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4 **Orthostatic Hypotension in Parkinson Disease: Impact on Health Care**  
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7 **Utilization**  
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45 Word count: 1456  
46  
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51 Keywords: Parkinson's disease; Autonomic; Syncope; Orthostatic hypotension; Supine  
52 hypertension.  
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4 **ABSTRACT**  
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6 **Introduction.** Orthostatic hypotension (OH) represents a frequent yet overlooked source of  
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8 disability in Parkinson disease (PD). In particular, its impact on health care utilization has been  
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10 insufficiently examined. We sought to determine the differential health care utilization in PD  
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12 patients with (PDOH+) and without OH (PDOH-).  
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18 **Methods.** We quantified the emergency room (ER) visits, hospitalizations, outpatient clinic  
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20 evaluations, phone calls, and e-mails from PD patients on whom supine and orthostatic blood  
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22 pressure (BP) measurements were obtained during routine clinical practice between June 2013  
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24 and July 2016. Comparative costs between PDOH+ and PDOH- were adjusted for age, disease  
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26 duration, motor severity, levodopa equivalent daily dose, and Montreal Cognitive Assessment.  
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33 **Results.** From a total of 317 PD patients, 29.3% were classified as PDOH+ (n= 93) and 70.6% as  
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35 PDOH- (n= 224) over  $30.2 \pm 11.0$  months, in which there were 247 hospitalizations, 170 ER  
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37 visits, 2386 outpatient evaluations, and 4747 telephone calls/e-mails. After-adjusting for relevant  
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39 covariates, PDOH+ was associated with more hospitalization days (+285%; p= 0.041), ER visits  
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41 (+152%; p= 0.045), and telephone calls/e-mails than PDOH- (+142%; p= 0.009). The overall  
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43 health care-related cost in PDOH+ was 2.5-fold higher than for PDOH- ( $\$25,510 \pm \$6,650$  vs.  
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45  $\$10,152 \pm \$4,204$ /person/year; p= 0.041).  
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53 **Conclusion.** OH increases health care utilization in PD independently from age, disease  
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55 duration, motor severity, dopaminergic treatment, and cognitive function.  
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**FUNDING STATEMENT**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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4 **INTRODUCTION**  
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6 In healthy individuals, baroreflex responses to postural changes maintain a constant blood  
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8 pressure (BP) and cerebral perfusion regardless of positional changes. Disruption of this  
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10 autonomic compensatory mechanism, which involves the synchronized activity of the  
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12 sympathetic and parasympathetic systems, results in hemodynamic instability, predominantly  
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14 expressed as orthostatic hypotension (OH).  
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21 OH, defined by a BP fall greater than 20 mm/Hg systolic or 10 mm/Hg diastolic within 3  
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23 minutes of standing from a sitting or supine position [1], represents a major determinant of  
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25 disability in elderly patients with or without neurodegenerative diseases. In a study evaluating  
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27 12,661 subjects enrolled in the Atherosclerosis Risk in Communities (ARIC), OH was found to  
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29 be an independent predictor of falls [2], resulting in greater rate of head trauma and hip fractures.  
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31 The management of OH is even more challenging in Parkinson Disease (PD) given the additional  
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33 autonomic dysfunction, which has a prevalence of over 30% [3], and the associated hypotensive  
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35 effect of dopaminergic medications needed for symptomatic treatment [4]. Despite its frequency,  
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37 OH is frequently under-recognized [5]. As a result, PD patients with OH are often untreated (or  
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39 undertreated even when recognized) and left with potentially greater net disability - and  
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41 healthcare utilization - than those without OH.  
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50 To evaluate the effect of OH on health care utilization among PD patients we obtained data on  
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52 days of hospitalizations, number of ER visits, outpatient clinic evaluations, telephone calls and e-  
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54 mails to health care providers in a cohort of PD patients for whom supine and orthostatic blood  
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56 pressure measurements were obtained as part of their routine bedside evaluation to screen for  
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58 OH.  
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4 **METHODS**

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7 *Study Design*

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9 We retrospectively analyzed electronic medical records from consecutive PD patients with  
10 orthostatic BP measurements at the Gardner’s Family Center for Parkinson’s disease and  
11 Movement Disorders (University of Cincinnati, USA) between June 2013 and July 2016. Data  
12 related to health care utilization and costs were compared between PDOH+ and PDOH-.  
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21 *Participants*

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23 Inclusion criteria were idiopathic PD [6] with at least two clinical evaluations during the three-  
24 year study period, and availability of orthostatic BP measurements. Exclusion criteria were  
25 diabetes mellitus or other diseases potentially associated with autonomic neuropathy [7], any  
26 atypical features affecting the diagnostic certainty of idiopathic PD, and medical conditions  
27 associated with non-neurogenic OH, such as chronic hypertension, dehydration, anemia, or use  
28 of alpha-blockers [8]. Patients were classified as PDOH+ or PDOH- as per the “20/10 criteria”,  
29 which consists of a fall in systolic BP  $\geq$  20 mm/Hg or diastolic BP 10 mm/Hg within 3 minutes  
30 of standing after a minimum of 5 minutes of supine rest [1]. The University of Cincinnati  
31 Institutional Review Board approved this study.  
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48 *Measures and Outcomes*

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50 *Definitions.* Hospitalization was defined as admission to an inpatient unit for at least one night.  
51 Fall was defined according to the World Health Organization (WHO) as “an event that results in  
52 a person coming to rest inadvertently on the ground or floor or other lower level.” Dementia was  
53 defined as per the Movement Disorders Society Criteria, as an impairment in at least two  
54 cognitive domains with a significant impact on patient’s autonomy in daily living activities  
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4 (ADL) [9]. Levodopa equivalent daily dose (LEDD) was calculated according to a validated  
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6 conversion table [10].  
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11 ***Health care utilization.*** Electronic medical records (Epic Systems Corporation, Verona,  
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13 Wisconsin) were searched for hospitalizations (number, days, and indications), ER visits  
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15 (number and indications), and number of outpatient clinic evaluations, telephone calls and e-  
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17 mails sent to health care providers from patients or caregivers. Clinical and demographic data  
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19 extracted included gender, age, disease duration, follow-up duration, falls, motor subscale of the  
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21 Movement Disorders Society Unified Parkinson’s disease rating scale (MDS-UPDRS-III),  
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23 Montreal Cognitive Assessment (MoCA), and medications.  
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31 ***Costs.*** Average daily direct costs for hospitalizations, ER visits, and outpatient clinic visits for  
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33 the 2016 period were extracted from the University of Cincinnati Medical Center Patient Price  
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35 Information List [11]. Costs associated with e-mails and telephone calls were calculated based on  
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37 a 5-minute unit-of-exchange time and according to the average reported 2016 salary for a  
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39 Neurologist in the state of Ohio (obtained from Doximity, a network of US healthcare  
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41 professionals [12]). Total cost was calculated multiplying the absolute frequency of each event  
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43 by its estimated cost. Indirect costs (e.g., lost work days by caregivers) and costs without  
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45 validated method of calculation were not considered.  
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### 53 ***Statistical Analyses***

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55 Demographic and clinical data were described with appropriate summary measures (frequency,  
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57 mean  $\pm$  standard deviation) and compared using the Mann-Whitney non-parametric test or  
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59 Fisher’s exact test, as appropriate. Analysis of covariance (ANCOVA) was used to estimate  
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4 differences in the annualized number of ER visits, outpatient clinic visits, telephone calls/e-  
5 mails, and days of hospitalizations (dependent variables) between PDOH+ and PDOH-  
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7 (independent variable), adjusting for age, disease duration, MDS-UPDRS motor score, total  
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9 LEDD, and MoCA score (covariates). Similarly, health-care cost metrics (dependent variables)  
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11 were compared between PDOH+ and PDOH- (independent variable) adjusting for the same  
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13 covariates. Indications for ER visits and hospitalizations were summarized with descriptive  
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15 statistics and compared between PDOH+ and PDOH- using the Fisher's exact test. All p-values  
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17 were two-tailed with 0.05 as a statistical threshold of significance.  
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## 26 **RESULTS**

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28 A total of 317 PD patients underwent supine and orthostatic BP measurements, allowing a  
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30 classification of PDOH+ in 29.3% (n= 93) and PDOH- in 70.6% (n= 224). During the study  
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32 period of  $30.2 \pm 11.0$  months there were 247 hospitalizations, 170 ER visits, 2386 outpatient  
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34 clinic evaluations, and 4747 telephone calls/e-mails.  
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41 Unadjusted data showed that PDOH+ patients were older ( $p < 0.001$ ), had longer PD duration  
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43 ( $p= 0.016$ ), and worse MDS-UPDRS-III score ( $p < 0.001$ ) than PDOH- (Table 1). After adjusting  
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45 for age, PD duration, MDS-UPDRS-III score, total LEDD, and MoCA, PDOH+ remained  
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47 independently associated with more days of hospitalizations (+285%;  $p= 0.041$ ), ER visits  
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49 (+152%;  $p= 0.045$ ), and telephone calls/e-mails (+142%;  $p= 0.009$ ) compared to PDOH- (Figure  
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58 *Health care utilization.* There was a higher rate of hospitalizations and ER visits for  
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60 neuropsychiatric complications ( $p= 0.043$  and  $p= 0.025$ ) and falls ( $p= 0.034$  and  $p= 0.045$ )  
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4 among PDOH+ compared to PDOH-, as well as a higher rate of hospitalizations for  
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6 rehabilitation or musculoskeletal complications (p= 0.009) (Figure 2).  
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11 *Costs.* There were a 3-fold higher hospitalization costs (+281%; p= 0.041), 1.5-fold higher ER  
12 visits costs (+150%; p= 0.045), and 1.4-fold higher telephone calls/emails costs (+144%; p=  
13 0.009), adjusting for age, PD duration, MDS-UPDRS-III score, total LEDD, and MoCA score.  
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15 Overall costs per patient per year were 2.5-fold higher in PDOH+ than PDOH- (+251%; p=  
16 0.041) (Table 2).  
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## 26 **DISCUSSION**

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28 After adjusting for age, disease duration, motor severity, dopaminergic therapies, and cognitive  
29 function, PDOH+ was associated with greater health care utilization than PDOH-, independently  
30 increasing days of hospitalization by 285% and number of ER visits by 152% as well as  
31 increased health-care related cost per patient per year by 251%. These findings reflect the greater  
32 financial impact of the care of PD patients when OH complicates the clinical picture.  
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43 OH represents a major determinant of PD-related functional disability [5, 13] and a potentially  
44 treatable cause of falls and related complications, such as fractures [2, 14]. To the challenges of  
45 its clinical management, namely the hypotensive effects of dopaminergic therapies used to treat  
46 PD motor symptoms [15, 16] and the frequent association with supine hypertension (SH), which  
47 dampen the assertiveness of BP-increasing strategies [4, 17], our study adds the increased burden  
48 on health care systems.  
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4 The strength of our conclusions is tempered by some limitations. First, the retrospective design  
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6 may have underestimated health care utilization and cost data. Second, the available orthostatic  
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8 BP data used as inclusion criteria likely increased the probability of a selection bias of a  
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10 population with a greater prevalence of PDOH+ patients, as this screening tool is enacted more  
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12 often among patients complaining of postural dizziness/lightheadedness. Third, the classification  
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14 into OH+ and OH- based on bedside testing rather than continuous BP monitoring might have  
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16 underestimated the actual point prevalence of OH. However, continuous BP monitoring has  
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18 remained a research tool, not yet widely available for patient care. Fourth, the definition of OH  
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20 was based on the widely-used 20/10 criteria. Recent data suggests that a more conservative  
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22 cutoff of 30 mmHg (systolic) and 15 mmHg (diastolic) may be more appropriate [18]. Finally,  
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24 we lacked data relating to silent end-organ damage, which would have required a comprehensive  
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26 evaluation of cerebral, vascular, cardiac, and renal function –and may have accounted for  
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28 potentially additional (if ostensibly unrelated) utilization and costs.  
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38 In sum, these findings further support a large negative impact of OH in overall PD-related health  
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40 care burden [19, 20] and highlight the need to improve programs for prompt recognition and  
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42 appropriate management of OH. Future studies are needed to clarify the risk/benefit ratio  
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44 associated with different target of orthostatic and supine BP and the cost effectiveness of  
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46 management strategies to minimize the associated health care burden and costs.  
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4 **CONTRIBUTORSHIP STATEMENT**  
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6  
7 A. Merola: conception and design of the study, analysis and interpretation of data; writing of the  
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9 first draft and review and critique of the manuscript  
10

11 R. P. Sawyer: acquisition of data, interpretation of data; review and critique of the manuscript  
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14 C. A. Artusi: acquisition of data; review and critique of the manuscript  
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16 R. Suri: acquisition of data; review and critique of the manuscript  
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19 Z. Berndt: acquisition of data; review and critique of the manuscript  
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21 J. R. Lopez-Castellanos: acquisition of data; review and critique of the manuscript  
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23 J. Vaughan: acquisition of data; review and critique of the manuscript  
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26 J. A. Vizcarra: analysis and interpretation of data; review and critique of the manuscript  
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28 A. Romagnolo: analysis and interpretation of data; review and critique of the manuscript  
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31 A. J. Espay: conception and design of the study; interpretation of data; review and critique of the  
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33 manuscript  
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38 All the listed authors gave their final approval of the final version of the manuscript  
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43 **FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST**  
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45 Dr Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL  
46  
47 Behring, Cynapsus Therapeutics, and UCB Pharma  
48

49  
50 Dr Sawyer reports no disclosures  
51

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53 Dr Artusi reports no disclosures  
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55 Dr Suri reports no disclosures  
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58 Dr Berndt reports no disclosures  
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60 Dr Lopez-Castellanos reports no disclosures  
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4 Dr Vaughan reports no disclosures  
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7 Dr Vizcarra reports no disclosures  
8

9 Dr Romagnolo has received grant support and speaker honoraria from AbbVie, speaker  
10 honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco and UCB Pharma.  
11

12  
13 Dr Espay is supported by the NIH and has received grant support from CleveMed/Great Lakes  
14 Neurotechnologies, Davis Phinney Foundation, and Michael J Fox Foundation. Dr. Espay was  
15 investigator in the Chelsea-sponsored Droxidopa studies and has acted as scientific advisor to  
16 Lundbeck, current marketer of Droxidopa. Dr. Espay has no financial interest in either company.  
17  
18

19 He received personal compensation as a consultant/scientific advisory board member for Solvay,  
20  
21 Abbott, Chelsea Therapeutics, TEVA, Impax, Merz, Lundbeck, and Eli Lilly; honoraria from  
22  
23 TEVA, UCB, the American Academy of Neurology, and the Movement Disorders Society; and  
24  
25 publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and  
26  
27 Springer.  
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### 38 **ETHICAL STANDARD**

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40 The authors declare that they acted in accordance with the ethical standards laid down in the  
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42 1964 Declaration of Helsinki. The ethical committee approval was obtained.  
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4 **FIGURE CAPTIONS**  
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7 **Figure 1. Health-Care Utilization**  
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10 Number of events per person per year, adjusting for age, disease duration, MDS-UPDRS motor  
11 score, total LEDD, MoCA score. OH: Orthostatic hypotension; ER: Emergency Room; MDS-  
12 UPDRS: Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale.  
13 LEDD: Levodopa Equivalent Daily Dose. MoCA: Montreal Cognitive Assessment. \*  $p < 0.05$   
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22 **Figure 2. Cause-Specific Hospitalization Rate and Emergency Room Visits**  
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25 Indications for Emergency Room visits and Hospitalizations per 100,000 persons per year. OH:  
26 Orthostatic hypotension; ER: Emergency Room. \*  $p < 0.05$  in *a*: ER visits; *b*: Hospitalizations;  
27 and *c*: ER visits and Hospitalizations.  
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**TABLE 1. Unadjusted Clinical, Demographic, and Pharmacological Data**

	<b>Cohort (n= 317)</b>	<b>PD-OH+ (n= 93)</b>	<b>PD-OH- (n= 224)</b>	<b>P-value</b>
<b>Demographics</b>				
Gender (males %)	(65.6%)	(63.4%)	(66.5%)	0.345
Age (years)	71.0 ± 10.2 (36 - 93)	74.4 ± 9.5 (54 - 93)	69.6 ± 10.2 (36 - 92)	<b>&lt;0.001</b>
Age at PD onset (years)	59.4 ± 12.0 (26 - 90)	62.1 ± 12.2 (29 - 90)	58.3 ± 11.7 (26 - 84)	<b>0.009</b>
<b>Clinical Data</b>				
PD duration (years)	11.6 ± 5.6 (1 - 34)	12.7 ± 5.8 (3 - 34)	11.1 ± 5.5 (1 - 34)	<b>0.016</b>
Follow-up duration (months)	30.2 ± 11.0 (12 - 47)	31.0 ± 11.4 (12 - 47)	29.9 ± 9.1 (12 - 44)	0.436
UPDRS-III (score)	33.5 ± 14.4 (3 - 74)	39.4 ± 13.6 (17 - 72)	31.0 ± 14.0 (3 - 74)	<b>&lt;0.001</b>
Dementia (prevalence)	(10.1%)	(12.9%)	(8.9%)	0.192
Systolic blood pressure (mm/Hg)	124.0 ± 23.3 (90 - 218)	123.0 ± 27.9 (90 - 204)	124.4 ± 21.2 (95 - 218)	0.251
Diastolic blood pressure (mm/Hg)	70.7 ± 12.4 (45 - 107)	69.8 ± 12.4 (45 - 107)	71.1 ± 12.4 (50 - 107)	0.193
<b>Pharmacological Data</b>				
LEDD (mg/day)	1158.8 ± 804.9 (0 - 2700)	1153.7 ± 656.4 (0 - 2700)	1160.9 ± 860.4 (0 - 2600)	0.387
Use of dopamine agonists (prevalence)	(21.5%)	(19.4%)	(22.3%)	0.335
Use of anti-OH medications (prevalence)	(10.1%)	(32.3%)	(0.9%)	<b>&lt;0.001</b>

Data are reported as mean ± standard deviation, unless specified differently. PD: Parkinson's disease; OH: Orthostatic hypotension; MDS-UPDRS: Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale; LEDD: Levodopa Equivalent Daily Dose.

**TABLE 2. Healthcare Utilization Cost in United States Dollars per Patient per Year**

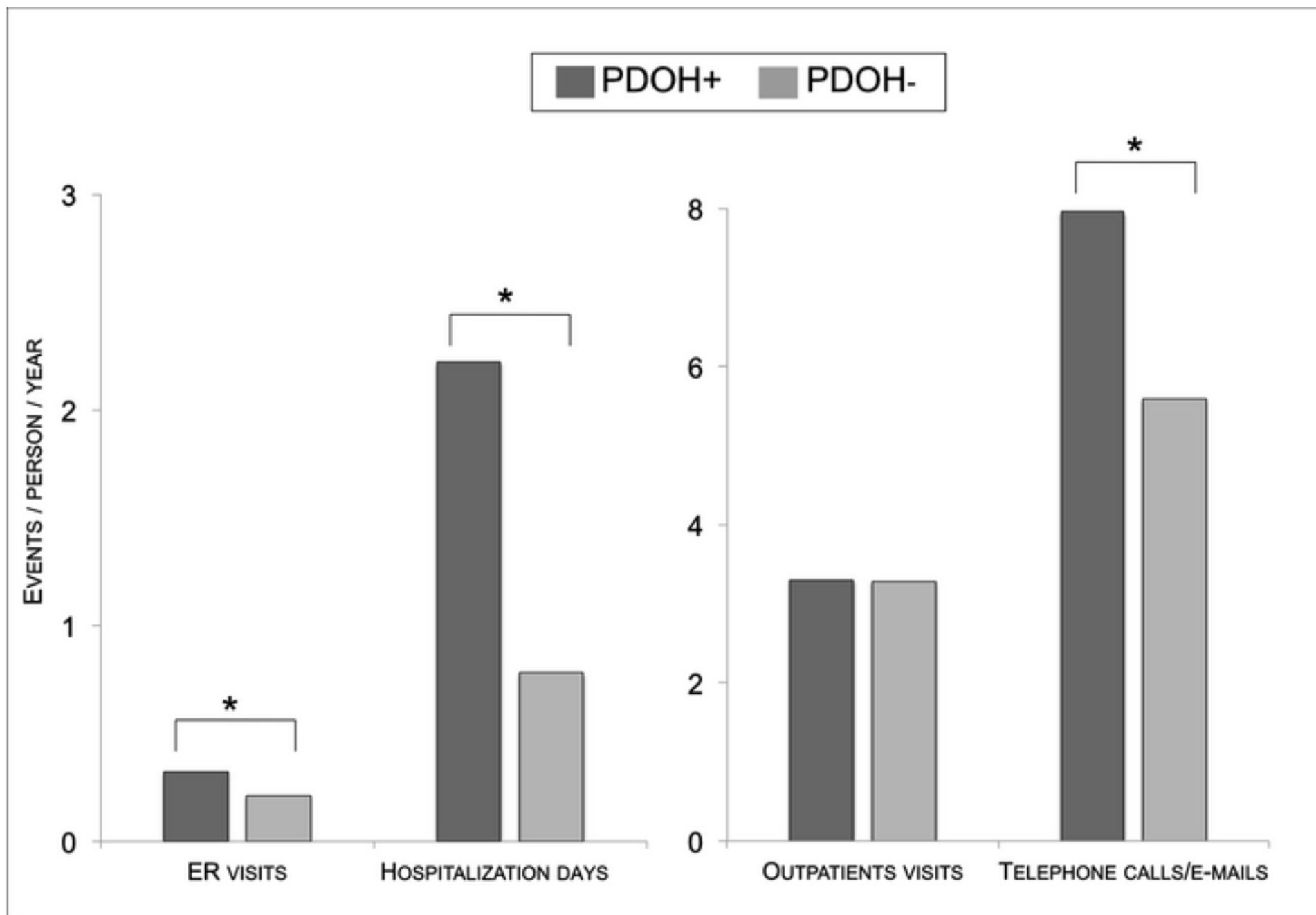
	<b>PD-OH+</b> <b>(n= 93)</b>	<b>PD-OH-</b> <b>(n= 224)</b>	<i><b>P-value</b></i>
<b>Hospitalizations</b>	\$22,986 ± \$6,360	\$8,180 ± \$4,022	<b>.041</b>
<b>ER visits</b>	\$1,518 ± \$495	\$1,014 ± \$313	<b>.045</b>
<b>Outpatients visits</b>	\$919 ± \$66	\$913 ± \$41	<b>.934</b>
<b>Telephone calls/e-mails</b>	\$65 ± \$6	\$45 ± \$4	<b>.009</b>
<b>TOTAL</b>	\$25,510 ± \$6,650	\$10,152 ± \$4,204	<b>.041</b>

Data are reported as mean ± standard error and expressed as United States Dollars per patient per year, adjusting for age, disease duration, MDS-UPDRS motor score, total LEDD, MoCA score.

OH: Orthostatic hypotension; ER: Emergency Room; MDS-UPDRS: Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale. LEDD: Levodopa Equivalent Daily Dose.

MoCA: Montreal Cognitive Assessment.

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