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Research Report

Treatment of Alzheimer's Disease in the New Era of Monoclonal Antibodies Against Cerebral Amyloid-β: Pharmacological Prescription and Knowledge in Argentina

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Abstract.
Background: Alzheimer's disease (AD) presents a significant global health challenge. Understanding the current and upcoming treatment landscape is crucial for effectively managing patients.
Objective: The aim of this study was to assess the pattern of prescription and knowledge about new therapies by physicians who treat AD patients in Argentina.
Methods: A cross- sectional and analytic study was conducted. A survey was elaborated about pharmacological treatment in AD. Statistical analysis of answers of specialists in cognitive disorders (SCD), non-specialists in cognitive disorders (NSCD), recommended treatment, non-recommended treatment (NRT), and *off-label* treatment was performed.
Results: 155 physicians answered the survey. A 19.35% prescribed at least one NRT for dementia. 78.06% prescribed at least an *off-label* treatment or an NRT for mild cognitive impairment (MCI). 31% would prescribe monoclonal antibodies (MABs) against cerebral amyloid-β (Aβ) to AD patients, and 42.6% responded that they were not aware of any adverse effect of these. Quetiapine was the most frequent treatment for psychotic symptoms (88.4%) and escitalopram (32.3%) for apathy. A 70% of potential prescribers of MABs ($n = 100$) would request biomarkers of cerebral Aβ in the initial assessment. There were significant differences between the responses of SCD and NSCD regarding the prescription of MABs (52.17% versus 23.08, respectively) and knowledge about adverse events (76.09% versus 38.46%, respectively).
Conclusions: A considerable percentage of physicians indicated NRT and *off-label* medication in MCI and dementia. In Argentina, there are many physicians who would indicate a MABs for AD, but many are not completely aware of its safety profile.

Keywords: Alzheimer's disease, drug therapy, epidemiology, health policy, monoclonal antibodies

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INTRODUCTION

It is estimated that in the coming years, the increase in life expectancy will increase the number of individuals with cognitive impairment and dementia. The main causes are neurodegenerative disorders, with Alzheimer's disease (AD) being the most prevalent. AD is a chronic and progressive disorder characterized by cerebral deposits of amyloid-β (Aβ) protein and neurofibrillary tangles. It causes cognitive, behavioral, and psychological symptoms, with the amnesic dysfunction being the most characteristic. It compromises the independence of patients, requiring the assistance and care of relatives over years, with the consequent increase in direct and indirect cost [1].

According to the World Health Organization (WHO) there are currently more than 55 million patients with dementia in the world, estimating 78 million for the year 2030 and 139 million for 2050. This will generate a socioeconomic impact on world health systems [2]. According to the Alzheimer's Association, in 2020 all patients with AD and other dementias represented an estimated economic cost of US$ 305 billion, without including the contribution of informal caregivers [3]. One of the variables that influence increase in spending is disability grade of AD patients. In the early stages of the disease, the percentage of costs of pharmacological treatment is higher compared to caregivers. In later stages, this relationship is reversed [1].

A few studies on the situation of AD in Argentina have been published. Approximately 500,000 people have dementia in the country. In the city of Buenos Aires, there are an estimated 50,000 patients with dementia and 100,000 with cognitive impairment [4]. According to Rojas et al. [5], an annual direct cost of US$4,625 is estimated for patients with dementia due to AD. According to the study by Larraya et al. [6] the prevalence of dementia was 12.18% in patients older than 65 years (5.85% to AD and 3.86% to vascular dementia, of the total). However, no complete epidemiological studies have been conducted in Argentina [7].

There is worldwide interest in the development of new pharmacological therapies against neurodegenerative diseases. In recent years, new drug treatments have been developed with the objective to modifying the course of AD. Monoclonal antibodies (MABs) against cerebral Aβ protein are one of these. The first of this group approved by the Food and Drug Administration (FDA) was aducanumab in 2021, and recently, lecanemab was approved in 2023. Aducanumab obtained emergency approval, primarily hinging on its capacity for brain amyloid removal, as determined through amyloid PET imaging. However, the observed clinical efficacy remained minimal. Consequently, Aducanumab underwent only very restricted utilization and was withdrawn from the market by its manufacturer, Biogen®, after the cessation of a clinical trial intended for full FDA approval. The very high cost (US$56,000/year), adverse effects and very limited cognitive benefits certainly contributed to the decision. Donanemab is another MABs that has been shown to slow the progression of AD in its clinical trials, and is being considered by the FDA [8]. The above constitutes a new paradigm in the therapy of AD, since up to now treatments have focused on symptomatic management and patient care. At the time of publication of this study, there is no MABs available or approved in Argentina.

This new scenario encourages physicians treating patients with AD to have up-to-date and evidence-based knowledge in pharmacological management. Many of the upcoming treatments would have the potential to modify the course of the disease.

Therefore, the objective of this paper is to assess and describe the current pattern of prescription and pharmacological opinion and knowledge about new therapies by physicians who treat AD patients in Argentina.

MATERIALS AND METHODS

The design of our study was cross- sectional and analytic. An electronic survey was elaborated about personal data and attitudes regarding the pharmacological treatment of AD (see Supplementary Material). It was written and reviewed by five neurologists from the "Sanatorio de la Trinidad Mitre" in Argentina. This study aimed at physician members of the Argentine Neurological Society (ANS). who attend patients with cognitive disorders. It was distributed electronically through ANS's official page and via email to all its members. Prior to answering the survey, all participants agreed to the terms and conditions of participating in this work. Data collection was conducted from June to July 2022. The anonymity of each participant was maintained, and no researcher obtained any economic benefit in carrying out this study. Physicians specializing in cognitive disorders (SCD) were defined as those who in the survey considered themselves specialists in

cognitive disorders. Otherwise, they were defined as non-specialists in cognitive disorders (NSCD).

To delineate the pharmacological treatment modalities for patients diagnosed with mild cognitive impairment (MCI) and AD, we employed the classification criteria outlined by Bustin et al. [9] in their study on pharmacological prescriptions. This classification system encompasses three distinct categories: Recommended Treatments (RT), Non-Recommended Treatments (NRT), and *off-label* treatments. RT for dementia due to AD were defined as: acetylcholinesterase inhibitors (AChEI; donepezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine. NRT were defined as all drugs without indications or endorsement in international literature (such as vitamin supplements, nimodipine, citicoline, among others). In MCI, a predementia syndrome in which individuals demonstrate cognitive impairment without functional consequences, there is not any RT for the different clinical and etiological subtypes of this condition [9]. However, there is some evidence of benefits of donepezil and memantine in MCI [10, 11]. For the above, *off-label* treatments for MCI were defined as AChEI and memantine because they are not *formally* approved by drug regulatory agencies for this indication in Argentina.

Regarding the prescription of MABs, there were only questions about aducanumab because at the time this study was conducted, the FDA only approved this treatment. Those who answered the following were considered doctors who knew about the adverse effects of MABs: ARIA-E (amyloid related imaging abnormalities-edema), ARIA-H (amyloid related imaging abnormalities-hemosiderin deposition), falls, headache, or anaphylactic reaction. Otherwise, those who answered at least one of the following were considered doctors who knew not about the adverse effects: does not know, none, oncogenesis, or immunosuppression. The description reported in the literature was used as criteria for this [12], and the label of aducanumab [13]. During the analysis of this study, the approval of lecanemab by the FDA occurred. Therefore, we incorporated its labeled prescription into the analysis, given that the overall indications and adverse effects of MABs were taken into consideration [14].

The chi-square test, Fisher's exact test, and Student's *t* test were used to calculate probabilities. A significant difference was defined as $p < 0.05$. The responses of SCD and NSCD physicians were compared. We also analyzed RT, NRT, and *off-label* for MCI and dementia. A literature review was performed in PubMed. There were included articles in Spanish and English. Indications and recommendations on the management of cognitive disorders were sought according to international publications.

RESULTS

A total of 155 physicians (10.3% of 1,500 total active members of the ANS) were surveyed. The percentage of women was 43.9%. The median age was 44 years (Q3:59, Q1:36). A 45.2% practiced in the city of Buenos Aires, 28.4% in the province of Buenos Aires, and 24.4% in the rest of the provinces of Argentina. Regarding medical specialties, 121 were neurologists, 23 psychiatrists, 3 geriatricians, 11 residents of neurology, 2 neurosurgeons, and 2 internists. The median number of years of medical care practice was 17 years (Q3:30, Q1:9). A 67.1% of those surveyed thought they were NSCD and 29.7% SCD.

Regarding the treatment of dementia due to AD, 94.2% indicated AChEI and 91% indicated memantine (Table 1). A 19.35% ($n = 30$) indicated at least one NRT for dementia.

In the treatment of MCI due to AD, most prescribed AChEI (65.2%). Only 21.9% did not prescribe pharmacological therapies (Table 1). A 78.06% ($n = 121$) indicated at least one *off-label* treatment or one NRT for MCI. There were no significant differences between the responses of SCD and NSCD regarding the prescription of *off-label* medication or NRT in the cognitive disorders evaluated (Table 2).

Thirty-one percent would indicate MABs in the treatment of AD, 35.5% answered "No", and 33.5% answered "Don't know". There were significant differences between the responses of SCD and NSCD regarding this, with the first being who most would prescribe it (52.17% versus 23.08, $p < 0.05$, Table 3). It did not occur when age, sex, location, or specialty and MABs prescription were compared.

Most (69%) believed that the main weakness of MABs treatment was the "high cost" of the this, followed by "slight cognitive improvement of treated patients" (32.3%), "lack of proven evidence on cerebral Aβ reduction" (17.4%), and "adverse effects outweigh the benefits" (16.8%). A 23.9% considered that they did not know about the weaknesses of MABs treatment.

A 39.4% answered that the most frequent adverse effect of MABs is cerebral edema (ARIA- E), 35.5% stated that microhemorrhage/superficial siderosis

Table 1
Responses about pharmacological treatment of MCI and dementia due to Alzheimer's disease

	Respondents ($n = 155$)			
	Dementia		MCI	
Recommended treatments	*n*	%	*n*	%
AChEI	146	94.2	NA	NA
Memantine	141	91	NA	NA
MAB[1]	0	0	1	0.6
Non-recommended treatments				
Vitamin/Aminoa acid supplements	21	13.5	19	12.3
Nimodipine	1	0.6	1	0.6
Citicoline	3	1.9	2	1.3
Nimodipine- citicoline	1	0.6	1	0.6
Idebenone	0	0	0	0
Ergot derivatives	0	0	0	0
Gingko Biloba	2	1.3	3	1.9
Gangliosides	0	0	1	0.6
Cerebrolysin	1	0.6	1	0.6
Acetylcarnitine	2	1.3	1	0.6
Resveratrol	1	0.6	0	0
Piracetam	1	0.6	1	0.6
Antidepressants	1	0.6	1	0.6
Treatments "off label"				
AChEI	NA	NA	101	65.2
Memantine	NA	NA	40	25.8
No drug treatment	3	1.9	34	21.9

MCI, mild cognitive impairment; AChEI, acetylcholinesterase inhibitors; MAB, monoclonal antibodies; NA, not applicable [1]MABs were considered as Recommended Treatment for MCI.

Table 2
RT and NRT for MCI and dementia

	Treatment for dementia[1]			
Specialists in cognitive disorders[2]	NRT		RT	*p*
Yes ($n = 46$), *n* (%)	12 (26.09)		34 (73.91)	$p > 0.05$
No ($n = 101$), *n* (%)	16 (15.84)		85 (84.16)	
	Treatment for MCI[3]			
Non specialists in cognitive disorders	NRT	*Off label*	No pharmacological treatment	*p*
Yes ($n = 46$), *n* (%)	7 (15.22)	31 (67.39)	8 (17.39)	$p > 0.05$
No ($n = 104$), *n* (%)	16 (15.38)	63 (60.58)	25 (24.04)	

RT, recommended treatments; NRT, non-recommended treatments; MCI, mild cognitive impairment. [1]Those who did not indicate pharmacological treatment were excluded. Those that only indicate RT and those that indicate at least one NRT were compared. [2]Those who did not know if they were specialists in cognitive disorders were exclude [3]Those who did not indicate pharmacological treatment, only off-label treatment, and those who indicated at least one NRT were compared.

(ARIA-H). However, most (42.6%) surveyed "Don't know" adverse effects. A sub-analysis was performed between physicians who knew and knew not adverse effects. There was a significant difference in the responses of SCD and NSCD ("Know adverse effects" 76.09% versus 38.46%, $p < 0.05$, respectively, Table 3).

In the pharmacological treatment of disruptive psychotic symptoms in AD, most (88.4%) answered that they used quetiapine. Regarding apathy, the highest percentage of physicians (32.3%) surveyed that they indicated escitalopram (Table 4).

The most frequent answers about effect of antidementia treatments was "Improve cognitive symptoms in some cases" (75.5%). "Temporarily stopping neurodegeneration in some cases" obtained 41.9%, and the rest of the options were less than 8% each one.

The qualification of current pharmacological treatments available in Argentina obtained a mean response of 4.08 (SD $\pm$ 1.64). The scale presented values from 0 (poor effectiveness) to 10 (outstanding). There were no statistically significant differences between the SCD and NSCD groups (4.41 versus 3.95; $p = 0.117$).

Table 3
Questions related to the use of MABs

	Would it indicate the use of MABs in the treatment of AD?			
Specialists in cognitive disorders[1]	Yes	No	Don't know	*p*
Yes ($n=46$), *n* (%)	24 (52.17)	14 (30.43)	8 (17.39)	$p<0.05$
No ($n=104$), *n* (%)	24 (23.08)	39 (37.5)	41 (39.42)	
Age				
Over 50 y ($n=59$), *n* (%)	19 (32.2)	16 (27.12)	24 (40.68)	$p>0.05$
Less than or equal to 50 years ($n=96$), *n* (%)	29 (30.2)	39 (40.63)	28 (29.17)	
Sex[2]				
Men ($n=86$), *n* (%)	29 (33.72)	33 (38.37)	24 (27.9)	$p>0.05$
Women ($n=68$), *n* (%)	19 (27.94)	22 (32.35)	27 (39.71)	
Location[3]				
They only practice in CBA ($n=57$), *n* (%)	20 (35.09)	23 (40.35)	14 (24.56)	$p>0.05$
They do not practice in CBA ($n=85$), *n* (%)	25 (29.41)	25 (29.41)	35 (41.18)	
Speciality[4]				
Neurology ($n=114$), *n* (%)	35 (30.7)	41 (36.96)	38 (33.33)	$p>0.05$
Not neurology ($n=26$), *n* (%)	9 (34.62)	8 (30.77)	9 (34.62)	
	What are the most frequent adverse effects currently described associated with the use of anti-cerebral amyloid antibodies?			
Specialists in cognitive disorders	Know adverse effects		No known adverse effects	
Yes ($n=46$), *n* (%)	35 (76.09)		11 (23.91)	$p<0.05$
No ($n=104$), *n* (%)	40 (38.46)		64 (61.54)	
The following questions were only for those who would indicate a MAB or did not know				
	If you start treatment with MABs in patients with suspected AD, would you request routine cerebral amyloid markers (imaging or cerebrospinal fluid)?			
Specialists in cognitive disorders	Know[5]		No know	
Yes ($n=31$), *n* (%)	28 (90.32)		3 (9.68)	$p<0.05$
No ($n=65$), *n* (%)	43 (66.15)		22 (33.85)	
	If it were approved in Argentina, would you prescribe Aducanumab in the treatment of AD?			
Specialists in cognitive disorders	Yes		No	
Yes ($n=29$), *n* (%)	21 (95.45)		1 (4.55)	$p>0.05$
No ($n=64$), *n* (%)	30 (90.91)		3 (9.09)	
	In the event of indicating anti-cerebral amyloid antibodies, in what stage or stages of AD would it indicate it?			
Specialists in cognitive disorders	MCI and mild dementia		Other stages	
Yes ($n=32$), *n* (%)	12 (37.5)		20 (62.5)	$p<0.05$
No ($n=65$), *n* (%)	5 (7.69)		60 (92.31)	

MAB, monoclonal antibody; AD, Alzheimer's disease; CBA, City of Buenos Aires; MCI, mild cognitive impairment. [1]Those who did not know if they were specialists in cognitive disorders were excluded from these analyses. [2]Those who considered themselves to be of the other sex were excluded because they were not statistically significant ($n=1$). [3]Those who practiced in both groups (CABA and Buenos Aires at the same time) were excluded. [4]Residents and those belonging to both groups (e.g., neurologist and psychiatrist) were excluded. Residents and those belonging to both groups (e.g., neurologist and psychiatrist) were excluded. [5]Those who knew they would request the study and did not request it were included in the "Know" group. One respondent who would request ApoE3 was excluded, as it was not significant ($n=1$).

Potential prescribers of MABs

Physicians who would prescribe MABs and those who did not know if they would do so were analyzed in a joint group (n: 100). These were considered potential prescribers of MABs. Most of these (70%) would request biomarkers for cerebral Aβ in the initial assessment of patients with suspected AD. If aducanumab were approved in Argentina, 52% would indicate it, 39% did not know, and 5% would not (4% did not specify their answers). Regarding the question about which stage of AD would indicate a MABs, MCI and mild dementia were most frequent answers (48% and 46%, respectively). There were significant

Table 4
Psychopharmacological treatment to psychosis and apathy in Alzheimer's disease

	Respondents ($n = 155$)	
Antipsychotics	*n*	%
Quetiapine	137	88.4
Risperidone	71	45.8
Olanzapine	40	25.8
Pimavanserin	30	19.4
Aripiprazole	16	10.3
Haloperidol	16	10.3
Clozapine	13	8.4
Levomepromazine	7	4.5
Promethazine	2	1.3
Lurasidone	1	0.6
AChEI	1	0.6
Not Know	1	0.6
None	0	0
Apathy		
Escitalopram	50	32.3
Sertraline	44	28.4
Bupropion	41	26.5
Modafinil	35	22.8
Venlafaxine	33	21.3
Methylphenidate	18	11.6
None	16	10.3
Armodafinil	10	6.5
Not Know	8	5.2
Mirtazapine	1	0.6
AChEI	1	0.6
Paroxetine	1	0.6

AChEI, acetylcholinesterase inhibitors.

differences between SCD and NSCD, (37.5% versus 7.96%; respectively $p < 0.05$) (Table 3). A 55% did not know about the adverse effects of MABs.

In parallel, only physicians who would indicate MABs ($n = 48$) were analyzed. A 14.58% answered that they would indicate at least one NRT for dementia. An 87.5% at least one *off-label* treatment or one NRT for MCI. A 31.25% did not know about adverse effects of MABs. They answered that the main weakness of treatment was the high cost (31.25%). Quetiapine was the most chosen pharmacological treatment in this group (87.5%) to treat disruptive psychotic symptoms.

DISCUSSION

In this cross-sectional and analytic study, we have analyzed the responses of physicians regarding pharmacological treatments for AD. From our study, we can infer a part of care situation in Argentina, allowing us to see how these professionals position themselves in the face of the new challenges in drug management of AD.

Distribution of physicians

The localities with the highest density of physicians were city of Buenos Aires, Province of Buenos Aires, Córdoba, Santa Fe, and Neuquén. Our work revealed a distribution of physicians in Argentina similar to published in the literature. In 2015, Zuin et al. [15] revealed this. The survey was answered mostly by medical specialists in neurology, which constitutes a bias in the research method (survey distributed to members of ANS).

Actual cognitive drug prescription

We observed that the prescription of NRT and *off-label* medication in MCI and dementia by AD is considerable. There is not international consensus regarding the indication of any kind of pharmacological treatment in MCI [16]. A Cochrane´s review of 2009 on the use of donepezil in MCI concluded that there is no evidence to use it in these patients and was associated with significant side effects [17]. Nevertheless, in our work the majority answered that they prescribe AChEI in MCI, and almost a fifth did not prescribe any medication. There were no significant differences between SCD and NSCD regarding the use of RT or NRT in MCI or mild dementia. This agrees with the work published by Bustin et al. [9] in 2019, where of a total of 3,255,438 prescriptions for patients with cognitive impairment, 59% were RT and 41% were NRT.

MABs situation

Regarding the decision to prescribe MABs, it is notable that there was an equitable distribution on the response by physicians. This indicates that in Argentina, there is no dominant trend on this topic, despite being a new, expensive, and hopeful drugs for patients and their families.

From the group of potential prescribers of MABs, most would request biomarkers such as cerebral Aβ to complement the study before initiating treatment. This conduct, according to international prescriptions and publications [13, 14, 18], could increase the costs per patient in a disease with a high prevalence. Biomarkers for cerebral Aβ enhance AD diagnostic accuracy in typical symptomatic patients (for example, amnestic syndrome) by detecting premortem anatomopathological changes [19]. These can be detected it in early stages of AD characterized by minimal disability; therefore. pharmacological

intervention could have a greater response. Furthermore, these treatments require periodic evaluations with brain MRI to monitor possible adverse effects (ARIA-H and ARIA-E), increasing costs. Health systems should assess this scenario when planning of public policies. In this new paradigm, treatment demand high economic cost and accurate diagnosis. Currently, biomarkers are not available in most healthcare centers in Argentina, limiting accessibility of this recourse and, therefore, the treatment. Potential prescribers of MABs also had a greater tendency to prescribe it in MCI and mild dementia stages of AD. This is congruent with the current literature. MABs, such as aducanumab and the recently approved lecanemab, in their formal indications and clinical trials, have indications only for MCI and mild dementia caused by AD [13, 14, 20, 21]. Another, such as donanemab in the phase 3 trial, is indicated in the early stages of disease [8]. This last drug is not approved at the time of this publication by any medication regulatory agency.

The most frequent adverse effects described by MABs are infusion- related reactions, headache, falls, ARIA-E, and ARIA-H [12, 20]. To know and detect the adverse effects of these new treatments, is crucial for the care of patients. Nevertheless, most of the respondents were unaware of them, including potential prescribers of MABs. Constant medical education is necessary in the next years with the advent of new therapies against AD.

In parallel, the response profile of the physicians who answered "Yes" to whether they would indicate MABs was analyzed. A considerable percentage indicated NRT and *off-label* drugs for MCI and mild dementia. A third considered that they did not know about the adverse effects of MABs and that the only weakness was it high cost. Quetiapine was the most used antipsychotic drug by this group.

Psychiatric symptoms

There is no international consensus on the treatment of AD psychosis. In our study, there were heterogeneous drug indications, with a predilection for quetiapine. A recent Cochrane's review of 2021 [22], analyzed the efficacy and safety of pharmacological treatment for agitation and psychosis in AD and vascular dementia. The authors concluded that typical and atypical antipsychotic drugs have a slight efficacy in decreasing agitation which is negligible to psychosis. Otherwise, they also increase the risk of serious adverse events. Risperidone is approved for use in some parts of the world [23, 24]. Recently, brexpiprazol was approved for prescription in AD agitation by FDA [25]. It is notably, almost a fifth of the respondents would use pimavanserin. At present, this medication is approved only for use in Parkinson's disease psychosis [26]. The HARMONY study [27] analyzed the efficacy of pimavanserin for psychosis in various types of dementia. At present, efficacy of pimavanserin in AD psychosis is uncertain. Nonetheless, the chronic use of antipsychotic drugs is discouraged for a long term in older patients. These therapies increases risk of somnolence, falls, cerebrovascular accidents, myocardial infarction, death, among others [22]. Therefore, benefits must overweigh the risks.

At present, there is a growing interest in the treatment of AD apathy. It is one of the most frequent neuropsychiatric symptoms in AD and is important to differentiate it from depressive symptoms. A Cochrane's review [28] of 2018 analyzed studies published on antidepressant drugs for AD apathy. The results were considered to be uncertain due to very low quality by selective reporting, indirectness of results, and publication bias. Nevertheless, in our study, antidepressant drugs were the most prescribed treatment for AD apathy, with escitalopram being most prescribed in this group. Several studies have been published using methylphenidate [28]. The ADMET 2 trial [29] of 2021, concluded that methylphenidate was a safe and effective medication for the treatment of apathy in AD. This drug favors the synaptic transmission of catecholamines, with a good response. However, it has potential moderate to severe adverse effects (weight loss, anxiety, arterial hypertension, arrhythmias, among others) in a population associated with various medical comorbidities. In our study, methylphenidate was indicated only by 11% of the respondents for AD apathy.

Our study

There are a few published surveys on pharmacological prescription in dementia patients [30–33]. A recent Belgian study [34] of 2021, analyzed the drug management of general practitioners. They found a considerable percentage of NRT prescriptions (Ginko biloba, vitamin E). All these studies mentioned are not focusing on the pharmacologic management of AD and none to prescription and knowledge about MABs.

In Argentina, in 2007, Serrano et al. [35], conducted a survey on attitudes towards MCI. Two groups of physicians were surveyed: dementia experts ($n = 24$) and general practitioners ($n = 30$). Only two questions related to pharmacological treatment were asked. 55% of expert physicians and 30% of general practitioners used AChEI for treating MCI. Furthermore, memantine was used by 33% of dementia experts and 13% of general practitioners in these patients.

As strengths of our study, we can mention that it is the first survey entirely directed to the pharmacological management of AD carried out in Argentina, including information on the prescription of MABs and psychotropic drugs. We have not found similar studies in the literature or in other parts of the world. Another feature to highlight was the high rate of responses received within a period of one month. After this, we received no more responses.

As the main weaknesses of our study, we mention that the sample was relatively small and that we could not obtain many responses from psychiatrists and geriatricians. These facts could be a methodological bias in the dissemination of the survey, which could have influenced the results obtained. Labeling specialist or non-specialist in cognitive disorders based on self-report is also a limitation of our study. The absence of a previously published and endorsed survey was another weakness of our research.

Conclusion

We observed a considerable percentage of physicians who would prescribe NRT and use *off-label* medication in patients with MCI and dementia. There were no significant differences between SCD and NSCD. Even though some doctors would indicate MABs, many are not aware of its adverse effects. From the above, we conclude that there is limited knowledge about the current and future pharmacological management of AD. Optimization of the drug treatment of patients with cognitive disorders implies a substantial change in regional and global health policies. Through medical education and updating of knowledge, it is possible to gradually modify prescriptive behaviors that are not optimal for the clinical management of the patient or for the correct administration of health system resources. Only with an adequate provision of human and financial resources will it be possible to face the future growth of this type of disease, a situation that will have a significant health impact in the coming years, both in Argentina and globally.

AUTHOR CONTRIBUTIONS

Jonathan Cubas Guillen (Conceptualization; Formal analysis; Investigation; Writing – original draft); Galeno Rojas (Conceptualization; Writing – review & editing); Ignacio Demey (Conceptualization; Writing – review & editing); Diego Sarasola (Conceptualization; Writing – review & editing); Xavier Merchan del Hierro (Supervision); Gabriel Persi (Supervision); Victoria Aldinio (Supervision); Nahuel Pereira de Silva (Supervision); Julian Fernández Boccazzi (Visualization); Josefina Segui (Visualization); Santiago Muniagurria (Visualization); Afra Gilbert (Visualization); Emilia Gatto (Supervision; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-240018.

REFERENCES

[1] Castro DM, Dillon C, MacHnicki G, Allegri RF (2010) The economic cost of Alzheimer's disease Family or public-health burden? *Dement Neuropsychol* **4**, 262-267.

[2] WHO (2021) Global status report on the public health response to dementia.
[3] (2020) 2020 Alzheimer's disease facts and figures. *Alzheimers Dement* **16**, 391-460.
[4] Demey I, Ollari JA, Rojas G, Bagnati P, Sarasola D, Román F, Tarulla A, Blake A, Sevlever G, Caridi A, Allegri RF Recomendaciones para la detección y diagnóstico de pacientes con demencia debida a Enfermedad de Alzheimer en la Ciudad de Buenos Aires. *Vertex* **144**, 85-96.
[5] Rojas G, Bartoloni L, Dillon C, Serrano CM, Iturry M, Allegri RF (2011) Clinical and economic characteristics associated with direct costs of Alzheimer's, frontotemporal and vascular dementia in Argentina. *Int Psychogeriatr* **23**, 554-561.
[6] Larraya FP, Grasso L, Marí G (2004) Prevalencia de las demencias del tipo Alzheimer, demencias vasculares y otras demencias del DSM-IV y del ICD-10 en la República Argentina. *Rev Neurol Argent* **29**, 148-153.
[7] Aranda M, Calabria A (2019) Social and economic impact of Alzheimer's disease. *Neurol Argent* **11**, 19-26.
[8] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, Collins EC, Solomon P, Salloway S, Apostolova LG, Hansson O, Ritchie C, Brooks DA, Mintun M, Skovronsky DM, TRAILBLAZER-ALZ 2 Investigators (2023) Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA* **330**, 512-527.
[9] Bustin J, Rojas G, O'Neill S, Sarasola D, Triskier F, Urtasun M, Cañás M, Mastai R, Demey I (2020) What is happening with not recommended drugs for dementia in Argentina? Prescription patterns and direct costs analysis. *Int J Geriatr Psychiatry* **35**, 270-275.
[10] Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, Richardson S; Donepezil 401 Study Group (2004) Efficacy of donepezil in mild cognitive impairment: A randomized placebo-controlled trial. *Neurology* **63**, 651-657.
[11] Ilhan Algin D, Dagli Atalay S, Ozkan S, Ozbabalik Adapinar D, Ak Sivrioz I (2017) Memantine improves semantic memory in patients with amnestic mild cognitive impairment: A single-photon emission computed tomography study. *J Int Med Res* **45**, 2053-2064.
[12] Konstantinos I. Avgerinos, Luigi Ferrucci DK (2021) Effects of monoclonal antibodies against amyloid-β on clinical and biomarker outcomes and adverse event risks: A systematic review and meta-analysis of phase III RCTs in Alzheimer's disease. *Ageing Res Rev* **68**, 101339.
[13] U.S. Food & Drug Administration. Drugs@FDA: FDA-Approved Drugs - Aducanumab. Reference ID 4807032. 2021
[14] U.S. Food & Drug Administration. Drugs@FDA: FDA-Approved Drugs - Leqembi. Reference ID 5203190. 2023
[15] D, Zuin D, Nofal P, Tarulla A, Reynoso F, Ollari J, Alves A, Barboza A, Bartoloni L, Bestoso S, Bruera G, Buonanotte F, Casali JI, Colombo O, Alejandra M, Figueroa R, Gómez R, Iguzquiza O, Jacobo M, Kohler E, Leiva M, Lozano C, Menendez C, Murillo M, Patricio L, López D, Lucero C, Nadelman B, Piran G, Romano L, Salman J (2015) Relevamiento de recursos neurológicos en Argentina: Puesta al día del estado del ejercicio de la Neurología. *Neurol Argent* **7**, 225-233.
[16] Kasper S, Bancher C, Eckert A, Förstl H, Frölich L, Hort J, Korczyn AD, Kressig RW, Levin O, Palomo MSM (2020) Management of mild cognitive impairment (MCI): The need for national and international guidelines. *World J Biol Psychiatry* **21**, 579-594.
[17] Birks J, Flicker L (2009) Donepezil for mild cognitive impairment. *Cochrane Database Syst Rev*, CD006104.
[18] Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, Bejanin A, Bombois S, Epelbaum S, Teichmann M, Habert MO, Nordberg A, Blennow K, Galasko D, Stern Y, Rowe CC, Salloway S, Schneider LS, Cummings JL, Feldman HH (2021) Clinical diagnosis of Alzheimer's disease: Recommendations of the International Working Group. *Lancet Neurol* **20**, 484-496.
[19] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, Dekosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL (2014) Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol* **13**, 614-629.
[20] van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2023) Lecanemab in early Alzheimer's disease. *N Engl J Med* **388**, 9-21.
[21] Cummings J, Rabinovici GD, Atri A, Aisen P, Apostolova LG, Hendrix S, Sabbagh M, Selkoe D, Weiner M, Salloway S (2022) Aducanumab: Appropriate use recommendations update. *J Prev Alzheimers Dis* **9**, 221-230.
[22] Mühlbauer V, Möhler R, Dichter MN, Zuidema SU, Köpke S, Luijendijk HJ (2021) Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev* **12**, CD013304.
[23] Allegri RF, Arizaga RL, Bavec CV, Colli LP, Demey I, Fernández MC, Frontera SA, Garau ML, Jiménez JJ, Golimstok Á, Kremer J, Labos E, Mangone CA, Ollari JA, Rojas G, Salmini O, Ure JA, Zuin DR (2011) Alzheimer's disease. Clinical practice guideline. *Neurol Argent* **3**, 120-137.
[24] Yunusa I, El Helou ML (2020) The use of risperidone in behavioral and psychological symptoms of dementia: A review of pharmacology, clinical evidence, regulatory approvals, and off-label use. *Front Pharmacol* **11**, 596.
[25] Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, Slomkowski M, Baker RA, McQuade RD, Cummings JL (2020) Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: Two 12-week, randomized, double-blind, placebo-controlled trials. *Am J Geriatr Psychiatry* **28**, 383-400.
[26] Cummings JL, Devanand DP, Stahl SM (2022) Dementia-related psychosis and the potential role for pimavanserin. *CNS Spectr* **27**, 7-15.
[27] Tariot PN, Cummings JL, Soto-Martin ME, Ballard C, Erten-Lyons D, Sultzer DL, Devanand DP, Weintraub D, McEvoy B, Youakim JM, Stankovic S, Foff EP (2021) Trial of pimavanserin in dementia-related psychosis. *N Engl J Med* **385**, 309-319.
[28] Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S LK (2018) Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database Syst Rev* **52**, 457-459.
[29] Mintzer J, Lanctôt KL, Scherer RW, Rosenberg PB, Herrmann N, Van Dyck CH, Padala PR, Brawman-Mintzer O, Porsteinsson AP, Lerner AJ, Craft S, Levey AI, Burke W, Perin J, Shade D (2021) Effect of methylphenidate on

apathy in patients with Alzheimer disease: The ADMET 2 randomized clinical trial. *JAMA Neurol* **78**, 1324-1332.

[30] Colenda CC, Rapp SR, Leist JC, Poses RM (1996) Clinical variables influencing treatment decisions for agitated dementia patients: Survey of physician judgments. *J Am Geriatr Soc* **44**, 1375-1379.

[31] Mayoral VF de S, Villas Boas PJF, Jacinto AF (2021) Knowledge and attitudes in dementia held by general practitioners in the primary care setting of Botucatu, São Paulo, Brazil. *Arq Neuropsiquiatr* **79**, 107-113.

[32] Jacinto AF, de Oliveira EC, Citero V de A (2015) Adaptação transcultural para o Brasil de um instrumento sobre o conhecimento e as atitudes dos médicos diante da demência. *Dement Neuropsychol* **9**, 245-250.

[33] Turner S, Iliffe S, Downs M, Wilcock J, Bryans M, Levin E, Keady J, O'Carroll R (2004) General practitioners' knowledge, confidence and attitudes in the diagnosis and management of dementia. *Age Ageing* **33**, 461-467.

[34] Jan DL, Delfine D, Eileen VDP, Herlinde VE, Jan S, Birgitte S (2021) The management of dementia by Flemish GPs: It remains a difficult job. *Acta Clin Belgica* **76**, 264-271.

[35] Serrano CM, Allegri RF, Caramelli P, Taragano FE, Camera L (2007) Deterioro cognitivo leve encuesta sobre actitudes de medicos especialistas y generalistas. *Medicina (B Aires)* **67**, 19-25.