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Polypharmacy is a determinant of hospitalization in Parkinson's disease

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Abstract. – OBJECTIVE: Patients with Parkinson's disease (PD) are at a higher risk of hospitalization and recurrent hospitalizations, with consequent complications. Polypharmacy is associated with several adverse outcomes, including hospitalization, increased length of hospital stay, and mortality. The aim of this study was to evaluate among patients with PD the association between the number of medications and incident hospitalizations.

PATIENTS AND METHODS: We analysed the data of 165 patients with Parkinson's disease attending a geriatric Day Hospital who were enrolled in a cohort study and followed for a median of two years.

RESULTS: Over the follow-up, 46 participants (46%) were hospitalized at least one time; multiple admissions were observed in 12 subjects (7%). The median number of agents was 5 (4-7). In Cox regression, the number of drugs was associated with increased hospitalization rates (HR=1.23; 95% CI=1.06-1.43), also after excluding non-neurological medications (HR=1.18; 95% CI=1.01-1.38). Using Poisson regression, polypharmacy (i.e., use of >5 drugs) predicted the number of repeated hospitalizations (IRR=2.62; 95% CI=1.28-5.36; *p*=.008).

CONCLUSIONS: Among patients with PD, the number of daily medications is associated with increased risk of hospitalization; an increasing number of drugs is associated with increasing number of hospitalizations.

Key Words:
Elderly, Hospitalization, Number of drugs, Parkinson's disease, Personalized medicine.

Introduction

Patients with Parkinson's disease (PD) are at a higher risk of hospitalization[1]. Once admitted, these patients are also at higher risk of prolonged hospital stay and medication errors, have poorer motor outcomes, and are at a higher risk of readmission. This aspect is even more relevant in the actual pandemic situation[2]. Nevertheless, only few studies have so far addressed interventions aiming at reducing the need for hospitalization in these patients, with inconclusive results[3]. Indeed, conditions other than PD in itself are generally reported as the primary reason for hospitalization: it has been reported that the first diagnosis for hospitalization among 761 admissions of PD patients was related to neurological symptoms only in 116 cases (15%)[4].

Multimorbidity and the resulting use of multiple medications (polypharmacy) are common conditions in older populations[5]. Polypharmacy is associated with several adverse outcomes including mortality, falls, adverse drug reactions, frailty, increased length of hospital stay, and early readmission[6-8].

The aim of the present study was to assess the association, if any, between the number of medications and 24-month hospitalization rates among subjects with PD.

Patients and Methods

This retrospective study involved all patients with PD consecutively admitted to the geriatric

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Day Hospital of the A. Gemelli University Hospital, Rome, between October 1st 2011, and March 30th, 2015, who were enrolled in a cohort study of older patients with movement disorders. PD was the first diagnosis for all participants, based upon the United Kingdom Parkinson's Disease Society Brain Bank (UK-PDS-BB) criteria[9]. All participants were visited by the study physicians, who received specific training, and whose diagnostic concordance was tested using dummy cases. The study researchers performed physical examination and completed a questionnaire that included participants' data on socioeconomic status, lifestyle habits, and quality of life according to a standardized protocol[10]. Information on drug therapy was collected from patients and caregivers, and further verified by inspection of medicine packs. All drugs taken at the time of interview were recorded, including over-the-counter drugs and as-needed administrations.

The Institutional Review Board approved the protocol (P72CE2013), and all patients provided written informed consent.

Coding of Drugs

Drugs were coded according to the Anatomical Therapeutic and Chemical codes/Defined Daily Dose[11]. Polypharmacy was defined as the use of five or more agents[5].

Hospitalization

Data on 2-year hospitalization were collected by telephone interview, and further confirmed by collection of medical records.

Covariates

Education was expressed as years of school attendance. Smoking was calculated as total lifetime pack-years for current and former smokers.

Diagnoses were coded according to the International Classification of Diseases, ninth edition, Clinical Modification codes[12]. On admission, adjudicated disease diagnoses were based on self-reported history, clinical documentation, and medication use. Comorbidity was quantified using the Charlson score[13].

The total levodopa equivalent daily dose (LEDD) was estimated using a standard conversion formula[14].

Functional ability was estimated using the Katz' activities of daily living (ADLs) and the Lawton and Brody scale for instrumental activities of daily living (IADLs)[15,16]. Depressive symptoms were evaluated using the 15-item Italian version of the Geriatric Depression Scale (GDS)[17]. Cognition was assessed using the Mini Mental State Examination[17]. Parkinson's disease severity was assessed using the Unified Parkinson Disease Rating Scale (UPDRS)[18]. Nutritional status was evaluated using the Mini Nutritional Assessment (MNA)[19].

Body Mass Index (BMI) was calculated as weight (Kg) divided by height squared (m^2)[20].

Muscle strength was assessed by grip strength, measured using a hand-held dynamometer (hydraulic hand BASELINE; Smith & Nephew, Agrate Brianza, Milan, Italy). Two measurements were obtained for each hand; the highest value of the strongest hand was used for statistical analyses.

Blood samples were obtained after overnight fasting. Glomerular Filtration Rate was estimated using the Cockcroft-Gault equation.

Statistical Analysis

Data were recorded using a dedicated software with automatic coding of drugs and diagnoses. Statistical analyses were performed using SPSS for Mac 26.0. Differences were considered significant at the $p<.050$ level. Data of continuous variables are presented as mean values ± standard deviation (SD). Medians and inter-quartile ranges were provided for non-normally distributed variables. Analysis of variance (ANOVA) for normally distributed variables was performed according to the occurrence of incident hospitalization; otherwise, the nonparametric Mann-Whitney U H test was adopted. The two-tailed Fisher exact test was used for dichotomous variables. The Kaplan-Meier analysis using the log-rank test was adopted to examine the unadjusted association number of drugs with hospitalization.

Cox regression was used to estimate the adjusted association of variables of interest, including the number of drugs, with hospitalization. In addition, the same model was analyzed also after the exclusion of 24 outliers for the duration of PD, as identified by a Mahalanobis distance $p<.001$. Also, the multivariable model was analyzed considering increasing tertiles of the number of drugs. Analysis of the interaction term "MNA*number of drugs" was performed to assess whether the association between number of drugs with incident hospitalization varied according to nutritional status expressed by the MNA. To rule out confounding by the severity of the neurological disease, the same multivariable model was analysed after excluding drugs taken for PD treatment. Abnormally distributed variables were analyzed after log transformation. All models were checked for goodness of fit by likelihood ratio chi square test

(all *p*-values<.050); diagnostics by the correlation matrix of regression coefficients indicated no significant collinearity between the covariates. Eventually, after assessing the distribution of hospital stay by the Kolmogorov-Smirnov test, we applied the Poisson regression modelling using the number of hospitalizations as the dependent variable, and a number of drugs above the median as explanatory variable, as well as other significant covariates.

Results

Forty-six patients (46%) reported at least one hospitalization in the previous two years. Among hospitalized patients, the median number of hospital stay was 1 (1-2); 30 hospital admissions (67%) were through the emergency department. The causes of hospitalization were: infections (20; 43%); fall-related injury without fracture (10; 22%); acute myocardial infarction (4; 9%); stroke or transient ischemic attack (4; 9%); hip fracture (5; 11%); and other fractures (3; 6%). The median number of drugs was 5 (4-7).

Of notice, participants who reported at least one hospitalization presented with a higher number of medications (N=6; IQR: 5-9 *vs.* N=5; IQR: 3-7; *p*=.002). After the exclusion of outliers, the mean age of subjects with at least one hospitalization was 75 (5) years, as compared with 75 (4), *p*=.731, among those without hospitalization; the median time from Parkinson's diagnosis was 54 (36-98) months among hospitalised patients, and 49 (18-84) months, *p*=.671, among other participants. The median number of drugs taken did not change after the exclusion of outliers.

In Kaplan-Meier analysis the log rank test indicated that hospitalization rates differed significantly according to the number of drugs (χ^2=26.9; *p*=.005); the same was found also after the exclusion of outliers (χ^2=21.05; *p*=.035).

The main characteristics of patients, compared according to the occurrence of at least one hospitalization, are shown in Table I.

Patients who were hospitalized, as compared with others, were less educated, had a more prevalent diagnosis of chronic pulmonary disease, and had higher Charlson Comorbidity Index and UPDRS scores. They showed lower serum albumin levels, and a lower MNA score; eventually, they took a higher number of drugs, as compared with subjects who were not hospitalized.

Multivariable Analyses

According to Cox regression, the number of medications was associated with increased risk of hospitalization in the crude model, after adjusting for age and sex (Table II), as well as in the multivariable model (HR=1.23; 95% CI=1.06-1.43; Table II), adjusted for those variables which showed significant differences in univariate analyses (Table I). The same association was observed after the exclusion of outliers (HR=1.21; 95% CI=1.04-1.41).

In addition, the MNA score was significantly and inversely associated with hospitalization (HR=.97; 95% CI=.94-.98) in the same multivariable model. Analysis of the interaction term indicated that the association between the number of drugs and incident hospitalizations did not differ according to nutritional status (*p* =.050). An increasing number of medications was associated with increasing risk of at least one hospitalization (*p* for linear trend=.027; Figure 1).

Using the same analyses, the number of drugs was a risk factor for incident hospitalization also after excluding medications for PD in the crude model, adjusting for age and sex (Table II) and in the multivariable model (HR=1.18; 95% CI=1.01-1.38, Table II).

According to Poisson regression modelling, among patients who were hospitalized, polypharmacy (i.e., >=5 daily agents) predicted an increased number of hospitalizations (IRR=2.62; 95% CI=1.28-5.36; *p*=.008), also after the exclusion of outliers (IRR=2.33; 95% CI=1.14-4.77; *p*=.022).

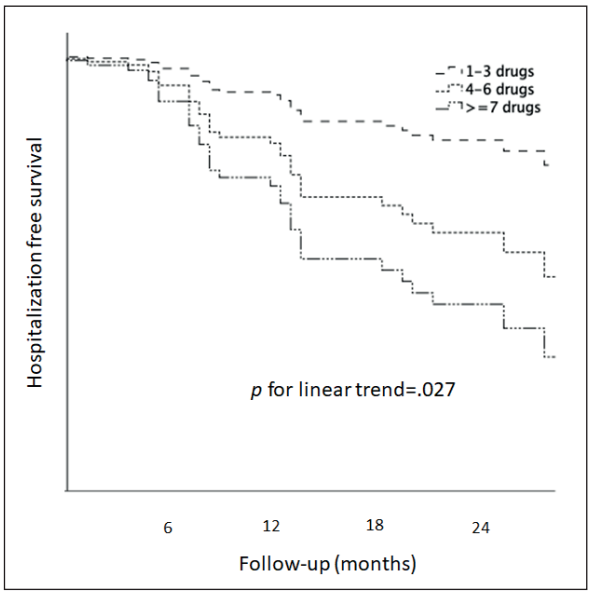

Figure 1. Association between number of drugs and hospitalization.

Table I. Characteristics of 165 participants according to incident hospitalization.

	Participants with incident hospitalization (n =46) n (%) or mean ± SD	Participants without incident hospitalization (n =119) n (%) or mean ± SD	*p*
Demographics & lifestyle habits			
Age (years)	74 (6)	73 (9)	.
Sex (female)	14 (30)	45 (38)	.469
Education (years)	8 (5-13)	13 (8-16)	.008
Current alcohol consumption a	1 (0-7)	3 (0-7)	.381
Smoking (Total lifetime pack years)	12.2 (7.3-23.3)	13.7 (6.2-25.2)	.886
Time from Parkinson's diagnosis (months)	48 (26-84)	33 (12-78)	.095
Comorbid conditions			
Diabetes	10 (22)	18 (15)	.356
Heart failure	1 (2)	5 (4)	.998
Chronic pulmonary disease	11 (24)	11 (9)	.020
Stroke	2 (4)	6 (5)	.999
Liver disease	1 (2)	5 (4)	.998
History of cancer	6 (13)	6 (5)	.096
Atrial fibrillation	4 (9)	6 (5)	.468
Coronary disease	5 (11)	7 (6)	.318
Charlson Comorbidity Index	2 (0-2)	1 (0-1)	.032
Medications			
ACE-inhibitors	11 (24)	23 (20)	.525
Benzodiazepines	8 (18)	14 (12)	.443
Beta-blockers	13 (29)	22 (19)	.202
Selective serotonin reuptake inhibitors	9 (20)	19 (16)	.642
Loop diuretics	8 (18)	11 (10)	.174
Antaggregants	22 (49)	44 (38)	.216
NSAIDs	2 (4)	4 (3)	.672
Total levodopa equivalent daily dose (mg/Kg)	452 (300-820)	500 (314-796)	.789
Levodopa daily dose (mg/Kg)	400 (300-675)	400 (225-600)	.819
Dopamine agonists daily dose (mg/Kg)	52 (0-157)	54 (0-140)	.850
Total number of drugs	6 (5-9)	5 (3-7)	.002
Drugs taken not for PD	5 (3-7)	3 (2-6)	.012
Objective tests			
Hemoglobin (g/dL)	13.5 (1.5)	13.7 (1.2)	.367
Glomerular Filtration Rate (mL/min)	65.4 (19.1)	74.2 23.3	.031
Serum albumin (g/dL)	4.2 (0.3)	4.3 (0.2)	.024
Unified Parkinson's Disease Rating Scale	47 (17)	41 (16)	.041
Hoen & Yahr scale	2 (2-3)	2 (1-3)	.080
Cognitive impairment b	11 (25)	12 (10)	.024
15-item Geriatric Depression Scale	4 (2)	5 (3)	.369
Katz' Activities of Daily Living	4 (2)	5 (1)	.166
Instrumental Activities of Daily Living	4 (2)	5 (2)	.061
Body Mass Index (Kg/m2)	26.7 (4.9)	27.6 (4.4)	.224
Grip strength	21.7 (9.5)	22.2 (8.9)	.775
Mini Nutritional Assessment	23.3 (3.9)	25.1 (3.1)	.003

[a]Number of wine glasses per week; b defined as a MMSE score < 24.

Discussion

The results of this study indicate that among older patients with PD the number of daily medications is associated with an increased risk of hospitalization, after adjusting for potential confounders. Accordingly, the number of drugs is independently associated with the number of hospitalizations. Cox regression modeling indicated that nutritional status is another in-

dependent predictor of hospitalization in these patients.

This finding is relevant, as PD is associated with increased rates and length of hospitalization[1]. Aside from the impact of hospital stay on patients' quality of life and healthcare costs, the hospitalization of patients with PD is associated with increased risk of complications, including falls, delirium, loss of mobility, and infections[20,21]. Administration of inappropriate drugs, such as antidopaminergic agents, is frequently found during the hospital stay of patients with PD[20]. Effort is therefore being devoted by researchers to reduce the incidence of hospitalizations in these patients, but so far with modest results[3]. Our study suggests that careful deprescribing might reduce the hospitalization rates of patients with PD. Use of several medications is common in PD, due to the complex nature of the disease, and to the burden of comorbidities that characterizes both the disease and the advanced age of most PD patients[22]. Polypharmacy is most commonly defined by use of five or more daily medications[5]; interestingly, this cut-off value best predicted the occurrence of hospitalization in our population (Table I). The median number of drugs taken in this study was five, which confirms the representativeness of our PD population as a clinical model of frailty. Polypharmacy might contribute to the occurrence of adverse drug reactions, which are a leading cause of hospitalization in advanced age. In addition, it has been demonstrated that polypharmacy is associated with cognitive decline in subjects with first diagnosis of PD[23]; this is relevant, because cognitive impairment has been associated with hospitalization[24]. Due to the prevalence of cognitive decline in general older populations, as well as in PD patients, polypharmacy might represent an important, potentially reversible risk factor for both hospitalization and the progression of dementia in PD[23,25].

In our population, about 43% of participants were hospitalized because of infections. Polypharmacy derives from multimorbidity, which in turn has been associated with antibiotic resistance, that might contribute to recurrent hospitalizations[26,27]. In addition, polypharmacy increases the risk of falls and fractures, including hip fractures; about 28% of hospitalizations in this study were due to these conditions[28]. Drug treatment for PD targeting the dopaminergic system alone may include several drugs, and treatment of motor and non-motor symptoms may require additional specific medications[22]. However, in our population the number of drugs represented a risk factor for hospitalization even after excluding specific agents for PD. This result might reflect the multimorbidity of PD patients; in fact, PD is thought to represent a model of frailty and biological aging[29-32]. Independently of the determinants of polypharmacy, withdrawal of inappropriate or unnecessary medications based upon acknowledged criteria (i.e., deprescribing) is recommended as an essential component of the prescription process for frail, older populations[33,34].

Results of this study indicate that other factors might be targeted to reduce the risk of hospitalization of patients with PD. Poor nutritional status represents an acknowledged risk factor for several adverse outcomes in frail subjects, including PD patients[35]. According to our analyses, PD severity and renal function

Table II. Association (HR coefficients, and 95% confidence intervals, CI) of incident hospitalization with number of drugs; all covariates were entered simultaneously into the model..

	HR	95% CI	p
Total number of drugs taken			
Crude model	1.23	1.09-1.39	.001
Age- and sex adjusted model	1.22	1.07-1.38	.002
Multivariable model*	1.23	1.06-1.43	.006
Number of drugs taken not for PD			
Crude model	1.21	1.07-1.37	.003
Age- and sex adjusted model	1.19	1.05-1.35	.008
Multivariable model*	1.18	1.01-1.38	.032

* adjusted for: age, sex, education, chronic pulmonary disease, Charlson Comorbidity Index, Glomerular Filtration Rate, serum albumin level, Unified Parkinson's Disease Rating Scale score, cognitive impairment, and Mini Nutritional Assessment score.

were associated with increased risk of hospitalization. PD severity has been associated with several adverse outcomes, including sarcopenia[36,37], which is an acknowledged risk factor for hospitalization in older subjects, including patients with PD[38]. In addition, impairment of renal function is a recognized marker of accelerated senescence, and thus associated with disability, hospitalization rates and mortality of frailer subjects[35]. Therefore, treatment of older patients with PD requires the cooperation of multidisciplinary teams, aiming at optimizing health resources, and targeting patients centered care[39].

This study included a representative population of community-dwelling patients with PD, with extensive information regarding demographic characteristics, comorbid conditions, and objective parameters. However, due to its monocentric design, results may not be generalizable and should be confirmed by multicenter studies.

Conclusions

Polypharmacy is a risk factor for hospitalization in elderly PD patients. Identifying potentially inappropriate medications might therefore improve the outcomes of this condition. Further research is needed to develop specific evidence-based therapy for elderly patients with PD.

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Conflict of Interest
The Authors declare that they have no conflict of interests.

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