Treatment Options for Patients with Alzheimer’s Disease in Mexico: Findings from the Mexican Group of Specialists in Dementia Survey

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Abstract

Objective: To gain knowledge of the main drug therapy options for Alzheimer’s disease in Mexico, whether or not they are being used properly according to findings in international literature.

Design, patients and settings: Patients with objective memory impairment were subjected to a clinical survey in medical centers specialized in memory loss. Each patient’s consultation was conducted like a routine clinical practice. Patients’ data was recorded using an anonymous patient survey. The most commonly used cognitive impairment related drugs were recorded as well as their combination and lack of its use.

Results: Thirty-four centers and 42 investigators participated in the study. A total of 1350 patients were included, 41.48% (n=560) of the total were diagnosed with AD, 85.54% (n=479) of these patients received a cognitive impairment related therapy from which 45.72% (n=219) received an Acetylcholinesterase inhibitor: 21.71% (n=104) received Rivastigmine, 13.78% (n=66) received Donepezil and 10.23% (n=36.53) received Galantamine; finally 36.53% (n=175) received Memantine. Combinations were found in 17.75% (n=85) of the patients.

Conclusion: Ache as a group has become the backbone of AD’s treatment, whether they are used unique therapy or as a combined treatment with other types of drugs, they offer cognitive impairment delay when used properly (this including correct dosage, combinations and initiation of treatment). Memantine has positioned itself as the prime option for combined therapy among Mexican patients with AD.

ABBREVIATIONS
AD: Alzheimer’s Disease; MMSE: Mini-Mental State Examination; CIR: Cognitive Impairment Related; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; NMDA: N-Metyl-D-Aspartate; AChEIs: Acetylcholinesterase Inhibitors; AChE: Acetylcholinesterase; BuChE: Butyrylcholinesterase; LAMIC: Low and Middle Income Countries; MNCS: Medication for Non-Cognitive Symptoms; FDA: Food and Drug Administration; VD: Vascular Dementia

INTRODUCTION

Alzheimer’s disease (AD) treatment has evolved throughout the years based on the deeper understanding of the disease natural history; initial changes such as amyloid β (Aβ) accumulation and intracellular neurofibrillary tangles containing abnormal phosphorylated tau protein occur significantly earlier before the appearance of the first cognitive impairment symptoms [1,2,3] when such symptoms become evident, an important alteration in neurotransmitters has already taken place involving diverse...
According to aforementioned evolution, the first line of treatment for AD includes the acetyl cholinesterase inhibitors such as donepezil, galantamine and rivastigmine which are indicated in patients with mild to moderate symptoms (MMSE score 14-26 for mild and MMSE score 10-13 for moderate), and as a second stage treatment N-methyl-D-aspartate receptor antagonist such as memantine for patients with severe symptoms (MMSE score <10 points), which is used to normalize glutamatergic neurotransmission [4,5].

Available drug types for AD (Memantine and the AChEIs) have showed efficacy when used as monotherapy and since they target different pathways of AD, there is an increasing interest to determine whether or not their use as a combined treatment is superior to monotherapy and when it is better to use such combination [6,7].

This subject has become relevant since in recent years it has been confirmed an increased prevalence and incidence in dementias including AD [8]; while it remains undecided whether this increase is due to the amelioration of the life expectancy, the result of changes in lifestyle or an improvement in diagnosis precision, epidemiological data shows that AD has become the most common type of dementia; it accounts for an estimated 60 to 80 % of all causes of dementia [9,10] and affects approximately 24.2 millions of people; almost two thirds of the total living currently in Low and Middle Income Countries (LAMIC) [11-15]. Considering that there is serious discrepancy between the amount and characteristics of available information, we must remain cautious, since current projections might be underestimating the real impact of AD and other dementias in the global population, especially in developing countries.

With the purpose to put together a national survey to screen the way specialized memory centers diagnose and therapeutically approach this disease, the Group of Specialist in Dementia was created [16].

MATERIALS AND METHODS

This is a descriptive, prospective, cross-sectional multicenter study. Forty-two researchers worked in 34 different memory-specialized centers around Mexico. From February 1st to December 1, 2012, each center recruited randomly a minimum of 5 new subsequent patients with subjective cognitive impairment. All patients that assisted a memory center or memory specialist (hospital or ambulatory) and had cognitive impairment or expressed moderate to severe memory loss were included in this study. Patients with subjective memory complaints associated with non-central nervous system disease or space-occupying lesions, those whose diagnosis after consultation was different from cognitive impairment, patients who were not able to complete a MMSE or patients with a life expectancy of less than 6 months were also excluded.

Each patient’s visit was carried out according to a standardized clinical practice of each investigator, in which the investigator made an interrogation, physical exam, reviewed the laboratory and imaging tools and performed a questionnaire. For treatment, the investigators were given the liberty to choose whichever drug they considered more appropriate based on their knowledge and past experience once the diagnosis was made, and were asked to deliver such information afterwards.

Out of these variables, the qualitative ones were analyzed by their frequency of appearance in each patient. The SPSS software version 20.0 was used to obtain and quantify our data.

RESULTS AND DISCUSSION

The final sample included 1350 patients, being the female population the most prevalent subgroup (n=880 female subgroup; n=470 male subgroup), with an age median of 78.39, minimal age was 27 and the elder patient had 112 years.

Of the total of patients from our population, we observed a clear dominance from the patients which received any type of cognitive impairment related treatment, whether it was in the monotherapy group or in the combined treatment group (n=879; 65.11%), in comparison with those patients which received no treatment at all (n=410; 30.37%), the first group even doubling the second.

There was in our population, a subgroup of patients which received exclusively treatment with drugs that were not part of the AChEIs or memantine (n=61; 4.61%).

Monotherapy demonstrated to be the first choice of treatment in dementia specialized centers in Mexico. The most commonly used drug was memantine, since 347 of our patients were undergoing therapy with this particular drug, on addition it was also the most frequently combined drug when the patient received more than one cognitive impairment related drug.

For practical reasons, the treatments that were not part of AChEIs or memantine were grouped under the label of “other treatment”, and classified according to its usefulness regarding dementia. The most commonly type of medication used in this group were the antidepressants (n=112; 49.56%).

**Pharmacological treatment for Alzheimer’s disease**

In our study, from the total of patients, 560 patients diagnosed AD where included, out of this, 85.53% (n=479) where receiving some type of cognitive impairment related therapy at the moment of the study, while 20.1% (n=113) of the patients in this subgroup, where receiving medication for non-cognitive symptoms (MNCS).

Even though a final statement has not been made in the literature to support combined treatment, our group found that a considerable percentage of the patients with AD were using such combination, out of this AChEI and Memantine combinations represented a substantial group within our sample.

Combinations of two AChEI were also found in a small percentage specifically donepezil with galantamine and as donepezil with rivastigmine. It is worth noting that even though they belong to the same group of cognitive impairment therapy, they target two different enzymes of the cholinesterase family: Acetylcholinesterase (AChE) whose major function is to terminate the action of acetylcholine by hydrolyzing it to choline and acetate, and Butyrylcholinesterase (BuChE) which...
constitutes 1 to 10% of the total amount of cholinesterase in the adult CNS.

Donepezil in vitro is highly selective for AChE as well as galantamine, whereas rivastigmine is more active on BuChE. This difference in specificity does not improve cognitive outcome when combining two AChEIs, but it does increase the unwanted side effects caused by cholinergic overstimulation such as nausea, vomiting, diarrhea, dizziness, anorexia and asthenia [17]. There is a lack of studies involving the co-administration of two AChEIs and it is not recommended to do so [18].

Further analysis of the group of patients diagnosed with AD, showed that 22.8% (N = 94; n = 24) for mild symptoms group, 12.2% (N = 344; n = 42) for the moderate symptoms group and 11.8% (N = 122; n = 14) of the severe symptoms group, were not receiving any type of treatment, the cause varied, but mostly it was due to reluctance from the patients’ families.

On the other hand, in patients receiving treatment, AChEI was the most commonly used group surpassing the Memantine group. Combined, the mild and moderate symptoms group accounted a total of 438 patients, and had a larger number of patients which received AChEIs consistent with the literature.

For the group of patients with severe cognitive impairment symptoms (N = 122), 31.2% (n = 38) received memantine while only 29% (n = 35) received AChEIs this being the only group in which the latter were not the most commonly used drug therapy, information that is consistent with the Pathophysiology proposed targets for drug therapy in AD.

**Discussion**

Considering both drug types, AChEI and Memantine (NMDA receptors competitive antagonist) have different and potentially complementary action mechanisms; the next logical step in AD treatment would be to combine them expecting to obtain better results in global function, Activities of Daily Living (measured by Katz scale) [19], and cognitive symptoms; however clinical studies have shown mixed results.

International guidelines consider early diagnosis as well as an early beginning of treatment as a corner stone for success in pharmacological treatment for AD, which can improve the functional status for AD patients [20, 21].

For mild to moderate disease (considering MMSE) the AChEIs have shown improvements in daily life activities, behavior alterations, cognitive function and global function [22-25]. Two prospective, open, non-randomized studies have found that patients that received a higher dose of AChel presented a better functional state as opposed to the patients that received a lower dose [26,27].

For patients with moderate to severe symptoms studies have shown significant improvement in cognitive function, functionality, global status and conduct when treated with memantine [28], which is especially adequate for fragile patients [29,30].

Current options for pharmaceutical treatment of dementia, offer no improvement concerning mortality rates, and only offer short-term improvement in symptoms.
Despite the previous data, international literature, supports the use of AChEIs as the main option for treatment of Alzheimer’s disease, and even though it has not been approved officially by the Food and Drug Administration (FDA) in the United States, this group of drugs is used for Vascular Dementia (VD) as well [31]. N-methyl-D-aspartate receptor antagonist offer blockage of the over activated glutamate receptors, whose continuous activation (even in a mild proportion) leads to neuronal damage [32]; even though memantine has been used for moderate and severe cognitive impairment symptoms, pathophysiology suggest an early treatment implementation (especially in combination with AChEIs) may be beneficial for the patients outcomes measured with ADL, psychiatric symptoms and overall progression of dementia.

This data supports and validates the data obtained from our survey, since the participant centers have been treating their patients in accordance with international literature.

It is also important to point out the fact that non cognitive symptoms and its management have acquired an special place in dementia treatment; this fact is also evident in our study since as we mentioned before, the most common type of medication used (aside from cognitive impairment treatment) were antidepressants, being the Selective Serotonin Receptor Inhibitors the main group used in our sample, its importance is related to the high prevalence of depression and anxiety in the population with dementia.

We must not lose sight of the upcoming treatment tendencies particularly since numerous studies have been carried out in order to determine the role of combined therapy, so far, showing promising results.

CONCLUSION

The Mexican Group of Specialists in dementia was assembled with the purpose to obtain knowledge of the current situation of patients with dementia throughout Mexico, including the main therapy options for cognitive impairment. Fortunately the main drug therapy lines have become available in Mexico and all the centers included in the study follow the tendencies found on international literature including the relatively new and promising approach of early combined treatment even though the “traditional” tritrated option (Selecting with AChel in early stages and continuing with N-methyl-D-aspartate antagonist [memantine] when the clinical spectrum of dementia worsens) is still a strong one among these centers.

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