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Pharmacological modulation of cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease☆,☆☆,★

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ABSTRACT

To evaluate correlations of pharmacological treatment with cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease with low schooling, subjects were assessed for demographic features, neuropsychiatric symptoms, cognitive decline, functionality, caregiver burden, *APOE* haplotypes and pharmacological treatment. Among 217 patients, use of cholinesterase inhibitors with or without Memantine was associated with less neuropsychiatric symptoms, while anti-psychotics and/or anti-epileptic drugs were associated with lower instrumental functionality. Anti-psychotics were also associated with more neuropsychiatric symptoms in moderately impaired patients, possibly reflecting the greater need for such treatment when behavioral symptoms are present. Patients receiving more medications were usually younger, obese, married, with higher schooling and more neuropsychiatric symptoms. APOE4+ haplotypes were correlated with earlier dementia onset, but not with pharmacological treatment. Higher caregiver burden was associated with more psychotropic drugs. A trend was found for treatment with cholinesterase inhibitors and Memantine to be associated with longer lengths of dementia for moderately impaired but not for severely impaired patients, regardless of *APOE* haplotypes, translating into a synergistic effect among such medications for slowing cognitive decline but not for prolonging survival. Further longitudinal studies may be required to assess dose–response relationships regarding treatment with psychotropics for patients with dementia.

1. Introduction

A progressive decline in cognition and functionality is the hallmark of Alzheimer's disease, with significant impacts over caregiver burden. Established therapies for patients with Alzheimer's disease have shown mild effects over slowing of such decline, but their efficacy for patients with low schooling had not been previously evaluated.

Pharmacological treatment for neuropsychiatric symptoms is still controversial in view of the few off-label therapeutic alternatives available, and many studies are subject to financing bias from pharmaceutical companies. Atypical neuroleptics are modestly efficacious but bring serious side effects particularly for the elderly, including venous thromboembolism, stroke and death [1–3].

We sought to assess correlations of pharmacological treatment with cognitive and behavioral symptoms in a university hospital based sample of patients with dementia due to Alzheimer's disease (AD) [4] in several stages and with variable levels of education, with no bias from pharmaceutical corporations.

2. Methods

Consecutive outpatients with AD in several levels of clinical evolution were recruited from the Behavioral Neurology Section of *Hospital São Paulo*, Federal University of São Paulo — UNIFESP, from November 2010 to February 2013 (28 months). After diagnostic confirmation, they were assessed for: gender, age, schooling, estimated age of onset of AD, marital status, quantification of current alcohol consumption or smoking, body mass index, and scores on the Neuropsychiatric Inventory [5], Mini-Mental State Examination [6], Severe Mini-Mental State Examination [7], Clinical Dementia Rating [8] (CDR), a 15-item Clock Drawing Test [9] (free drawing), the Index of Independence in Activities of Daily Living [10], Lawton's Scale for Instrumental Activities of Daily Living [11], and

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the Brazilian Version of the Zarit Caregiver Burden Interview [12]. Current use of any medications, but particularly cholinesterase inhibitors (ChEis), Memantine, anti-depressants, anti-psychotics and anti-epileptic drugs, was also quantified considering that patients had been receiving them for at least three months before the evaluation. All cognitive assessments and body mass index measurements were conducted on weekdays at morning time, by the same examiner (FFO).

Diagnosis of AD was in accordance with the National Institute on Aging–Alzheimer's Association criteria [4]. Obesity was diagnosed when body mass index was over 30 kg/m^2.

For the validated version of the Clock Drawing Test [9] that was used in this study, patients were instructed to freely draw a clock that marked 11:10, setting the hands and numbers on the face (repetition was allowed). Scoring comprised 15 items, each scored as zero or one: outer circle present and closed; acceptable circle diameter; intact sequence 1–12, with no omissions or intrusions; only Arabic numerals; correct sequential order of the numerals; paper is not rotated for number placement; proper symmetrical spacing; all numbers inside the circle; only two hands present; any mark to indicate the hour; any mark to indicate the minute; minute hand longer than hour hand; no pointless intrusions; both hands connected, or up to 2 mm space between them; and center of the clock drawn or inferred where hands meet.

The Index of Independence in Activities of Daily Living [10] reflects behavioral levels of six sociobiological functions: bathing, dressing, toileting, transfer, continence, and feeding. Each function was scored as zero for dependency or one for independence, according to information from caregivers, with an index total of zero to six. A trichotomous version (1 = unable; 2 = able with help; 3 = able without help) of Lawton's Scale for Instrumental Activities of Daily Living [11] was employed, with scores for using the telephone, getting to places beyond walking distance, grocery shopping, meal preparation, housekeeping, doing handyman work, doing laundry, taking own medications, and handling finances; information had to be obtained from caregivers, with a total score of 9 to 27.

The Brazilian Version of the Zarit Caregiver Burden Interview [12] comprises 14 questions graded on a scale of zero to four. It was adapted from the original version, with comparable reliability for assessing caregiver burden in AD.

After blood samples were collected from all patients in tubes with EDTA 0.1%, genomic DNA was extracted for genotyping. *APOE* haplotypes were determined for all patients (SNPs rs7412 and rs429358 assessed by way of Real-Time Polymerase Chain Reactions using TaqMan® SNP Genotyping Assays). Real-Time Polymerase Chain Reactions were undertaken on the Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems®, USA) following the standard protocols of the manufacturer.

Statistical comparisons for continuous variables were conducted by way of Mann–Whitney test when two groups were compared, or Kruskal–Wallis test for three or more groups. Linear regression models were employed for comparisons regarding medication intake and independent variables (test results, body mass index, alcohol consumption). Spearman correlations were estimated for age at examination, schooling, and medication intake. The threshold of significance was set at $\rho < 0.05$.

This study is part of the research project 1067/10 (CAAE 0540.0.174.000-10) approved by the Ethics Committee of *Hospital São Paulo*, Federal University of São Paulo — UNIFESP, on August 2010. All invited patients and their legal representatives agreed to participate on the research and signed the Informed Consent Form before the evaluation, with no exceptions.

3. Results

A total of 217 patients were included; 147 were female (67.7%) and 70 were male (32.3%); 109 (50.23%) were married, while 6 (2.76%) were divorced, 19 (8.76%) were single, and 83 (38.25%) were widowers; 56 (25.8%) had history of alcohol consumption, whereas 11 (5.1%) were regularly drinking at survey time; 79 (36.4%) had smoking history, whereas 14 (6.5%) were regular smokers at survey time. Obesity was diagnosed in 36 patients (16.6%). Table 1 shows full demographic data and test results.

Overall, 170 patients (78.34%) were using ChEis at survey time: among these, 60 used Rivastigmine (35.3%), 58 used Donepezil (34.1%), and 52 used extended-release Galantamine (30.6%); 52 patients (23.96%) were treated with Memantine, while 88 (40.55%) used anti-depressants; 53 patients used anti-psychotics (24.42%), namely Quetiapine ($n = 42$), Risperidone ($n = 10$) and Olanzapine ($n = 1$), while 19 used anti-epileptic drugs (8.76%), mostly Carbamazepine ($n = 7$) and Valproic Acid ($n = 6$).

Use of ChEis had no differential impact over scores on the Clock Drawing Test [9] ($\rho = 0.116$), Index of Independence in Activities of Daily Living [10] ($\rho = 0.474$), Lawton's Scale for Instrumental Activities of Daily Living [11] ($\rho = 0.472$), or the Brazilian Version of the Zarit Caregiver Burden Interview [12] ($\rho = 0.491$). However, when caregiver burden scores were higher, patients were more likely to use Memantine with or without ChEis ($\rho = 0.015$). Patients with higher global scores on the Neuropsychiatric Inventory [5] were also more likely to use Memantine ($\rho = 0.001$).

Treatment with any anti-depressants had no differential impact over scores on the Clock Drawing Test [9] ($\rho = 0.458$), Neuropsychiatric Inventory [5] ($\rho > 0.26$), Index of Independence in Activities of Daily Living [10] ($\rho = 0.696$), Lawton's Scale for Instrumental Activities of Daily Living [11] ($\rho = 0.395$), or the Brazilian Version of the Zarit Caregiver Burden Interview [12] ($\rho = 0.642$), regardless of CDR scores. Treatment with anti-psychotics and/or anti-epileptic drugs had no impact over the Clock Drawing Test [9] ($\rho = 0.095$) or the Index of Independence in Activities of Daily Living [10] ($\rho = 0.586$), but had highly significant associations with lower scores on Lawton's Scale for Instrumental Activities of Daily Living [11] ($\rho < 0.001$) and with higher scores on the Brazilian Version of the Zarit Caregiver Burden Interview [12] ($\rho = 0.018$).

Table 2 shows the distribution of neuropsychiatric symptoms according to each dementia stage, while Table 3 shows comparisons of neuropsychiatric symptoms according to pharmacological treatment in different dementia stages. With the exception of scores for anxiety, all other items from the Neuropsychiatric Inventory [5] had higher scores for more impaired patients, but more remarkably apathy and

Table 1
Demographic data and test results.

Variable (units), $n = 217$	Mean	SD[a]	Range
Age at examination (years-old)	78	6.2	60–95
Age of dementia onset (years-old)	73.19	6.8	52–88
Length of the dementia syndrome (years)	5.4	2.9	0.5–14.5
Schooling (years)	4.21	3.7	0–15
Body mass index (kg/m^2)	25.75	4.3	14.28–41.62
Daily amount of different medications	4.52	2.5	0–12
Daily amount of pills/injections	6.21	3.6	0–16
Lifetime alcoholic drinking load (liters per year)	17.26	50.8	0–315
Current alcoholic drinking load (liters per year)	1.67	11.3	0–120
Lifetime smoking load (packs per year)	48.75	103.7	0–700
Current smoking load (packs per year)	14.38	62.1	0–365
Neuropsychiatric Inventory (0–120 points)	22.6	16.6	0–87
Mini-Mental State Examination (0–30 points)	15.64	5.8	0–29
Severe Mini-Mental State Examination (0–30 points)	26.43	4.9	0–30
Clock Drawing Test (0–15 points)	6.26	4.5	0–15
Index of Independence in Activities of Daily Living (0–6 points)	5	1.6	0–6
Lawton's Scale for Instrumental Activities of Daily Living (9–27 points)	14.21	4.7	9–27
Brazilian Version of the Zarit Caregiver Burden Interview (0–56 points)	16.58	10.7	0–54

[a] SD = standard deviation.