while minimizing potential adverse drug events.

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Table 1. Baseline characteristics of included patients (N=595)

Baseline characteristics	**Value**
Socio-Demographics	
Age in years (mean ± SD)	77.5 ± 6.8
Female (%)	71.3
Education ≥ high school graduation (%)	17.4
Alzheimer's disease related data	
Years from first signs (mean ± SD)	3.3 ± 2.2
Mini-mental state examination (mean ± SD)	20.1 ± 4.2
Activities of daily living (mean ± SD)	5.5 ± 0.8
Clinical dementia rating ≥ 2 (%)	22.7
Currently treated with cholinesterase inhibitors [a] (%)	87.9
Comorbidities	
Past or current high blood pressure (%)	43.9
Past or current diabetes mellitus (%)	9.8
Past or current depression (%)	37.5
Past or current musculoskeletal disease (%)	14.7
Number of other drugs received (mean ± SD)	3.4 ± 2.3
Other	
Body mass index (mean ± SD)	24.7 ± 4.0

[a] At the time of enrollment, only cholinesterase inhibitors were available for the treatment of Alzheimer's disease in France.

Table 2. Prevalence of acute and persistent analgesic use during follow-up visits

	Follow-up (months)								
Parameter	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**
Number of patients	595	569	491	407	347	307	267	239	206
Mean Mini-mental state examination ± SD	20.1 ± 4.2	19.6 ± 5.0	18.3 ± 5.7	17.3 ± 5.9	16.4 ± 5.9	15.9 ± 6.3	15.4 ± 6.3	14.8 ± 6.7	14.3 ± 6.4
Prevalence of acute analgesic use (% [95%CI]) [a]	8.4 [6.3-10.9]	9.2 [6.9-11.8]	11.2 [8.6-14.3]	11.2 [8.4-14.8]	12.6 [9.4-16.6]	10.8 [7.5-14.8]	13.6 [9.6-18.2]	15.9 [11.5-21.2]	10.4 [6.4-15.2]
Prevalence of persistent analgesic use (% [95%CI]) [b]		6.4 [4.5-8.7]	6.4 [4.3-8.9]	5.8 [3.8-8.7]	5.5 [3.3-8.4]	6.6 [4.0-9.9]	7.3 [4.3-10.9]	8.5 [5.2-12.6]	7.2 [4.1-11.7]

[a] defined as the use of analgesic at the relevant visit

[b] defined as analgesic use during the 2 consecutive visits

Table 3. Description of analgesic drugs/classes used during the first 6-month exposure among incident persistent analgesic users (n=77)

Analgesic compounds	**Proportion of patients among those using analgesic drugs chronically**
Paracetamol (acetaminophen) alone or in combination (n=52[a])	67.5%
Opioid drugs alone or in combination (n=28)	36.4%
Non-steroid anti-inflammatory drugs, anti-rheumatic drugs (n=24)	31.2%
Other analgesics[b](n=2)	2.3%

[a] 32 patients used paracetamol alone or in combination with vitamin C or caffeine.

[b] Carbasalate (n=1), the analgesic drug was not recorded (n=1)

Table 4. Characteristics of patients included in the nested case-control study (n=269)

Characteristics	**Cases (N=65)**	**Controls (N=204)**	**p-Value**
Socio-Demographics			
Age in years at baseline (mean ± SD)	78.0 ± 5.9	77.3 ± 6.6	NS
Female (%)	89.2	72.1	0.005
Education ≥ high school graduation (%)	12.34	23.6	0.055
Alzheimer's disease related data			
Years from first signs (mean ± SD)	3.2 ± 2.6	3.2 ± 2.0	NS
MMSE at baseline (mean ± SD)	20.4 ± 3.9	20.6 ± 4.2	NS
ADL at baseline (mean ± SD)	5.5 ± 0.7	5.5 ± 0.8	NS
CDR ≥ 2 at baseline (%)	14.5	24.1	NS
Cholinesterase inhibitors at baseline (%)	84.6	91.7	NS
Evolution of Alzheimer's disease			
Δ MMSE between last visit and analysis (mean ± SD)	-0.4 ± 3.6	-1.1 ± 2.9	0.061
Δ MMSE between baseline and analysis (mean ± SD)	-1.9 ± 4.5	-2.6 ± 4.4	NS
Comorbidities			
Past or current high blood pressure (%)	50.0	41.4	NS
Past or current diabetes (%)	6.9	10.0	NS
Past or current depression (%)	39.0	41.4	NS
Past or current musculoskeletal disease (%)	33.3	11.7	$< 10^{-4}$
Other drugs at baseline (mean ± SD)	4.4 ± 2.3	3.3 ± 2.3	$< 10^{-4}$
Other			
Body mass index at baseline (mean ± SD)	25.7 ± 4.6	24.7 ± 4.0	0.024

Abbreviations: ADL: activities of daily living, CDR: clinical dementia rating, MMSE: mini-mental state examination, NS: not statistically significant (p>0.05), SD: standard deviation.

Table 5. Factors associated with persistent analgesic use (matched case-control study, adjusted for age and baseline MMSE score) (n=269)

Parameter	Odds ratio	95% CI	p-Value
Female vs. male	3.11	1.19-8.12	0.021
Musculoskeletal disease	3.39	1.58-7.29	0.002
Number of other drugs[a]	2.99	1.54-5.79	0.001
First signs of AD > 5 years	0.44	0.21-0.91	0.028
Change in MMSE since last visit			0.045
Increase	3.62	1.58-7.29	0.002
No change	1		
Decrease	1.80	0.57-5.67	0.316

Abbreviations: AD: Alzheimer's disease, CI: confidence interval, MMSE: mini-mental state examination.

[a] Number of drugs apart from Alzheimer's disease medications and analgesics.