ORIGINAL ARTICLE

Drug-drug interactions and polypharmacy in patients with cognitive impairment

Interações medicamentosa e polifarmárcia em pacientes com déficit cognitivo

André Busato da Costa[1], Maruan Kaled Charkieh[1], Murilo Gadens[1], Urbano Borges Martins Terceiro[1], Ricardo Krause Martinez Souza[1], Nelson Felipe Dal Santos[1], Renato Nisihara[1]

ABSTRACT

Introduction: Patients with dementia are prone to taking multiple medications, contributing to increased drug-drug interactions. This study aimed to evaluate the frequency of polypharmacy cases in patients with dementia and to determine whether the use of the digital calculator is useful for identifying potential drug interactions.

Methods: This is an observational retrospective study. Patients were divided by the presence or absence of polypharmacy. The polypharmacy group was split into patients with dementia and mild cognitive impairment (MCI). The drug interactions were analyzed using Lexicomp® (UpToDate) and stratified at the following levels: A (no interaction), B (without evidence of interaction), C (benefits potentially higher than risks), D (consider a change of therapy), and X (risks potentially higher than the benefits).

Results: Of the 431 patients studied, 78.4% showed polypharmacy, with age significantly influencing this finding (P=0.0053). Alzheimer's disease was the most prevalent. In the polypharmacy group, patients with MCI were younger than those with dementia (P=0.032). Type C interactions were the most prevalent, and there was no difference in pairing the types of interaction between the studied groups, despite the 1.5% type X interactions in the polypharmacy group, which had rivastigmine as the primary drug responsible for drug-drug interactions.

Conclusion: Polypharmacy occurs in four of five patients with dementia, and patients with Alzheimer's disease have a significantly higher rate of polypharmacy than patients with mild cognitive impairment. Besides, polypharmacy did not influence the types of interaction between groups with and without polypharmacy. The use of the calculator helped to identify potential interactions between medications in this group of patients.

Keywords: Dementia, Cognitive dysfunction, Drug interactions, Polypharmacy.

RESUMO

Introdução: Pacientes com demência são mais propensos a utilizar múltiplos medicamentos, contribuindo para o aumento das interações medicamentosas. Este estudo teve como objetivo avaliar a frequência de casos de polifarmácia em pacientes com demência e determinar se o uso da calculadora digital é útil para identificar potenciais interações medicamentosas.

Métodos: Trata-se de um estudo observacional retrospectivo. Os pacientes foram divididos pela presença ou ausência de polifarmácia. O grupo polifarmácia foi dividido em pacientes com demência e comprometimento cognitivo leve (CCL). As interações medicamentosas foram anali-

[1]Universidade Positivo. Departamento de Medicina, Curitiba, (PR), Brazil

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sadas pelo programa Lexicomp® (UpToDate) e estratificadas nos seguintes níveis: A (sem interação), B (sem evidência de interação), C (benefícios potencialmente superiores aos riscos), D (considerar mudança de terapia), e X (riscos potencialmente superiores aos benefícios).
Resultados: Dos 431 pacientes estudados, 78,4% apresentaram polifarmácia, com a idade influenciando significativamente esse achado (P=0,0053). A doença de Alzheimer foi a mais prevalente. No grupo polifarmácia, os pacientes com CCL eram mais jovens que aqueles com demência (P=0,032). As interações tipo C foram as mais prevalentes e não houve diferença nos tipos de interação entre os grupos estudados. Foram encontradas 1,5% de interações tipo X no grupo polifarmácia, sendo que a rivastigmina foi o principal medicamento responsável pelas interações medicamentosas.
Conclusão: A polifarmácia ocorre em quatro em cada cinco pacientes com demência, sendo que os pacientes com doença de Alzheimer apresentam uma taxa significativamente maior de polifarmácia do que os pacientes com CCL. Além disso, a polifarmácia não influenciou os tipos de interação entre os grupos com e sem polifarmácia. O uso da calculadora ajudou a identificar potenciais interações entre os medicamentos nesse grupo de pacientes.

Palavras-chave: Demência, Disfunção cognitiva, Interações medicamentosas, Polifarmácia.

INTRODUCTION

Dementia is a clinical syndrome characterized by progressive cognitive impairment that severely interferes with social and occupational functions [1]. The updated version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) changed the term from dementia to “Major Neurocognitive Disorder,” and the term mild cognitive impairment (MCI) was replaced with “Mild Neurocognitive Disorder” (mNCD) [2].

Alzheimer’s disease (AD) is the most prevalent type of dementia syndrome [3], followed by vascular dementia [4]. Its incidence grows exponentially after 60 years of age and doubles every five years after this age [5]. Worldwide, the number of people living with dementia is around 50 million, which is estimated to triple by 2050 [6]. In addition, dementia syndromes substantially negatively impact global economic status, given that global spending on dementia is estimated at approximately one trillion dollars a year [6].

The management of multimorbidity among older adults is associated with the use of multiple medications, leading to polypharmacy [7]. There are some definitions for polypharmacy, but the most used refers to the use of concomitant use of five or more medications [7–9]. Patients with dementia are prone to take multiple medications [7,8,10,11] due to their association with other comorbidities [12,13] and the fact that dementia is common in most elderly individuals, the age group whose medication use is usually higher [8,9]. Senility is related to the physiological changes in the body that affect the pharmacodynamics and pharmacokinetics of drugs [14], and PP results in increased drug side effects and interactions between substances [15–18]. Nowadays, the use of digital tools for research and analysis of drug-drug interactions (DDIs) has been widespread in medical practice [19]. When stratifying DDIs, about one in ten outpatients show high-risk interactions with more significant adverse effects [20]. Other studies analyzing the use of technological tools to evaluate DDIs in patients with dementia, MCI, and PP are

unknown. Such data are of fundamental relevance to avoid iatrogenesis, a fact of particular relevance in the group of patients studied.

Therefore, this study aimed to evaluate the frequency of polypharmacy cases in patients diagnosed with dementia and MCI and drug interactions between patients with and without PP. Furthermore, it also aimed to determine whether the digital calculator helps identify potential DDIs in this group of patients.

METHOD

This is a retrospective study approved by the institution's research ethics committee under number 4.770.675. The data was collected from a "Database" of patients with cognitive impairment between 2014 and 2021. This study included patients diagnosed with dementia and MCI from a single private clinic specialized in diagnosing, treating, and follow-up patients with cognitive impairment, Curitiba Memory Center (CMC) [21], located in Curitiba, Paraná, Brazil.

The database was designed to group information from electronic medical records of patients with cognitive impairment of the CMC. All patients studied were seen and their data was recorded by a single doctor. The data collected from the database was regarding age, gender, diagnosis, associated comorbidities, and medication use.

Eligibility Criteria

The eligibility criteria consist of the following: a) women or men aged 18 years or older, b) patients should fulfill the classification criteria for dementia proposed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2] and diagnostic criteria for MCI [22], c) mandatory laboratory tests in the investigation of cognitive impairment according to guidelines of the Science Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology: complete blood count, urea, creatinine, free thyroxin (T4), thyroid stimulating hormone (TSH), albumin, hepatic enzymes test (ALP, ALT, and GGT), vitamin B_{12}, calcium, serological reactions for syphilis, and HIV serology in patients younger than 60 years of age, or atypical clinical picture of dementia or when there is suspicious epidemiology. All the exams showed expected results, [23] d) structural neuroimaging: every patient with suspected cognitive impairment should have a neuroimaging test, such as computed tomography or magnetic resonance imaging (MRI) of the brain [23].

For the diagnosis of dementia, the following criteria must be met (DSM-5): **A.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains: a) memory, b) language, c) executive function, d) attention, e) perceptual-motor, and f) social cognition; **B.** The cognitive deficit interferes with independence in everyday activities. The assistance should be required with complex instrumental activities of daily; C. The cognitive deficits only occur in the context of delirium; D. The cognitive deficits are not better explained by another mental disorder.

Diagnostic criteria for mild cognitive impairment (22): **A**. Cognitive complaints from the patient or family member; **B**. patient or informant report decline in cognitive functioning to previous abilities in the last

year; **C.** cognitive impairment evidenced by clinical evaluation (impairment in memory or another cognitive domain; **D**. cognitive impairment should not have significant impairment in activities of daily living; however, there may be difficulty in complex activities; and **E.** absence of dementia.

Inclusion and exclusion criteria

Inclusion criteria for the dementia syndromes were, for the diagnosis of Dementia in Alzheimer's Disease (NIA-AA) [24], for Major or Mild Vascular Neurocognitive Disorder (DSM-5) (2), for the fourth diagnostic consensus of Dementia with Lewy Bodie's consortium [25], for Frontotemporal Dementia [26,27], Progressive Supranuclear Palsy (PSP) (NINDS-SPSP) [28] and others.

Exclusion criteria consisted of patients with a) incomplete data in the database; b) undefined diagnosis; c) Altered laboratory tests such as TSH, vitamin B_{12} deficiency, and syphilis; d) MRI of the brain showing secondary causes such as subdural hematomas and tumors or other conditions.

Data collection

It included epidemiological and clinical information such as age, gender, diagnosis, and used treatment. The number of used drugs (>5) is characterized by the presence or absence of polypharmacy (PP). All drugs used by patients at the last medical appointment, including vitamins and medications for other causes that are not cognitive impairment, were considered for the analysis.

To make comparisons, the patients were divided into two groups, according to diagnosis: **A.** group with dementia and **B.** group with MCI. We compared the data for age, associated comorbidities, and the number of drug-DDIs.

In addition, the total sample was divided into patients with polypharmacy (POP) and the absence of polypharmacy (AOP).

Calculator

We used Lexicomp® (UpToDate) tool to identify the possible DDIs, a calculator that allows the grading risks corresponding to interactions. To access this tool, a paid subscription to UpToDate, an extensive evidence-based medical database, is required. The data is regularly updated by a community of more than 7,000 physicians worldwide, helping the daily clinical practice. The method consists in entering the name of the drugs used in a field provided in the calculator. Next, the drugs are stratified into A, B, C, D, and X levels, displayed in increasing order of known interaction severity. Levels A and B show, respectively, that has no interaction and little evidence of an interaction. At level C, monitoring is recommended, but the benefits of concomitant use overcome the risks. In contrast, at level D, close monitoring must be performed and, if necessary, change the dosage or consider changing the therapy. Lastly, level X is the most severe and shows that the simultaneous use of medications should generally be avoided.

Data analysis was performed using spreadsheets, making it possible to identify the drugs with the highest number of interactions, the number of DDIs per patient, the most prevalent diseases, and associa-

ted comorbidities, as well as the type of patient that is more susceptible to PP.

Statistical analysis

Nominal data was reported in frequency tables and expressed in percentages. Numerical data had distribution studied by the Shapiro-Wilk test. Comparison between nominal variables was done by chi-squared and Fisher test. For numerical variables, the Mann-Whitney U test was used if the distribution was non-parametric and the unpaired t-test if the distribution was normal. The adopted significance level was 5%. Tests were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com"

RESULTS

Flowchart 1 shows the studied patients. Among 915 medical records analyzed, we included 431 medical records in the study. We excluded the 484 records for being incomplete or not meeting the inclusion criteria. The patients were split into two groups, characterized by POP or AOP. Among the patients, 78.4% had PP; of these, 86.7% had dementia, against 13.3% with MCI. A total of 232 drugs were used, with an average of 8.5 drugs used by POP patients. **Figure 1** shows the number of drugs taken by patients with POP. The demographic data are described in **Table 1** and show a predominance of the female gender (65.9%). There was no difference between the gender in relation to PP (P = 0.62), although women with PP were older (P = 0.0008). The mean age was 76 ± 9.18 years in the POP group and 72 ± 10.31 years in the AOP group, showing a significant difference (P = 0.0053), as the POP group had more older people (94.4% vs. 84.9%; P = 0.004).

Regarding comorbidities, in the POP group, patients with dementia in the POP group had fewer cases of type 2 diabetes mellitus (P = 0.009) than those with MCI. In addition, people with dementia were older than those with MCI (P = 0.032). Hypertension was the most prevalent associated disease in both POP and AOP patients (61.8% vs. 29%), followed by dyslipidemia (54.4% vs. 26.9%). However, there was no significant difference between groups and comorbidities like cardiopathy and depression, comparing patients with or without dementia in the POP group.

Among patients with the diagnosis of dementia, AD was the most common in both the POP group (51.2%) and AOP group (37.6%), followed by Lewi bodies' dementia (LBD) (11.5% vs. 9.7%) and vascular dementia (VD) (5.6% vs. 5.4%). MCI represented 1/3 of the AOP patients (31.2%).

Regarding the PP findings, AD patients were the ones who showed the highest chance of having PP (51%) when compared to patients with MCI (13%; $P < 0.0001$) and without difference in relation to other dementias diagnosed. Furthermore, among the patients with PP, when the MCI and dementia groups were analyzed, there was no difference between them in the number of type D interactions (P = 0.11) and type X (P = 0.33).

Table 2 shows the total interactions found, dividing them among the drug-DDIs types. Overall, 2,040 interactions were identified. Type C interactions were the majority in POP and AOP groups (73.5% vs. 80%), while type D interactions occurred

of 11.5% in the POP group and 6% in the AOP group. Type X interactions occurred in 1.5% of the POP group, in contrast to zero in the AOP group. When paired by type of interaction, there was no significant difference between POP and AOP groups. All interactions found in the AOP group were also present in the POP group. Thus, the data from the second column of table 2 are contained in the first column, implying that the difference between the groups is not statistically significant.

As for the drugs that interacted the most, **Table 3** separates them by type of interaction. Among type X interactions, rivastigmine was the drug that most interacted with other drugs (17.2%), followed by levomepromazine (10.3%) and amiodarone (6.9%). In the type D DDIs, zolpidem was responsible for interactions in the POP group. Type C interactions were marked by the predominance of quetiapine in both groups, with escitalopram and acetylsalicylic acid closing the top three.

DISCUSSION

The data obtained in this study is of particular relevance because only a few studies analyzed PP in adults with cognitive impairment. The authors are unaware of any other study using a methodology like this one that has classified and evaluated the rate of harmful DDIs in patients with MCI and dementia caused by the usage of drugs.

This work shows that the frequency of PP is considerably higher than in other chronic diseases. Mesonero *et al.* [32] showed that about one in five patients with chronic bowel disease had PP, which was associated with age and other comorbidities. This study also shows higher prevalence of PP compared to Mesonero *et al.* [32] (78.4% vs 18.4%), which can be explained by a higher median age (76 *vs* 48 years). Despite that, the demographic data of this study showed a higher prevalence of cognitive impairment and PP, mainly in advanced-age patients, which is corroborated by the literature. Considering that most of these are elderly, the need to use drugs for causes that are not cognitive impairment, associated with physiological changes in the metabolism of older individuals, contributes to changes in substances depuration, which can result in toxic concentrations. Besides, renal function can be affected, and the number of DDIs tends to be much higher. Their care should be even more significant since inadequate management can offset primary diseases and result in harmful effects [3,5,17,29–32].

There was a discrepancy in the literature regarding the epidemiology of the most common types of dementia. While this study showed a higher prevalence of AD, followed by LBD and vascular dementia, the literature considers AD as the most common, vascular dementia as second, and mixed dementia or LBD as the third cause. The explanations for this may be due to the sample, which evaluated a specific segment with patients of mostly good socio-economic level; that is, they had easy access to health professionals and medications to control cardiovascular risk factors. Also, mixed dementia brings together causes not explicitly identified for its diagnosis, which may underestimate the individual causes of dementia [33–35].

The absence of a significant difference between the number of type D and X interactions in the MCI and POP dementia groups observed in this study may be

explained by the fact that the MCI group also used many of the medications used by patients with dementia. In addition, the authors analyzed drugs used for other causes besides cognitive impairment. Regarding the significantly higher age of patients with dementia compared to those with MCI, this data is corroborated by the medical literature on the tendency of these patients to develop dementia over the years [36].

In this study, type X interactions were mainly caused by rivastigmine, a substance of the acetylcholinesterase inhibitor (AChE) class that is used in the treatment of AD-related dementia, Parkinson's disease, and LBD. They were, in their entirety, associated with the use of beta-blockers. This combination is contraindicated because the drugs of both classes are bradycardia-inducing. Therefore, the synergistic action between them can lead to complications resulting from severe bradycardia. Although it has modest peripheral effects, the increase in vagal tone caused by AChE is responsible for the heart rate drop and other effects such as syncope, arrhythmias, and atrioventricular block, as well as inducing other events intrinsically associated with the previous ones, such as hip fracture and the need for a pacemaker [37–39].

In turn, levomepromazine, an antipsychotic, has its X-type interactions linked to dopaminergic agonists (amantadine and levodopa) and drugs containing ethanol in their composition (sertraline and dexamethasone). While levomepromazine has a dopaminergic antagonist effect, drugs such as amantadine and levodopa are dopaminergic agonists. Therefore, the concomitant use of substances of these classes results in a reciprocal antagonism [40,41]. In the second case, considering the central nervous system (CNS) depressant effect caused by alcohol and antipsychotics, the association between these two substances can also synergize the CNS [41].

Considering that rivastigmine, levomepromazine, and amiodarone together make up only a third of X-type DDIs, research for interactions between other medications becomes even more critical since there is always the possibility of finding some previously unknown effect, especially when considered drugs used for purposes that are beyond the field of performance of attending physician.

With the advancement of technology, tools such as the Lexicomp® (UpToDate) have become increasingly popular, raising concerns about which tool is best for daily clinical practice. Shakeel *et al.* [43] compared eight DDIs detection tools to analyze phytotherapy in oncologic treatment, considering the one used in our study. However, it is not a free version and proved to be the most effective for this purpose, appointing the Medscape calculator as the best option among the free ones. Kheshti *et al.* [44] concluded that Lexicomp® (UpToDate) is one of the best performance and accuracy-driven tools for identifying DDIs, recommending the association of tools to increase the sensitivity of the method.

Other studies used the same calculator for analyzing DDIs in other groups of patients. Nusair *et al.* [45] investigated the prevalence and severity of DDIs in adults with polypharmacy. Of 3,359 interactions found between the 196 drugs used by the patients in the study, 77.8% were type C, 8.4% were type D, and 1.6% were type X; the data was similar to the findings of this work. Al Qerem *et al.* [46] evaluated the prevalence of PP and DDIs in elderly patients. They found a statistically significant

correlation; in addition to reporting 74.9% of the sample as having PP, we found a number close to one in this study. Likewise, neither study could find a significant association between gender and the number of DDIs. Finally, both studies showed similar results regarding the positive association between DDIs number and age. There are similar content to this article, focusing on drug interactions and patients with dementia or cognitive impairment correlating the use of PP and its possible consequences [47, 48]. This was one of the motivations for choosing this group of patients, as well as the fact that, for the most part, they are older patients (median age of 76 years), which increases the chance of them having more comorbidities, and consequently using more medications.

This study has some limitations. As it is a retrospective study, the patients were unaware of the possible consequences of DDIs to which they were exposed. In addition, the impossibility of entering the dosage and type of administration of the drugs used in the calculator makes it challenging to analyze the safety of the concomitant use of two substances. Care is needed to generalize these findings to general population, because data were obtained of an only single private clinic, most of patients had higher socioeconomic level, which does not correspond to most of Brazilian population. However, the findings of this study are of significant relevance to medical practice, considering that they highlighted the importance of verifying the potential DDIs before prescribing a new drug to the patient, aiming at minimizing iatrogenesis. Future prospective studies may evaluate the long-term impacts of DDIs on patients and elucidate issues still seen as a gap in the current medical literature regarding this topic.

Conclusion

Polypharmacy occurs in almost four out of five patients with dementia. The population was predominantly older, which explain the high frequence of polypharmacy found. Patients with AD have a significantly higher rate of polypharmacy than patients with MCI. This finding could affect adherence to treatment and therapeutic accomplishments. In addition, the drug interaction calculator helped identify potential drug-DDIs. Therefore, polypharmacy did not influence the types of interaction between POP and AOP groups.

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Figure legends:

Flowchart 1 . Patients with cognitive impairment studied.

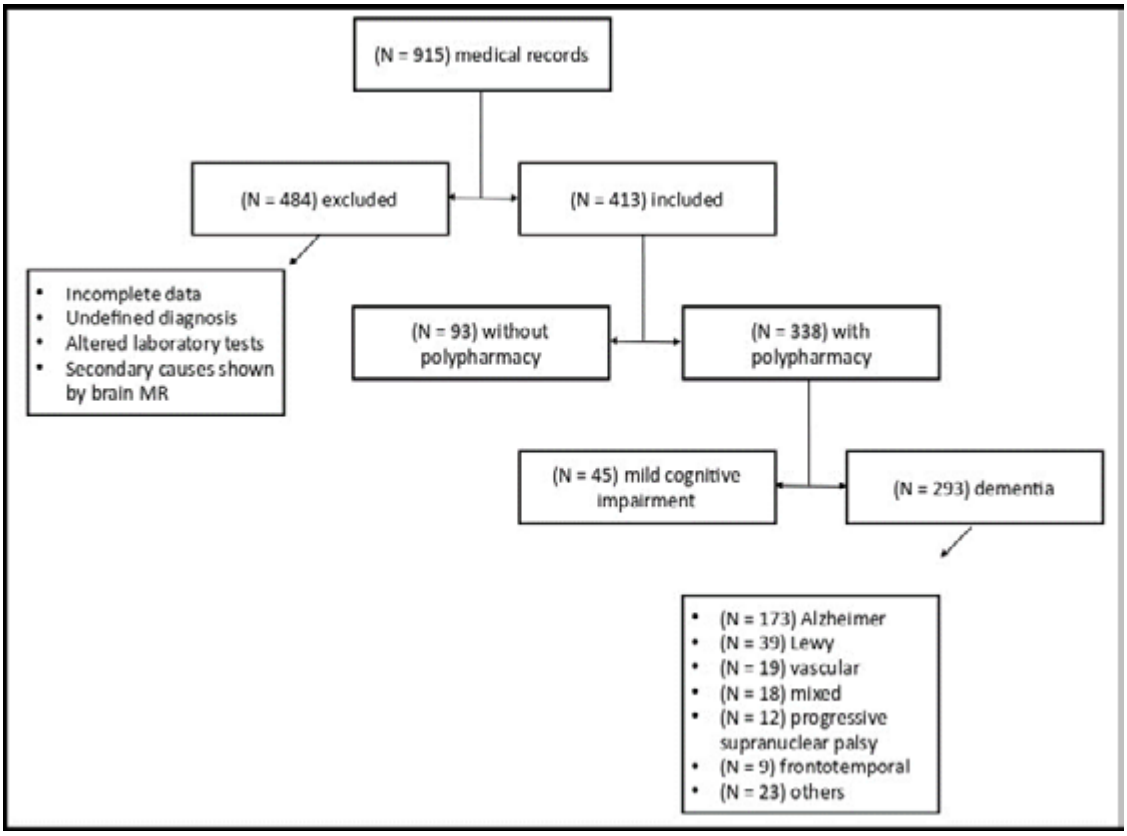
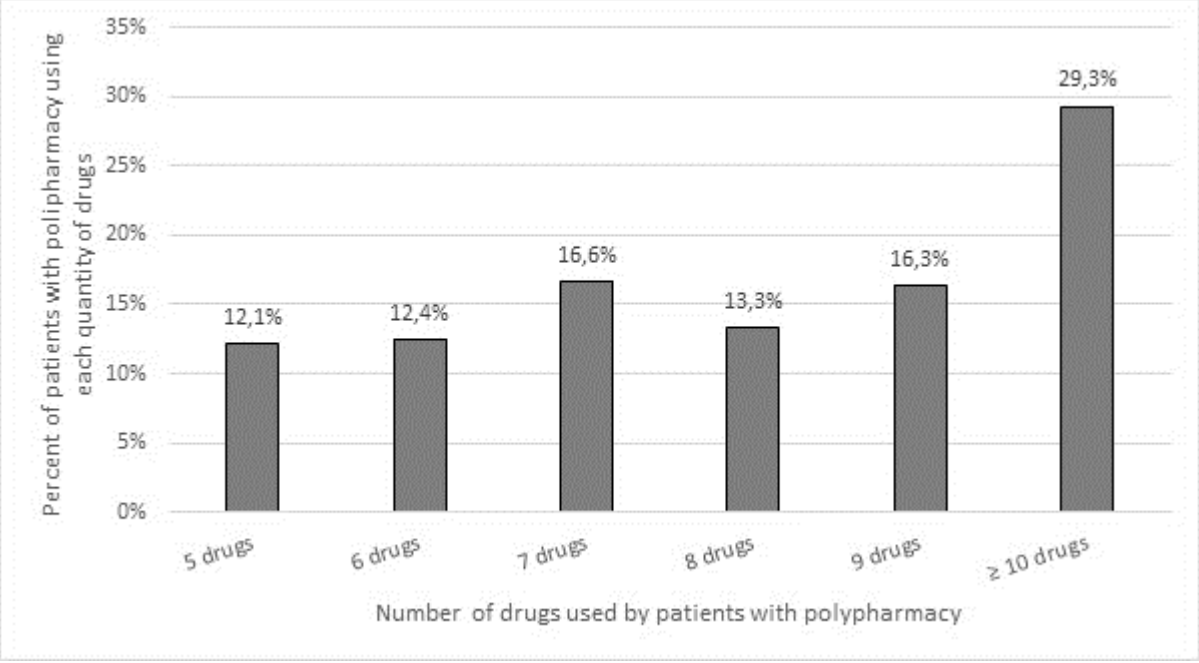


Figure 1. Number of drugs taken by patients with polypharmacy



		With poly-pharmacy % (N)	Without poly-pharmacy % (N)	Total sample% (N)	P Value
Gender	Female	65.1% (220)	68.8% (64)	65.9% (284)	
	Male	34.9% (118)	31.2% (29)	31.1% (147)	0.62
Age (years)	< 50	1.2% (4)	3.2% (3)	1.6% (7)	0.0053
	51-60	4.4% (15)	11.8% (11)	6% (26)	
	61-70	20.7% (70)	23.7% (22)	21.3% (92)	
	71-80	38.2% (129)	38.7% (36)	38.3% (165)	
	81-90	32.9% (111)	20.4% (19)	30.2% (130)	
	>90	2.6% (9)	2.2% (2)	2.6% (11)	
Comorbidities					
	Hypothyroidism	24.3% (82)	9.7% (9)	21.1% (91)	0.0036
	Heart Disease	21% (71)	22.6% (21)	21.3% (92)	0.32
	Dyslipidemia	54.4% (184)	26.9% (25)	48.5% (209)	<0.0001
	Hypertension	61.8% (209)	29% (27)	54.8% (236)	<0.0001
	Depression	20.7% (70)	12.9% (12)	19% (82)	0.12
	Diabetes	25.4% (86)	20.4% (19)	24.4% (105)	0.009
Diagnosis	Alzheimer's Disease	51.2% (173)	37.6% (35)	48.3% (208)	0.025
	Lewy bodies dementia	11.5% (39)	9.7% (9)	11.2% (48)	0.18
	Vascular dementia	5.6% (19)	5.4% (5)	5.6% (24)	0.57
	Mixed dementia	5.3% (18)	4.3% (4)	5.1% (22)	0.32
	Progressive supranuclear palsy	3.6% (12)	1.1% (1)	3% (13)	0.11
	Frontotemporal dementia	2.7% (9)	3.2% (3)	2.7% (12)	0.62
	Others	6.8% (23)	7.5% (7)	6.9% (30)	0.52
Non-dementia	Mild cognitive impairment	13.3% (45)	31.2% (29)	17.2% (74)	<0.0001

Table 1 – Demographical and clinical data of the studied sample.

Table2 – Quantity and types of drug interactions found in the studied sample

Type of interaction	**With polypharmacy % (N)**	**Without polypharmacy % (N)**	**P value**
Type A	0.1% (2)	0% (0)	0.92
Type B	13.4% (272)	14% (7)	0.82
Type C	73.5% (1500)	80% (40)	0.385
Type D	11.5% (236)	6% (3)	0.31
Type X	1.5% (30)	0% (0)	0.78
Total	2040	50	

Type X	With polypharmacy	% (N)	Without polypharmacy	% (N)
	Rivastigmine	17.2% (5)		
	Levomepromazine	10.3% (4)		
	Amiodarone	6.9% (2)		
	Others	65.6% (19)		
Type D	**With polypharmacy**	**% (N)**	**Without polypharmacy**	**% (N)**
	Zolpidem	8.5% (16)	Zolpidem	16.6% (1)
	Levomepromazine	6.4% (12)	Valproic acid	16.6% (1)
	Quetiapine	4.8% (9)	Lorazepam	16.6% (1)
	Tramadol	4.2% (8)	Amitriptyline	16.6% (1)
	Acetylsalicylic acid	3.7% (7)	Trazodone	16.6% (1)
	Gliclazide	3.7% (7)	Levomepromazine	16.6% (1)
	Lamotrigine	3.2% (6)		
	Codeine	2.7% (5)		
	Risperidone	2.7% (5)		
	Others	60.1% (113)		
Type C	**With polypharmacy**	**% (N)**	**Without polypharmacy**	**% (N)**
	Quetiapine	5.1% (76)	Quetiapine	15% (12)
	Escitalopram	2.9% (44)	Acetylsalicylic acid	7.5% (6)
	Acetylsalicylic acid	2.9% (43)	Escitalopram	6.3% (5)
	Hydrochlorothiazide	2.3% (35)	Donepezil	6.3% (5)
	Donepezil	2.2% (33)	Trazodone	6.3% (5)
	Duloxetine	2.1% (32)	Risperidone	6.3% (5)
	Amiodarone	2.1% (31)	Venlafaxine	5% (4)
	Trazodone	2.1% (31)	Clonazepam	3.7% (3)
	Olanzapine	2% (30)	Olanzapine	3.7% (3)
	Risperidone	2% (30)	Galantamine	3.7% (3)
	Sertraline	2% (30)	Others	36.2% (29)
	Others	72.3% (1085)		

Table 3. Drugs with the most interactions according to the type of interaction.

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
All authors contributed to the study conception and design. Material preparation and data collection were performed by ACC, AVCG, BMC and GCP. The data analysis and the first draft of the manuscript was done by all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
Conflicts of interest: All authors declare that there are not conflict of interest.

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Committee of Ethics in Research from Universidade Positivo under protocol number 4.770.675 from June 12th, 2021.

Consent to participate All participants signed an informed consent.

Consent for publication: Yes.

Transparency declaration

LIST OF ABBREVIATIONS:

AChE – Acetylcholinesterase inhibitor
AD – Alzheimer's disease
AOP – Absence of polypharmacy
ASA – Acetylsalicylic acid
CNS – Central nervous system
DDIs – Drug-drug interactions
LBD – Lewi bodies dementia
MCI – Mild cognitive impairment
mNCD – Mild Neurocognitive Disorder
PD – Parkinson's disease
POP – Presence of polypharmacy
PP – Polypharmacy
VD – Vascular dementia

Corresponding Author:
Renato Nisihara
renatonisihara@gmail.com
renatonisihara@up.edu.br

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