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Article

Impact of pharmacist intervention in patients with Alzheimer's disease.

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To assess the therapy relative to indication, effectiveness, safety and adherence in patients with Alzheimer's disease (AD). An interventional, prospective, non-randomized study was conducted in a single secondary care center in Brazil. The pharmacist-led Medication Therapy Management (MTM) was conducted to detect drug-related problems (DRPs) at baseline and after six months of intervention. The health status outcomes (i.e. cognitive screening tests; levels of glucose; total cholesterol; triglycerides; thyroid stimulating hormone; serum free thyroxine; and blood pressure) were measured. 66 patients with AD were included, of whom 55 patients completed the follow-up of six months. 36 patients (36/55) were non-adherent to AD drug therapy. Out of detected 166 DRPs, 116 were solved. Four patients were withdrawn from the AD protocol due to resolution of prodromal symptoms. On the conclusion of the study, the MTM improved and controlled blood pressure, glucose, total cholesterol and triglycerides levels ($p<0.05$). The pharmacist-led MTM was effective in solving 69.8% of DRPs, improving and controlling the clinical parameters evaluated.

Keywords: Elderly. Face-to-face. Medication adherence. Medication errors. Medication review.

INTRODUCTION

Dementia has become a major public health problem due to the increased prevalence, chronicity, caregiver overload, and high personal and financial costs of health and care, as well as being a major cause of disability (Alzheimer's Association, 2017; World Health Organization, 2012). The most prevalent type of dementia is Alzheimer's disease (AD) (Burns, Iliffe, 2009).

Patients with dementia are more susceptible to Drug Related Problems (DRPs) due to pharmacokinetic and pharmacodynamic changes (Reeve *et al*., 2017), cognitive impairment, changes in the blood-brain barrier (Mehta *et al*., 2015), and inadequate adherence to drug therapy (Hayes *et al*., 2009).

In addition, studies have found that among these patients, approximately 65 - 93% of them had at least one DRPs (Gustafsson *et al*., 2016; Wucherer *et al*., 2017), such as use of potentially inappropriate drugs (Forgerini *et al.,* 2020), therapeutic ineffectiveness, use of unnecessary drugs (Gustafsson *et al*., 2016), and treatment non-adherence that could range from 17% to 100% (Smith *et al*., 2017; Wucherer *et al*., 2017).

Nonetheless, few studies have evaluated the impact of pharmacist-led interventions on the outcomes of use of medications, since the majority of them focused on withdrawal of dementia drug therapy or antipsychotics

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medications (Nguyen *et al*., 2019). Thus, most of studies did not evaluate the impact of integration of information about patient assessment, drug therapy and clinical parameters considering AD, dementia or cognitive impairment, as well the comorbidities and therapeutic experience.

Hence, our hypothesis was to assess whether pharmacist-led Medication Therapy Management (MTM) in the full assessment contributed to the resolution of DRPs related to indication, effectiveness, safety, and adherence (IESA) in patients with AD.

METHODS

Study Design and Ethical Aspects

A prospective, uncontrolled, non-randomized, and interventional study was conducted by means of a before-after analysis (quasi-experimental study). Although a quasi-experimental study was not a true experimental study, the report was based on TREND Statement Checklist (Des Jarlais, Lyles, Crepaz, 2004), recommended for intervention and non-randomized studies.

The study was approved by the Research Ethics Committee (2.043.644) and was conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. This study was registered with ClinicalTrials.gov, number NCT02222181.

Setting and Participants

The study was conducted at the "Centro de Referência do Idoso de Araraquara (CRIA)", Brazil. CRIA is a care unit specialized in geriatric ambulatory care of the Public Health System with the use of protocols for forgetfulness, dementia, mild depression and sequelae of stroke.

The patients eligible for the study were those with diagnosis of AD enrolled in the Clinical Protocol and Therapeutic Guidelines of Alzheimer's disease (PCDTDA) (Costa *et al*., 2017).

According to the PCDTDA guidelines, the diagnosis of AD consists of an evaluation of the patients' clinical history; cognitive screening in accordance with clinical parameters of the Mini Mental State Examination (MMSE), and Clinical Dementia Rating (CDR); laboratory tests (blood count, electrolytes, blood glucose, urea, creatinine, thyroid-stimulating hormone, alanine aminotransferase, aspartate aminotransferase, vitamin B12, folic acid, serum serology for syphilis, and HIV tests); in addition to magnetic resonance or computed tomography (Costa *et al*., 2017). Furthermore, after diagnosis, the AD is classified as probable, possible (absence of other neurological, psychiatric or systemic disorders which may induce dementia) and defined (postmortem confirmation only) (Costa *et al*., 2017).

Therefore, patients enrolled in the PCDTDA and assisted at CRIA for at least a year were included. Patients who resided in nursing homes were excluded, due to ethical considerations.

For the recruitment of participants, all patients considered eligible were invited to participate in the study, therefore a convenience sample was obtained.

All the caregivers, relatives or patients provided written informed consent and agreed to participate in the follow-up period for at least six months.

The defined follow-up time of six months was established in accordance with the PCDTDA guidelines that provide for semiannual monitoring according to the clinical parameters of cognitive screening to evaluate the effectiveness of anticholinesterase treatment (Costa *et al*., 2017).

Interventions

The MTM is a clinical method that systematizes the process of identifying, solving and preventing DRPs, according to the taxonomy of drug evaluation of IESA (Cipolle *et al*., 2012; Strand, Cipolle, Morley, 1988).

Interventions were conducted by one pharmacist during three steps: initial patient assessment (identifying medication needs, DRPs and therapeutic experience); care plan (solving DRPs, and negotiating therapeutic goals), and care plan evaluation (clinical outcome assessment, therapeutic monitoring and identifying the new therapeutic experience) (Cipolle *et al*., 2012; Strand *et al*., 1988). Decision making was discussed with the pharmacist's team.

The follow-up and interventions were carried out with the patient and caregiver/relatives for six months, during scheduled appointment at the CRIA and at the patient's home. The first visit and returns lasted about an hour and 30 minutes, respectively. The frequency of returns depended on the medication needs and clinical condition of the patient; with the number of visits ranging from twice a week to fortnightly returns.

The interventions were stratified into pharmaceutical and educational interventions. The pharmacist acted in patient counseling, suggestions for adjusting in drug therapy, ordering laboratory tests, monitoring results, reporting and referral to other health care providers or services. A pill box, medication schedule, written reminders, wake-up calls and medication provided in dose-dispensing units were strategies adopted according to the patient's medication needs to promote adherence (Table I). In addition, interventions were also conducted together with CRIA healthcare professionals when needed.

TABLE I - Variables of interest and sources of measures and measurement

Variable	Sources of measures and measurement
Age, marital status and schooling	Self-report through interviews and medical records
Alzheimer's disease	Patient diagnosed with Alzheimer's disease according to criteria established by the Clinical Protocol and Therapeutic Guidelines of Alzheimer's disease (PCDTDA) (Costa *et al*., 2017) and in use at least of one of the drugs of AD drug therapy: galantamine, rivastigmine, donepezil or memantine.
Stage of Alzheimer's disease	Clinical Dementia Rating (Morris, 1993)
Cognitive screening	Mini-mental State examination (Folstein et al., 1975)
Comorbidity	Self-report in face-to-face interviews and interventions, medical records and drug therapy in use
Drug therapy in use (pharmaceutical active ingredient, pharmaceutical form, dose, dosage and route of administration)	Self-report in face-to-face interviews and interventions, medical records and prescriptions
Benzodiazepines use (drug, dose and time of use)	Self-report in face-to-face interviews and interventions, medical records and prescriptions
Hemodynamic parameter	Parameters of systolic and diastolic blood pressure by means of blood pressure measurement
Biochemical parameter	Postprandial capillary glucose; glycated hemoglobin; fasting total cholesterol; fasting triglycerides and prostate specific antigen established by means of self and laboratory tests
Biochemical parameters of confounding factors of Alzheimer's disease (hypothyroidism and depression)	Dosage of thyroid-stimulating hormone (TSH); free thyroxine (T4) and vitamin B12
Drug Related Problem	Classified in indication (unnecessary drug therapy and need for additional therapy); effectiveness (ineffectiveness and drug therapy in very low dose); safety (adverse drug event; medication error and drug therapy in high dose); and adherence (non-adherence) (Cipolle, R.J., Strand, L.M. and Morley, 2012)

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TABLE I - Variables of interest and sources of measures and measurement

Variable	Sources of measures and measurement
Therapeutic experience of patient and caregiver/relatives	Self-report on face-to-face interviews and interventions by patients answering the questions "*How do you see your state of health*?", "*What has been your experience with medications for your condition*?", "*How do you feel about your medications*?", "*What do you expect from your medicines*?", "*Do you have concerns about your medications*?" (Ramalho-de Oliveira et al., 2012)
Adherence to Alzheimer's disease drug therapy (adherent or non-adherent)	Non-adherence according to indirect method due to drug therapy possession with delay of three or more days (Obreli-Neto et al., 2011) and therapeutic experience of patient and caregiver/relatives about the drug therapy in use (Ramalho-de Oliveira *et al*., 2012)
Effectiveness of Alzheimer's disease drug therapy	Scores of Mini-mental State Examination and Clinical Dementia Rating according to the guidelines of the PCDTDA (Costa *et al*., 2017)
Pharmaceutical intervention	The pharmaceutical interventions consisted of adjustment of medication schedules, adjustment request for or suggestions of other alternatives/pharmaceutical forms for the prescriber; prescription of *over-the-counter medications*; guidance about administration and correct use of drug therapy; providing medication in dose-dispensing units by intake schedule and referral to other health professionals. Interventions of educational nature consisted of information on comorbidities, non-pharmacological strategies and self-care.

Note: The reference values used for hemodynamic parameters, biochemical comorbidities and confounding factors, as well as the MMSE and CDR scores are given in Appendix A.

Hypothesis

The hypothesis tested (H1) was that MTM would contribute to solving problems related to indication, effectiveness, safety and IESA in patients with AD.

Outcomes

The primary outcome measures were to evaluate the effectiveness of MTM in solving DRPs and improving physical and biochemical parameters. The secondary outcome measure was to assess the cognitive impairment resulting from chronic use of benzodiazepines (BZD).

The main source of information was interviews (face-to-face) with patients and caregivers; cognitive/mental assessment test; drug prescription; laboratory tests; and patient self-monitoring data. In addition, medical records were used as secondary sources of data.

Sample Size

As this was a convenience sample, as previously reported, the sample size was not calculated.

Blinding

There was no blinding of the researcher who conducted the interventions, or of those who assessed the outcomes. However, there was blinding of the statistics that led to the analyses.

Unit of Analysis and Statistical Methods

The Shapiro-Wilk test was used with the *software* Statistica 8.0® to analyze the normality, and for interpretation and analysis of the results, the Student's-*t* test (software Microsoft Excel 2010©) was used. The Student's-*t* test was applied for comparison of the

characteristics at baseline and after intervention. The level of significance was 5%.

The non-parametric Mann-Whitney test was used to compare the cognitive impairment of BZD users and non-users, because it was a small, independent and unpaired sample.

RESULTS

In this study, 66 patients were included, however, 55 patients completed the entire follow-up period (Figure 1).

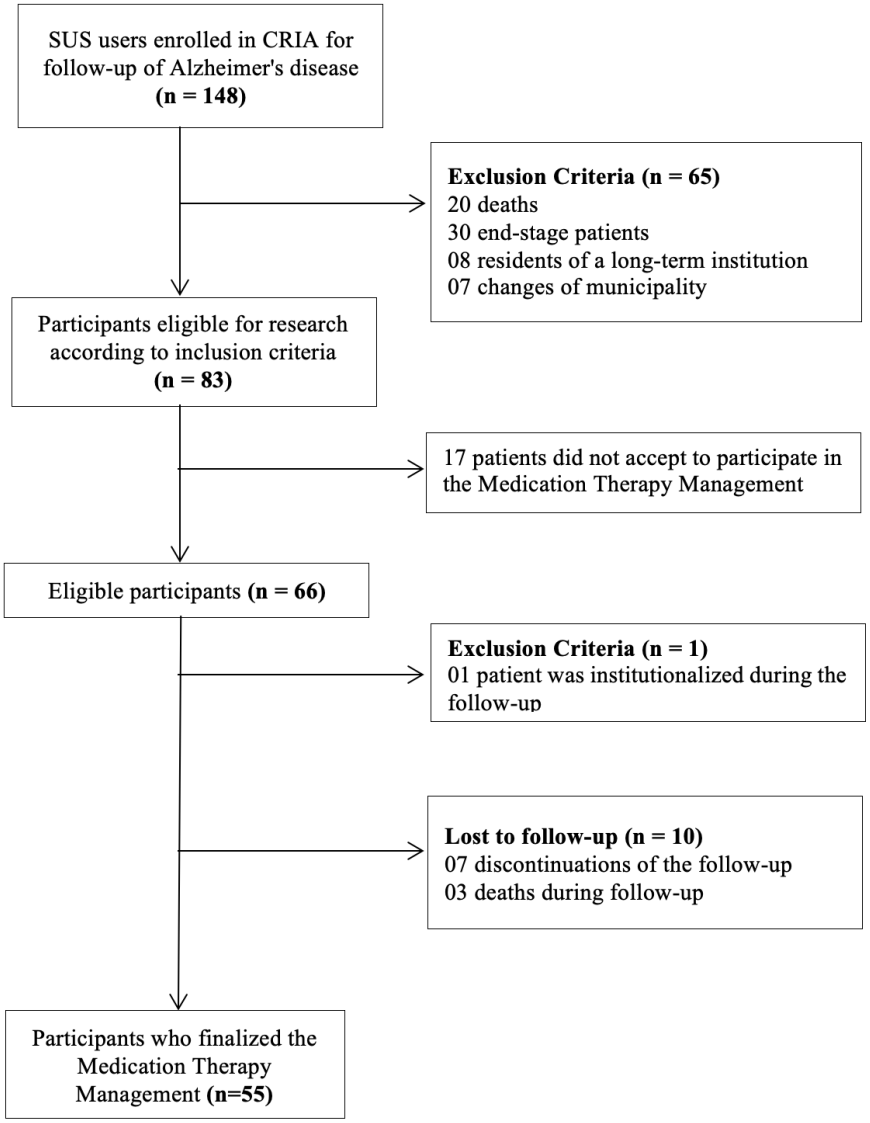

FIGURE 1 - Flowchart of patient selection for the Medication Therapy Management

The majority if the patients were women, aged 62 to 93, who had less than four years of schooling. The most frequent comorbidities were high blood pressure (n = 30), dyslipidemia (n = 22), depression (n = 14), diabetes (n = 14), insomnia (n = 13), and dysphagia (n = 08).

All patients had at least one DRP, with an average of three DRPs per patient. The mean number of interventions per patient was five (standard deviation: ± 2.8), and the patients with the most interventions were those with the highest number of DRPs.

In total, 285 interventions were performed: 190 pharmaceutical and 95 educational interventions with patients, caregiver/relatives, and healthcare professionals.

The most frequent pharmaceutical interventions were adjusting dosages (n = 61), referring patients to other health services (n = 41), home blood pressure and glycemic monitoring (n = 17), providing medication in dose-dispensing units (n = 16), withdrawing drug therapy (n = 10), among others. Half of the pharmaceutical interventions to improve therapeutic effectiveness and adherence were dosage adjustments relative to the medication schedule, mainly concerning administration of anticholinesterase donepezil for the night period. Interventions of an educational nature were related to health problems, appropriate use of the drug therapy and the benefits of adherence (n = 40); and healthy nutrition (n = 55) (Table II).

TABLE II - Description of interventions conducted with patients with diagnosis of Alzheimer's disease and their caregivers/ relatives and health professional and their absolute frequencies, Araraquara

Intervention	With patient and their caregiver/relative (n)	With healthcare professional (n)
Pharmaceutical intervention		
Dosage adjustments (change of medication intake time; dose modification and routine adjustment)	53	10
Medication in dose-dispensing units	16	-
Pharmacist indication	10	10
Medication taking reminder	09	-
Indication of alternative drug therapy	02	07
Replacement of pharmaceutical form	02	02
Drug therapy discontinuation	01	09
Report to the geriatric	-	18
Referral to other services	-	41
Subtotal	93	97
Interventions of educational nature		
Healthy eating habits	55	-
Comorbidities and drug therapy	40	-
Subtotal	95	-
Total	**188**	**97**

The most prevalent DRPs concerned indication and safety. As regards indication DRPs, the majority were related to the need for additional drugs for dyslipidemia and high blood pressure, identified through laboratory tests and residential blood pressure monitoring. Safety DRPs were associated with adverse drug events (ADE), medication errors and drug therapy in high doses.

Of the DRPs identified, 69.8% were solved. The DRPs were identified by using more than one strategy was used, the most common being face-to-face interviews and interventions, followed by monitoring the effectiveness of drug therapy through laboratory tests that contributed to identifying and monitoring half of the DRPs found (Table III; Table IV).

TABLE III - Description of Drug Related problem (DRP), according to nature, the adopted strategy and rate of problem-solving by Medication Therapy Management, Araraquara

DRP classification	Identified DRP Baseline	N (Rate of problem-solving) Six months follow-up
INDICATION		
Unnecessary drug therapy	37	33 (0.9)
Need for additional drug therapy	21	15 (0.7)
Subtotal	*58*	
EFFECTIVENESS		
Ineffectiveness	06	06 (1.0)
Drug therapy in very low dose	14	11 (0.8)
Subtotal	*20*	
SAFETY		
Adverse drug event	28	12 (0.4)
Medication error	16	04 (0.2)
Drug therapy in very high dose	05	05 (1.0)
Subtotal	*49*	
ADHERENCE		
Non-adherence	39	30 (0.7)
Subtotal	*39*	
Total	**166**	**116 (69.8)**

Legend: DRP= Drug Related problem.

TABLE IV - Request for laboratory tests to identify and monitor the Drug Related Problem (DRP) identified and the respective rate of problem-solving indices by the Medication Therapy Management, Araraquara

Nature of the DRP identified and request for laboratory tests	Identified DRP Baseline	N (Rate of problem-solving)
Indication		
Total cholesterol (>200 mg/dL)	07	02 (0.2)
Vit.B_{12} (<210 mg/dL)	03	01 (0.3)
Serum glucose (>99 mg/dL)	02	00 (0)
Glycated hemoglobin (< 7%)	01	01 (1.0)
Effectiveness		
Glycated hemoglobin (< 7%)	03	01 (0.3)
TSH (0,40 – 4,0 uUI/mL)	02	01 (0.5)
Triglycerides (>150 mg/dL)	01	01 (1.0)

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TABLE IV - Request for laboratory tests to identify and monitor the Drug Related Problem (DRP) identified and the respective rate of problem-solving indices by the Medication Therapy Management, Araraquara

Nature of the DRP identified and request for laboratory tests	Identified DRP Baseline	N (Rate of problem-solving)
Serum glucose (>99 mg/dL)	05	02 (0.4)
Safety		
Total cholesterol (>200 mg/dL)	02	02 (1.0)
Triglycerides (>150 mg/dL)	01	01 (1.0)
B_{12} vitamin (<210 mg/dL)	02	01 (0.5)
Adherence		
Total cholesterol (> 200 mg/dL)	03	01 (0.3)
Triglycerides (>150 mg/dL)	01	01 (1.0)
PSA (> 3ng/mL)	01	01 (1.0)

Legend: DRP= Drug Related Problem; B12 vitamin (cobalamin); TSH = Thyroid Stimulating Hormone; PSA = Prostate Specific Antigen.
Measures: mg/dL: milligrams per deciliters; ng/mL: nanograms per milliliters.

Thirty-six patients (36/55) were non-adherent to AD drug therapy. At the end of the study, 30 of the non-adherent patients started to comply with AD drug therapy. The main problems of non-adherence identified were negative therapeutic occurrences experienced by the patient and the caregiver, mainly of ADE type; little or no information regarding drugs, the complex therapeutic scheme, and comorbidities.

An important finding of this study was the fact that at baseline time, three patients had Mini Mental State Examination (MMSE) scores that classified them as having normal cognitive function; that is, the scores did not meet the criteria for patient enrollment in the PCDTDA. However, we did not exclude these patients from the study, because we proposed to solve possible DRPs that led to the patient having a possible cognitive impairment and consequently a misdiagnosis of AD.

Among the 55 patients included, 30 had preservation of cognitive function according to the MMSE score. In addition, six patients had improvement in cognitive function: four were discharged from the PCDTDA, because the problems of antidepressant drug therapy were effectively resolved; and in two patients, their cognitive function improved, and changed from advanced to moderate impairment. Whereas, 13 patients had a three-point decline in the MMSE score (Table V; Table VI).

When only the preservation of cognitive function of the patients who had some type of adherence problem was considered, preservation of cognitive ability was also observed, according to the MMSE and CDR screening test scores. This was because of the 36 non-adherent patients initially identified, 26 remained in the same range, and six showed evidence of an improvement in the degree of cognitive impairment.

In addition, among the 16 patients taking BZD (16/55), preservation of cognitive function was observed, irrespective of the use of this class of medication (Table V).

TABLE V - Assessment of cognitive impairment of patients with Alzheimer's disease (n=55) trough cognitive screening tests Mini Mental State Examination (MMSE) and *Clinical Dementia Rating* (CDR) and impact of chronic benzodiazepine use on these parameters performed by the Medication Therapy Management (before-after), Araraquara

Cognitive impairment (Score MMSE)	Baseline Patient (n)	6 months follow-up Patient (n)
Normal cognitive function (≥25)	03	04
Mild cognitive impairment (21-24)	06	04
Moderate cognitive impairment (10-20)	25	29
Advanced cognitive impairment (≤9)	21	18

Exposure to benzodiazepines	MMSE		CDR	
	Baseline	6 months follow-up	Baseline	6 months follow-up
Non benzodiazepine-users	14 (0-27)	13 (0-28)	02 (0-0)	02 (0-0)
Benzodiazepine users	09 (0-28)	10 (0-30)	02 (1-3)	02 (0-3)
*p-value	0.174	0.268	0.952	0.121

Legend: MMSE: Mini Mental State Examination; CDR: C*linical Dementia Rating*
Notes: Nonparametric data. Mann-Whitney test was conducted for this analysis.
Median (Minimum - Maximum)

TABLE VI - Assessment biochemical and hemodynamic parameters of patients (n=55) in Alzheimer's disease treatment, mean cognitive screening tests Mini Mental State Examination (MMSE) and staging of disease *Clinical Dementia Rating* (CDR), performed by the Medication Therapy Management (before-after), Araraquara

Biochemical and hemodynamic parameters	Baseline	6 months follow-up	p-value
Serum glycemia (mg/dL)	121.9±57.3	93.9±15.3	<0.001**
Total cholesterol (mg/dL)	202.2±41.6	187.6±39.5	<0.001**
Triglycerides (mg/dL)	154.1±63.2	137.8±48.7	0.025**
Systolic Blood Pressure (mmHg)	136.6±22.3	126.7±18.5	0.003**
Diastolic Blood Pressure (mmHg)	75.49±12.0	73.03.8±9.8	0.05

Notes:
Parametric data. Test T-*Student* was conducted for this analysis.
**p-value <0.05 difference between baseline and final time.
Mean ± Standard Deviation

DISCUSSION

Pharmacist intervention based on the underlying disease (AD), including evaluation of the therapeutic experience and monitoring of the indication, effectiveness, safety and adherence to the drug therapy, allowed the identification of the DRPs, and a resolution of 69.8% of these.

Machuca and Silva-Castro (2010) recommend that analysis of DRPs should begin with the underlying

disease to enable comprehensive evaluation of drug therapy for the purpose of knowing and excluding the potential confounding factors associated with the disease (Machuca González, Silva Castro, 2010).

During the clinical diagnosis of AD, other reversible causes, which may promote cognitive deficits are excluded, such as depression (Potter, Steffens, 2007), low vitamin B12 levels (Costa *et al*., 2017), and hypothyroidism (Ceresini *et al*., 2009). However, depression is a comorbidity that can be considered both a confounding factor for the diagnosis of AD, and a prodromal symptom of dementia itself (Muliyala, Varghese, 2010). This fact may erroneously influence the diagnosis of AD.

With regard to confounding factors, in our study, an integrated view allowed us to identify patients who had problems with therapeutic effectiveness of the antidepressants and when the DRPs were solved, the patients' mood and cognition improved. Consequently, they were excluded from the PCDTDA, since untreated depression can cause cognitive deficits (Potter, Steffens, 2007).

The proposed intervention was observed to make an effective contribution to compliance with the PCDTDA, as there were weaknesses in patient inclusion *(Picon et a*l., 2010) and monitoring of the protocol (Forgerini, Mastroianni, 2020).

Furthermore, the care taken of all patients' health problems and assessment of their comorbidities, such as diabetes mellitus, hypertension and dyslipidemia allowed the control of the physiological and biochemical parameters, which showed evidence in the solution of the adherence problems and effectiveness of the drug therapy.

Improvement in cognitive impairment scores was also observed in six patients after resolution of the DRPs, which could perhaps be associated with control of the clinical parameters of the comorbidities. We raised this hypothesis because studies have identified greater cognitive impairment when clinical parameters such as blood glucose, total cholesterol, triglycerides and systolic blood pressure were uncontrolled (Crane *et al*., 2013; Matsuzaki *et al*., 2011; Nation *et al*., 2012).

However, Sha *et al.* for instance, found that blood pressure control did not contribute to changes in cognitive status in the elderly (Sha, Cheng, Yan, 2018). Moreover, it should be taken into account that in our study, the patients had a progressive and neurodegenerative morbidity in which, even with AD drug therapy, there was continuous progression (Burns, Iliffe, 2009).

Another frequent comorbidity identified in the study was dysphagia, which is capable of compromising the medication taking process and adherence to it (Kelly, D'Cruz, Wright, 2010). In this context, quantitative ineffectiveness of the drugs donepezil, memantine and sertraline was observed, because of the need to adapt the pharmaceutical form by maceration and addition of water, to enable the administration of the drug (Benzi, Mastroianni, 2016; Mastroianni, Forgerini, 2018).

Adaptation of the pharmaceutical form for the elderly is commonly occurs, because frequently, there is no compatible form for individuals needs of the patient. However, little is known about the safety, quality and effectiveness of the drugs after this adaptation, which may lead to increased toxicity, decreased effectiveness and other safety and stability problems, and may expose the patient to ADE (Benzi, Mastroianni, 2016; Paradiso *et al*., 2008).

From another perspective, in the process of intervention, it is important to understand the patient's behavior and decision about taking medication. Knowledge about the patient's therapeutic experience contributes to improved adherence and clinical results. This is because if patients are satisfied with the results of their drug therapy, if there are no barriers in the communication between the patients and health-care professionals, and if there are no problems with the safety and effectiveness of their treatment to discourage them from taking their drugs, these factors are associated with better adherence (Manary *et al*., 2013).

Consequently, after the interventions conducted the majority of the patients began to move onto AD drug therapy. Such strategies and interventions can promote the patients' feelings of autonomy and co-responsibility relative to the medication process, or, particularly, those of the relatives/caregivers, who feel more motivated to adhere to treatment, shown by evidence that simple adjustments or uncomplicated interventions are efficient

(Arismendi *et al*., 2012; Mastroianni, Forgerini, 2019; Sabater *et al*., 2005; Santschi *et al*., 2014).

As regards the exposure to BZD, despite the controversies about the association between BZD use and dementia (Lucchetta *et al*., 2018) and relative to worsening cognitive impairment in patients who already have the diagnosis (Defrancesco *et al*., 2015), BZDs are often prescribed for the treatment of psychological and behavioral symptoms of dementia (Glass *et al.,* 2005; Høiseth *et al*., 2013).

Nonetheless, deprescription could be a necessary step (Pottie *et al*. 2018) due the association of ADE with the use of BZD. Whereas, the deprescription process is complex due to the positive therapeutic experiences of patients and family/caregivers, in addition the easy access to BZD - a standardized medication distributed by the public health system free-of-charge.

In the present study, it was not possible to relate the higher level of impairment to the use of BZD. However, this was not the primary outcome of this study, therefore no follow-up period or the necessary sample size relative to it were considered.

Statistical power was a limitation, since a convenience sample was used in the study and sample size had no statistical significance. However, the sample was complex due to AD being a neurodegenerative and progressive disease, in addition to the ethical issues involved and stigma attached to the entire morbidity. Moreover, to the best of our knowledge, this has been the only study that conducted a follow-up and performed interventions with AD patients, integrating all reported variables (Nguyen *et al*., 2019).

Despite the limitations of this study, our data provided support for the guidelines established by OFIL (Organización Farmacéuticos Ibero-Latinoamericanos., 2012), whose proposal would be the implementation of business incubators in partnership with universities for: undergraduate and postgraduate training in MTM (*education)* (Mendonça, Freitas, Oliveira, 2017), a model providing services for the dissemination and knowledge about MTM to the community (*extension*) (Silva *et al*., 2016), generating result indicators and establishing research to promote the safe use of medicines (*research*).

In addition, the larger number of qualified health service professionals and offer of MTM are in line with the Ministry of Health (Brasil, 2013) and World Health Organization (World Health Organization, n.d.) policies on patient safety, among whose proposed strategies, we highlight the training of health professionals for the third national challenge of safe medication.

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CONFLICT OF INTEREST

We authors state that there is no conflict of interest.

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