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# Sex Differences in the Treatment of People with Parkinson's Disease with a Device-Aided Therapy: A Prospective Real-World Study

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## Abstract

**Background and Objective:** Sex differences in the treatment of people with Parkinson's disease (PwP) with a device-aided therapy (DAT) have been poorly investigated. Our aim was to analyze sex differences in the management and response to a DAT in PwP in daily clinical practice (DCP). **Patients and Methods:** Data collected in the DATs-PD GETM Spanish Registry until 30 October 2025 were used. This is a descriptive, observational, prospective, and multicenter clinical registry with progressive inclusion of PwP treated with a DAT in DCP conditions in more than 40 centers from Spain. Sex differences in the DAT

received and changes in quality of life (QoL), motor symptoms (MS), non-motor symptoms (NMS), and autonomy for activities of daily living (AADL) after 6 months of treatment were analyzed. **Results:** A total of 618 PD patients (66.9 ± 9.5 years old; 57.6% men) were treated with a DAT. A significant difference was observed in the DAT type according to sex ($p = 0.006$), with 73.1% of PwP who were treated with deep brain stimulation being men. At the time of DAT indication, women were older, received a higher levodopa equivalent daily dose, and had a worse health-related QoL and AADL. OFF time decreased, whereas MS and NMS burden and health-related QoL improved at 6 months follow-up in both groups (men and women). AADL improved only in men during the OFF state. **Conclusion:** Sex differences were detected in the use of DATs in PwP. Improvement in OFF time, MS, NMS, and QoL was detected in both groups.

**Keywords:** advanced Parkinson's disease; device-aided therapies; effectiveness; real-world study; safety; sex

## 1. Introduction

Device-aided therapies (DATs) are treatment modalities that utilize medical devices to deliver continuous dopaminergic stimulation or neuromodulation. They include deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), continuous subcutaneous infusion of foslevodopa/foscarbidopa (fLD/fCD), continuous infusion of levodopa–carbidopa intestinal gel (LCIG), and continuous infusion of levodopa–entacapone–carbidopa intestinal gel (LECIG) [1]. DATs are indicated in patients with Parkinson's disease (PD) with persistent disabling symptoms despite conventional treatment. Selection among these options is individualized based on symptom profile, comorbidities, patient preference, and contraindications [2]. In particular, sex and gender significantly influence both the use and outcomes of DATs in people with PD (PwP). Women are less likely to receive DATs, such as DBS and LCIG, despite similar indications and potential benefits [3–5]. This disparity is multifactorial, involving later referral, longer disease duration at intervention, clinical phenotype, and sociocultural barriers, including reduced access to caregiving and healthcare resources [6]. Specifically, women are less likely to receive DBS and are often referred later in the disease course [7]. Motor outcomes after DBS are similar for both sexes, though men may experience greater improvement in bradykinesia and reduction in dopaminergic medication, while women may have more improvement in activities of daily living and cognition but also more mood-related complications postoperatively [8]. No evidence supports preferential use of levodopa intestinal gel (LCIG and LECIG) or continuous subcutaneous infusion therapy (fLD/fCd and CSAI) for either sex, but these therapies may be considered in patients with contraindications to surgery or higher risk of DBS-related complications [9]. Sex disparities in access to DATs persist, with women underrepresented in trials and less likely to be offered advanced therapies (including new fLD/fCD and LECIG), highlighting the need for more research and guidance on sex-specific considerations. Recently, clinical trial data for fLD/fCD demonstrate that a majority of participants were men (68% in the double-blind study [10] and 59.8% in the open-label study [11]). Regarding LECIG, the other recent DAT available, the frequency of men who received the treatment in recently published observational studies was 61.6% [12] and 59% [13]. Moreover, no studies with infusion therapies have reported sex-specific efficacy or safety data. All of these data are consistent with what was observed in a recent meta-analysis that found that women continue to be underrepresented in PD clinical trials, including those for infusion therapies [14]. Effectively addressing this

underrepresentation necessitates a holistic approach spanning research, clinical practice, and policy development.

In summary, data on sex-specific preferences for device-aided therapies remain limited, especially regarding new infusion therapies and in gender-diverse populations [15]. The aim of the present study was to analyze the sex differences in the selection, management, and response to a DAT in PwP in daily clinical practice in Spain.

## 2. Material and Methods

Data collected in the DATs-PD GETM Spanish Registry until 30 October 2025 were used. This is a descriptive, observational, prospective, and multicenter clinical registry with progressive inclusion of PwP treated with a DAT in daily clinical practice conditions in more than 40 centers from Spain (Appendix A) [16]. Specifically, the eligibility criteria are [16]: (1) diagnosis of PD according to the MDS criteria [17]; (2) start of treatment with a DAT from 1 January 2024 to; (3) the patient's desire to participate on a completely voluntary basis; (4) signing of an informed consent.

Data from the baseline visit (V1; before initiation the DAT) and first follow-up visit (V3.6M; 6 ± 3 months after initiation the DAT) were considered for the analysis [16]: sociodemographic data; data about PD (age onset, disease duration, motor phenotype, etc.); comorbidities; treatments; main reason for therapy indication; levodopa equivalent daily dose (LEDD) and dopamine agonist equivalent daily dose (DAEDD) [18]; motor symptoms (MS); non-motor symptoms (NMS), including cognition; Unified Parkinson's Disease Rating Scale (UPDRS-III) [19] during the OFF and during the ON state; Hoehn & Yahr (H&Y) [20] stage in OFF and in ON; Parkinson's Disease Questionnaire (PDQ-39; it was expressed as a summary index [PDQ-39SI]) [21]; European Health Interview Survey-Quality of Life 8-item index (EUROHIS-QOL8) [22]; Schwab and England Activities of Daily Living Scale (ADLS) [23] during the OFF and during the ON state. Moreover, a motor symptoms score (MSs) and a non-motor symptoms score (NMSs) ranging from 0 to 60 and from 0 to 80, respectively, were calculated based on 15 MS and 20 NMS collected at each visit (V1 and V3.6M), as it has been previously published [24] (Table S1—Supplementary Material). A specific "Dyskinesia score" (from 0 to 12) was also calculated using the same methodology with 3 items (percentage of the waking day with dyskinesia; dyskinesia severity; painful dyskinesia) [24]. Information was collected on therapy discontinuations and their reasons. However, this study did not specifically analyze aspects related to drug management and complications for each DAT by sex, which will be analyzed together with differences in the selection for each DAT by sex in detail in another manuscript.

Regarding sex, PD patients were classified according to biological aspect in men vs. women. Sex differences in the DAT received and changes in quality of life (QoL), MS, NMS, and autonomy for activities of daily living (AADL) after 6 months of treatment were analyzed.

### 2.1. Data Collection and Statistical Analysis

Data were collected using REDCap (https://project-redcap.org/). Data collected were transferred to a statistical package for subsequent analysis (SPSS 20.0 for Windows). Remote monitoring of the data was carried out (A.S.V.). The sample size was considered according to the data available for each of the analysis variables.

After checking for normality for continuous variables (Shapiro–Wilk's test), comparisons were carried out intra- and intergroup, applying parametric (Student's *t*-test for paired or unpaired data) or nonparametric tests (Wilcoxon's/Mann–Whitney's tests). Proportions were compared by chi-squared test. To evaluate the magnitude of the change, in addition to the difference between V1 and V3.6M, the relative change

[RC = mean (TestV3.6M − TestV1) × 100/mean TestV1)] [25] and Cohen's d effect size [ES = mean (TestV3.6M − TestV1)/SD TestV1] [26] were calculated. Cohen's d effect size was considered to be: absent, <0.2; small, 0.2–<0.5; moderate, 0.5–<0.8; large, 0.8–1.3; or very large, ≥1.3. Specifically, differences between men and women in the change in PDQ-39SI, EUROHIS-QOL8, daily OFF time, MSs, Dyskinesia score, NMSs, ADLS-OFF, and ADLS-ON from V1 to V3.6M were analyzed. The *p*-values were computed using general linear models (GLM) repeated measures without and after adjustment for covariates (age, disease duration, and days receiving the DAT).

### 2.2. Standard Protocol Approvals, Registrations, and Patient Consents

The project was conducted in accordance with the ICH Good Clinical Practice version 6 Revision 2 standard, the fundamental ethical principles established in the Declaration of Helsinki and the Oviedo Convention, as well as the Spanish legal requirements for biomedical research (Biomedical Research Law 14/2007). The Project was approved on 2 April 2024 by the IRB "Comité de Ética de la Investigación Clínica de Galicia from Spain" with code number 2024/109. Written informed consents from all participants in this study were obtained.

### 2.3. Data Availability

The protocol, statistical analysis plan and unidentified participant data will be available on request.

## 3. Results

A total of 618 PD patients were treated with a DAT. The mean age was 66.9 ± 9.5 years old, with 356 (57.6%) being men and 262 (42.4%) being women. Regarding the DAT type, the frequency was 49.0% (N = 303) fLD/fCD, 20.7% (N = 128) CSAI, 17.5% (N = 108) DBS, 10% (N = 62) LECIG, and 2.8% (N = 17) LCIG. The frequency of subcutaneous therapies (fLD/fCD + CSAI) was 69.7% versus 12.8% for enteral therapies (LECIG + LCIG). A significant difference was observed in the DAT type according to sex ($p = 0.006$) (Figure 1C). Specifically, 79 men (73.1%) were treated with DBS compared with 29 (26.9%) women. Regarding the rest of the DATs, the number of subjects who were treated with a DAT was greater in men vs. women (fLD/fCD, 170 vs. 133 CSAI, 67 vs. 61; LCIG, 10 vs. 7) except in the case of LECIG (30 vs. 32) (Figure 1B).

At baseline before DAT initiation (V1), women were older than men (69.2 ± 9.8 vs. 65.2 ± 8.9; $p < 0.0001$). Smoking, alcohol consumption, ischemic cardiopathy, hyperuricemia, and cancer were more frequent in men than in women (Table 1). The percentage of men with a principal caregiver was lower for men compared to women (50.3% vs. 59%; $p = 0.020$), with the partner being the principal caregiver in 81.2% of men compared to 64% of women ($p < 0.0001$; Table 1). Compared with women, men were being treated more frequently with a type-B monoamine oxidase inhibitor (56% vs. 44.3%; $p = 0.003$) and with a catechol-O-methyltransferase inhibitor (58.5% vs. 50.2%; $p = 0.027$), being the LEDD and the DAEDD significantly higher in men vs. women (Table 2). Significant difference between both groups was detected in weight ($p < 0.0001$) but not in the BMI (body mass index) (Table 2). Regarding cognitive impairment, more men were cognitively intact compared with women (78.5% vs. 69.5%; $p = 0.045$). With reference to PD symptoms, mean daily OFF time was 5.5 ± 3.1, without differences between both groups ($p = 0.907$) (Table 2). No differences were also found in time with fluctuations, H&Y, UPDRS-III, MSs, and NMs, but so in Dyskinesia score, being 3.0 ± 2.2 in women compared to 2.5 ± 2.0 in men ($p = 0.002$) (Table 2). In terms of QoL and AADL, women compared to men had at baseline a worse health-related QoL (PDQ-39SI, 42.8 ± 14.3 vs. 34.6 ± 15.5; $p < 0.0001$) and a lesser AADL

during the ON state (ADLS-ON, 77.9 ± 18.7 vs. 82.9 ± 17.2; $p < 0.0001$). Specifically, 65.4% of the men were independent for activities of daily living compared to 54.1% of the women ($p = 0.029$) (Table 2).

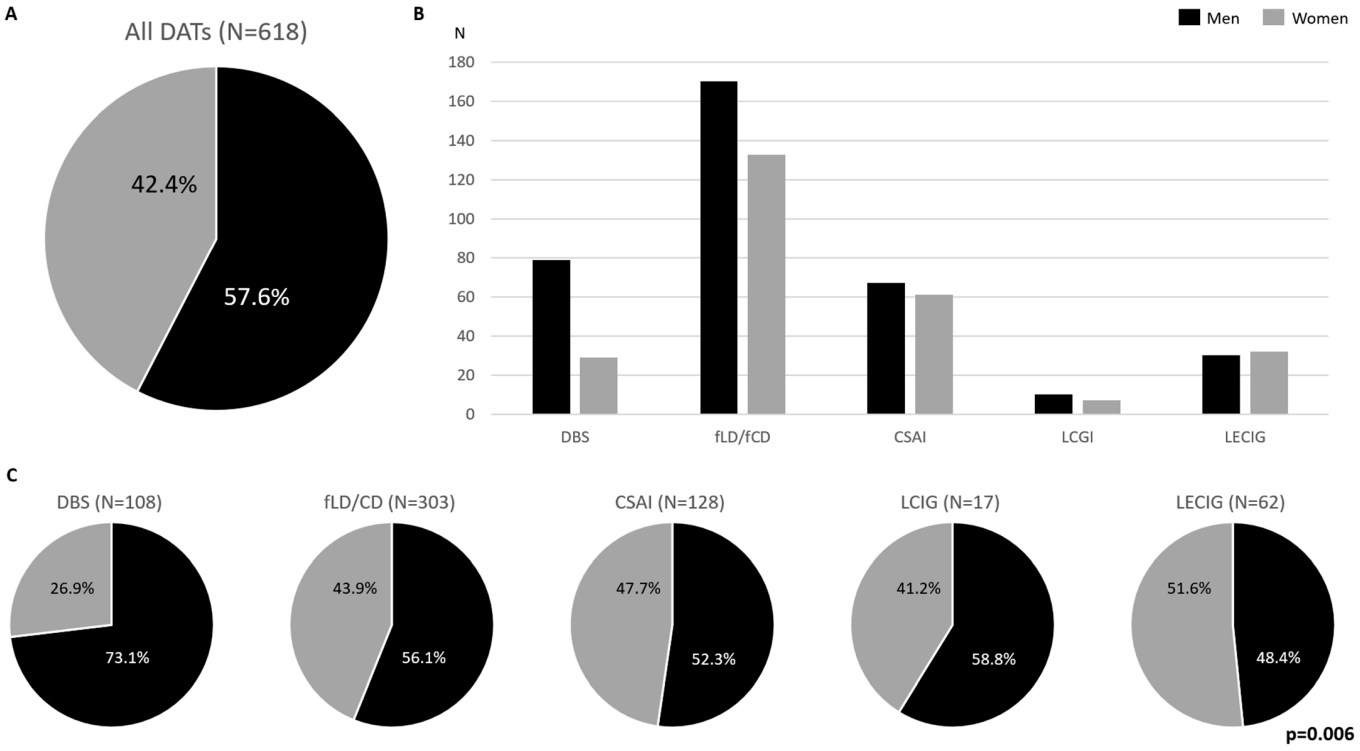


**Figure 1.** Total frequency (**A**) and specific frequency (**C**) and total number (**B**) of PwP who were treated with a different DATs according to sex.

**Table 1.** Sociodemographic and aspects related to comorbidities in PwP at baseline (before initiation with a DAT) in men vs. women from the DATs-PD GETM Spanish registry.

| | **All Cohorts N = 618** | **Men N = 356** | **Women N = 262** | *p* |
|---|---|---|---|---|
| Civil status (%): | | | | **<0.0001** |
| -Married | 72.7 | 78.1 | 65.5 | |
| -Single | 10.3 | 11.7 | 8.5 | |
| -Widowed | 9.7 | 4.3 | 17.1 | |
| -Other | 7.3 | 5.9 | 5.9 | |
| Living style (%): | | | | **<0.0001** |
| -With the partner | 73.9 | 81.2 | 64 | |
| -Alone | 10.5 | 9.7 | 11.6 | |
| -With a son/daughter | 7.7 | 3.1 | 14 | |
| -Institutionalized | 2 | 0.6 | 3.9 | |
| -Other | 5.9 | 5.4 | 6.7 | |
| Principal caregiver (%): | 54 | 50.3 | 59 | **0.020** |
| Caregiver (%): | | | | **<0.0001** |
| -Partner | 67.7 | 80 | 53.6 | |
| -Son/daughter | 16.8 | 9.1 | 25.5 | |
| -Other | 15.5 | 10.9 | 20.9 | |
| Smoking (%) | | | | **<0.0001** |
| -Active | 6.8 | 7.5 | 5.8 | |
| -Ex-smoker | 30.2 | 27.3 | 10.8 | |
| -Non-smoker | 73 | 65.2 | 83.4 | |
| Alcohol (%) | 24.4 | 32.6 | 13.3 | **<0.0001** |
| Comorbidities (%): | | | | |

**Table 1.** *Cont.*

| | All Cohorts N = 618 | Men N = 356 | Women N = 262 | *p* |
|---|---|---|---|---|
| -Arterial hypertension | 37.5 | 37.7 | 37.3 | 0.926 |
| -Diabetes mellitus | 14.7 | 17.1 | 11.5 | 0.055 |
| -Dyslipemia | 31.5 | 31.7 | 31.3 | 0.905 |
| -AF/arrhythmia | 7 | 6.2 | 8.1 | 0.375 |
| -Ischemic cardiopathy | 4.6 | 6.8 | 1.5 | **0.002** |
| -Lung disease | 7.8 | 8.5 | 6.9 | 0.467 |
| -Renal disease | 2.8 | 3.1 | 2.3 | 0.541 |
| -Polyneuropathy | 2.5 | 1.7 | 3.5 | 0.166 |
| -Hyperuricemia | 3.3 | 5.1 | 0.8 | **0.003** |
| -Cancer | | | | **0.011** |
| Previous | 8.4 | 9.1 | 7.3 | |
| Active | 1.8 | 3.1 | 0 | |
| Treatments (%): | | | | |
| -Antihypertensive | 34.8 | 36.7 | 32.3 | 0.263 |
| -Antidiabetics | 14 | 16 | 11.2 | 0.341 |
| -Hypolipidemic agents | 25.9 | 27.8 | 23.2 | 0.192 |
| -Antidepressant | 35.9 | 32.3 | 40.9 | 0.561 |
| -Benzodiazepine | 36.1 | 35.7 | 36.7 | 0.806 |
| -Antipsychotic | 12.4 | 13.8 | 10.3 | 0.569 |
| -Anti-dementia | 7.3 | 6.2 | 8.8 | 0.750 |

The results represent percentages; *p*, comparison between both groups, men vs. women. Chi-square test was applied. AF, atrial fibrillation.

The mean follow-up time in the total cohort (N = 313) was 188.6 ± 72.9 days (men [N = 199] 186.7 ± 65.2 days; women [N = 114] 192.0 ± 85.0; $p = 0.659$). PwP improved from V1 to V3.6M in daily OFF time (RC = −63.5%; Cohen's d = 1.14; $p < 0.0001$), dyskinesia (Dyskinesia score; RC = −38.5%; Cohen's d = 0.43; $p < 0.0001$), MS (MSs; RC = −41.6%; Cohen's d = 1.16; $p < 0.0001$), NMS (NMSs; RC = −27.1%; Cohen's d = 0.50; $p < 0.0001$), health-related QoL (PDQ-39SI; RC = −13.4%; Cohen's d = 0.34; $p < 0.0001$), and AADL during the OFF state (ADLS-OFF; RC = +8.3%; Cohen's d = 0.23; $p = 0.001$) (Table 3). According to sex, daily OFF time decreased significantly in both groups without differences, with a reduction of 3.2 ± 2.9 h in men (RC = −62.7%; Cohen's d = 1.10; $p < 0.0001$) and 3.6 ± 2.9 h in women (RC = −67.9%; Cohen's d = 1.24; $p < 0.0001$). From V1 to V3.6M, the Dyskinesia score, MSs, NMSs, and PDQ-39SI decreased significantly in both men and women, whereas the EUROHISQOL8 and ADLS-OFF increased significantly only in men (Table 3). After adjustment for age, disease duration, and days receiving the DAT, there was a significant difference in the change in Dyskinesia score from V1 to V6.M between both groups (from 2.5 ± 2.0 to 1.3 ± 1.7 in men vs. from 2.9 ± 2.3 to 2.1 ± 1.8 in women; $p = 0.002$), with a specific difference in the RC of 20.4% in favor of men ($p = 0.006$). Regarding QoL, although significant differences were detected between men and women in the change in the PDQ-39SI ($p = 0.005$) and the EUROHISQOL8 ($p = 0.035$) from V1 to V3.6M (Table 3) after adjustment to covariates, no significant differences were detected in the RC for both PDQ-39SI (−14.2% in men vs. −11.7% in women [$p = 0.679$]) (Figure 2A) and EUROHISQOL8 (+6.0% in men vs. +0.6% in women [$p = 0.188$]). According to the domains of the PDQ-39, only differences in the RC between men and women were detected in cognition (−15.7% in men vs. −1.2% in women; $p = 0.023$) and communication (−1.1% in men vs. −21.1%; Table 4 and Figure 2B). No other differences in the GLM repeated measures after adjustment to covariates were detected between groups (men vs. women) in other aspects.

**Table 2.** PD-related variables at baseline (before initiation with a DAT) in men vs. women from the DATs-PD GETM Spanish registry.

| | **All Cohorts N = 618** | **Men N = 356** | **Women N = 262** | ***p*** |
|---|---|---|---|---|
| Age at initiation of DAT | 66.9 ± 9.5 | 65.2 ± 8.9 | 69.2 ± 9.8 | **<0.0001** |
| Years since PD diagnosis | 11.2 ± 6.9 | 10.7 ± 5.6 | 11.8 ± 8.3 | 0.490 |
| Motor phenotype (%): | | | | 0.910 |
| -Tremor dominant | 34.2 | 33.4 | 35.2 | |
| -Indeterminate | 31.6 | 32.1 | 30.9 | |
| -PIGD | 34.2 | 34.5 | 33.9 | |
| Treatment for PD (%): | | | | |
| -MAO-B inhibitor | 65.5 | 65.4 | 65.6 | 0.513 |
| -COMT inhibitor | 51 | 56 | 44.3 | **0.003** |
| -Dopamine agonist | 55 | 58.5 | 50.2 | **0.027** |
| -Amantadine | 27.5 | 26.5 | 28.7 | 0.306 |
| Previous ODT | 47 | 47.4 | 46.3 | 0.424 |
| Previous DAT | 23.5 | 24 | 22.9 | 0.411 |
| LEDD (mg) | 1193.7 ± 559.2 | 1293.8 ± 606.9 | 1064.6 ± 461.0 | **<0.0001** |
| DAEDD (mg) | 106.5 ± 126.1 | 113.2 ± 123.3 | 97.5 ± 129.6 | **0.033** |
| Weight | 72.5 ± 14.9 | 78.8 ± 12.5 | 64.0 ± 13.6 | **<0.0001** |
| BMI | 26.8 ± 4.1 | 27.1 ± 3.2 | 26.1 ± 5.4 | 0.414 |
| Previous psychosis (%) | 10.3 | 8.8 | 12.4 | 0.101 |
| Cognitive impairment (%): | | | | **0.045** |
| -MCI (%) | 22.8 | 19.5 | 27.3 | |
| -Dementia (%) | 2.5 | 2 | 3.2 | |
| Time with fluctuations (y) | 5.2 ± 3.6 | 4.9 ± 3.3 | 5.5 ± 3.9 | 0.285 |
| H&Y—OFF | 3 [2, 4] | 3 [2, 4] | 3 [2, 4] | 0.249 |
| H&Y—ON | 2 [2, 2] | 2 [2, 2] | 2 [2, 3] | 0.073 |
| UPDRS—III—OFF | 38.7 ± 12.7 | 38.8 ± 12.7 | 38.5 ± 13.4 | 0.792 |
| UPDRS—III—ON | 20.9 ± 11.4 | 20.8 ± 11.7 | 21.0 ± 11.0 | 0.858 |
| Daily OFF time (h) | 5.5 ± 3.1 | 5.5 ± 3.0 | 5.5 ± 3.1 | 0.907 |
| MSs | 15.5 ± 6.0 | 15.4 ± 6.1 | 15.7 ± 5.9 | 0.560 |
| Dyskinesia score | 2.7 ± 2.1 | 2.5 ± 2.0 | 3.0 ± 2.2 | **0.002** |
| NMSs | 12.2 ± 7.1 | 11.9 ± 7.1 | 12.7 ± 7.1 | 0.142 |
| PDQ-39SI | 37.9 ± 25.6 | 34.6 ± 15.5 | 42.8 ± 14.3 | **<0.0001** |
| EUROHIS-QOL8 | 22.3 ± 5.0 | 22.7 ± 5.2 | 21.8 ± 4.7 | 0.093 |
| ADLS—OFF | 56.6 ± 24.0 | 57.9 ± 24.1 | 54.6 ± 23.8 | 0.122 |
| ADLS—ON | 80.8 ± 17.9 | 82.9 ± 17.2 | 77.9 ± 18.7 | **<0.0001** |
| Daily living activities (%): | | | | **0.019** |
| -Independence | 60.6 | 65.4 | 54.1 | |
| -Dependence for IADL | 23.9 | 20.6 | 28.4 | |
| -Dependence for BADL | 15.5 | 14 | 17.5 | |

The results represent percentages, mean ± SD or median [p25, p75]; *p*, comparison between both groups, men vs. women. Chi-square, Student t and/or Mann–Whitney/Wilcoxon tests were applied according to the type of analysis and distribution of the variables. The information was not collected for all patients. The lowest sample size was N = 43 (6.9%) for BMI, N = 333 (53.9%) for weight, N = 376 for UPDRS-III-ON (60.8%), N = 386 for EUROHIS-QOL8 (62.5%), N = 395 for PDQ-39SI (63.9%), N = 486 for UPDRS-III-OFF (78.6%), N = 494 (79.9%) for ADLS—OFF, and N = 500 (80.9%) for ADLS—OFF; the sample was >90% for the rest of the variables. MSs, NMSs, and Dyskinesia score were calculated according to previous publications (Santos-García et al. Mov Disord Clin Pract 2025 [15]; Santos-García et al. J Neural Transm 2025 [24]). The *p*-values < 0.05 are shown in bold. ADLS, Schwab and England Activities of Daily Living Scale; BADL, basic activities of daily living; BMI, body mass index; COMT, catechol-O-methyltransferase; DAEDD, dopamine agonist equivalent daily dose; DAT, device-aided therapy; EUROHIS-QOL8, European Health Interview Survey-Quality of Life 8-item index; H&Y, Hoehn & Yahr; IADL, instrumental activities of daily living; LEDD, levodopa equivalent daily dose; MAO-B, type-B monoamine oxidase; MCI, mild cognitive impairment; MSs, motor symptoms score; NMSs, non-motor symptoms score; ODT, on-demand therapy (i.e., inhaled levodopa or apomorphine); PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire; PIGD, postural instability gait difficulty; UPDRS, Unified Parkinson's Disease Rating Scale.

**Table 3.** Comparison between men and women treated with a DAT in the change from the baseline to the final visit at 6 months in the main variables analyzed related to PD.

| | All Cohorts | Men | Women | $p_a$ |
|---|---|---|---|---|
| **Daily OFF time (h)** | | | | |
| N | 264 | 169 | 95 | |
| V1 | 5.2 ± 2.7 | 5.1 ± 2.8 | 5.3 ± 2.8 | |
| V3.6M | 1.9 ± 1.9 | 1.9 ± 2.0 | 1.6 ± 1.8 | 0.693 |
| OFF time reduction (h) | 3.3 ± 2.9 | 3.2 ± 2.9 | 3.6 ± 2.9 | 0.724 |
| Relative change % | −63.5 | −62.7 | −67.9 | |
| Cohen's effect size | 1.14 | 1.10 | 1.24 | |
| *p*-value (change) | **<0.0001** | **<0.0001** | **<0.0001** | |
| **Dyskinesia score** | | | | |
| N | 203 | 191 | 112 | |
| V1 | 2.6 ± 2.1 | 2.5 ± 2.0 | 2.9 ± 2.3 | **0.001** |
| V3.6M | 1.6 ± 1.7 | 1.3 ± 1.7 | 2.1 ± 1.8 | **0.002** |
| Relative change % | −38.5 | −48.0 | −27.6 | |
| Cohen's effect size | 0.43 | 0.51 | 0.31 | |
| *p*-value (change) | **<0.0001** | **<0.0001** | **0.001** | |
| **MSs** | | | | |
| N | 289 | 179 | 110 | |
| V1 | 15.4 ± 6.1 | 15.1 ± 6.2 | 15.9 ± 5.9 | 0.272 |
| V3.6M | 9.0 ± 5.3 | 8.9 ± 5.1 | 9.3 ± 5.5 | 0.795 |
| Relative change % | −41.6 | −41.1 | −41.5 | |
| Cohen's effect size | 1.16 | 1.05 | 1.19 | |
| *p*-value (change) | **<0.0001** | **<0.0001** | **<0.0001** | |
| **NMSs** | | | | |
| N | 293 | 182 | 111 | |
| V1 | 11.4 ± 6.8 | 11.1 ± 6.6 | 11.9 ± 7.2 | 0.514 |
| V3.6M | 8.3 ± 5.8 | 8.3 ± 5.7 | 8.4 ± 6.0 | 0.878 |
| Relative change % | −27.1 | −25.4 | −29.7 | |
| Cohen's effect size | 0.50 | 0.49 | 0.52 | |
| *p*-value (change) | **<0.0001** | **<0.0001** | **<0.0001** | |
| **PDQ-39SI total score** | | | | |
| N | 161 | 104 | 57 | |
| V1 | 36.6 ± 15.3 | 33.7 ± 15.7 | 41.2 ± 13.0 | **0.001** |
| V3.6M | 31.7 ± 17.4 | 28.9 ± 17.4 | 36.4 ± 16.4 | **0.005** |
| Relative change % | −13.4 | −14.2 | −11.7 | |
| Cohen's effect size | 0.34 | 0.33 | 0.35 | |
| *p*-value (change) | **<0.0001** | **0.001** | **0.011** | |
| **EUROHIS-QOL8** | | | | |
| N | 161 | 100 | 61 | |
| V1 | 23.3 ± 4.8 | 23.4 ± 4.8 | 22.9 ± 4.7 | 0.072 |
| V3.6M | 24.2 ± 5.2 | 24.8 ± 5.6 | 23.1 ± 4.4 | **0.035** |
| Relative change % | +3.9 | +6.0 | +0.6 | |
| Cohen's effect size | 0.15 | 0.21 | 0.03 | |
| *p*-value (change) | 0.055 | **0.039** | 0.792 | |
| **ADLS—OFF** | | | | |
| N | 238 | 152 | 86 | |
| V1 | 58.2 ± 24.8 | 59.6 ± 25.1 | 55.7 ± 24.2 | 0.152 |
| V3.6M | 63.0 ± 23.2 | 64.6 ± 22.6 | 60.1 ± 24.1 | 0.707 |
| Relative change % | +8.3 | +8.4 | +7.8 | |
| Cohen's effect size | 0.23 | 0.25 | 0.18 | |
| *p*-value (change) | **0.001** | **0.002** | 0.088 | |
| **ADLS—ON** | | | | |
| N | 236 | 151 | 85 | |
| V1 | 82.9 ± 17.0 | 84.8 ± 15.2 | 79.4 ± 19.5 | **0.020** |
| V3.6M | 84.2 ± 16.5 | 85.7 ± 15.5 | 81.5 ± 18.1 | 0.238 |
| Relative change % | +1.5 | +0.9 | +2.4 | |
| Cohen's effect size | 0.08 | 0.05 | 0.12 | |
| *p*-value (change) | 0.204 | 0.464 | 0.287 | |

The results represent mean ± SD at V1 and at V3.6M, relative change (%), and Cohen's effect size. To calculate *p*-value change (from V1 to V3.6M), *p*-values were computed using general linear models (GLM) repeated measures; $p_a$, comparison between men vs. women. First, the unadjusted *p*-value for covariates is shown, and below, the *p*-value after adjustment for covariates (age, disease duration, and days receiving the DAT). The *p*-values < 0.05 are shown in bold. ADLS, Schwab and England Activities of Daily Living Scale; DAT, device-aided therapy; MSs, motor symptoms score; NMSs, non-motor symptoms score; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire. The *p*-values < 0.05 are shown in bold.

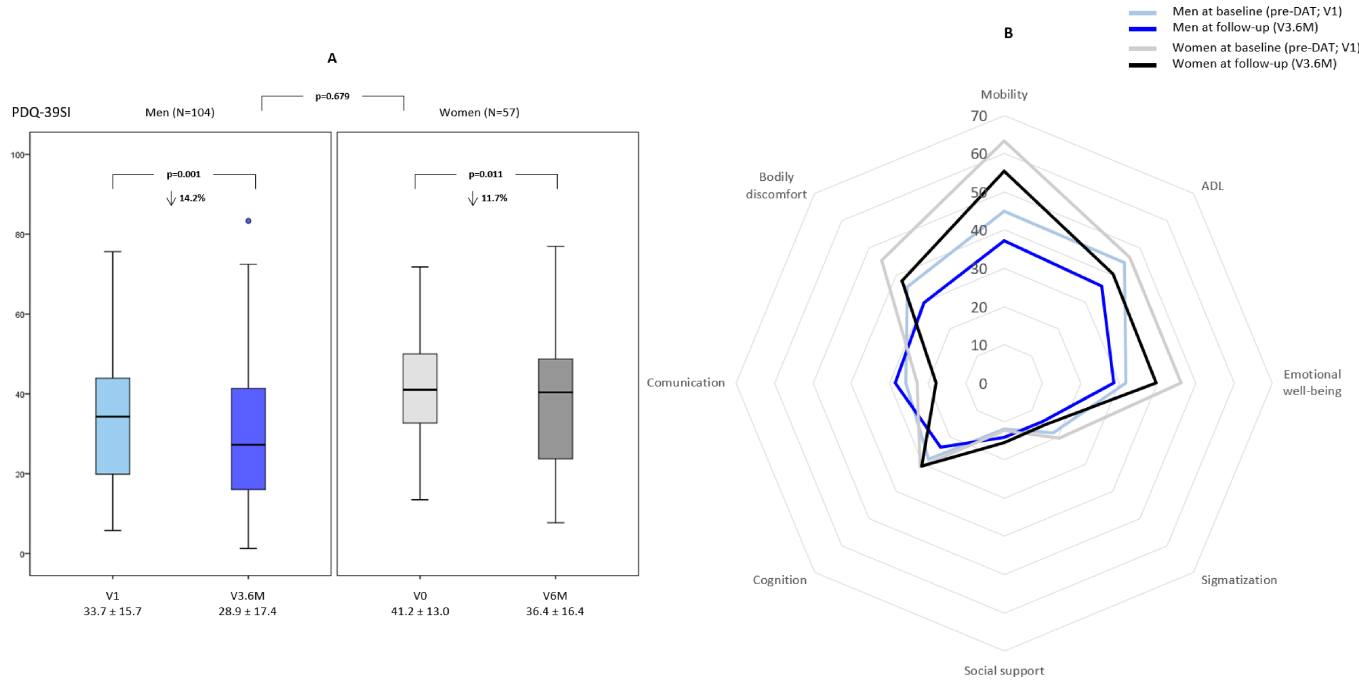


**Figure 2.** (**A**) Change from the baseline visit (pre-DAT; V1) to the follow-up visit at 6 ± 3 months (V3.6M) in the PDQ-39SI in men vs. women. Data are presented as box plots, with the box representing the median and the two middle quartiles (25–75%). Mild outliers (O) are data points that are more extreme than Q1—1.5. Nonparametric tests were applied. (**B**) Mean value of each domain of the PDQ-39 at V1 and at V3.6M in men (in blue) vs. women (in gray). Nonparametric tests were applied.

**Table 4.** Relative change in the PDQ-39SI domains from baseline (V1) to follow-up visit (6 ± 3 months [V3.6M]) in men vs. women PD patients from the DATs-PD GETM Spanish registry.

| RC % (V6M vs. V1) | All Cohorts N = 161 | Men N = 104 | Women N = 57 | *p* |
|---|---|---|---|---|
| Mobility | −14.9 | −16.9 | −12.6 | 0.236 |
| ADL | −17.1 | −19.1 | −13.4 | 0.802 |
| Emotional well-being | −11.7 | −9.7 | −14.1 | 0.697 |
| Stigmatization | −22.7 | −21.9 | −24.6 | 0.951 |
| Social support | +16.4 | +18.3 | +25 | 0.604 |
| Cognition | −10.3 | −15.7 | −1.2 | **0.023** |
| Communication | −0.4 | −1.1 | −21.1 | **0.014** |
| Bodily discomfort | −16.6 | −16.5 | −16.6 | 0.847 |

Mann–Whitney/Wilcoxon tests were applied; *p*, comparison between both groups, men vs. women. ADL, activities of daily living. The *p*-values < 0.05 are shown in bold.

In accordance with the data of the DATs-PD GETM Spanish Registry for this (N = 618) cohort until 30 October 2025, 101 out of 618 (16.3%) PwP discontinued with the therapy: 4/13 (23.5%) LCIG, 25/128 (19.5%) CSAI, 59/303 (19.5%) fLD/fCD, 11/62 (17.7%) LECGI, and 2/108 (1.9%) DBS. After excluding DBS, the rate of discontinuation of the DATs–pump group was 99/510 (19.4%). No differences were found in the discontinuation of the DAT, being 15.4% in men (55/356) and 17.6% (46/262) ($p = 0.484$). The percentage was 19.1% in men and 19.7% in women when only a pump system was considered ($p = 0.863$). The reasons for the discontinuation of the DAT were any complication related to the therapy (N = 47; 7.6%), a direct decision of the patient and/or principal caregiver (N = 20; 3.2%), another reason (N = 33; 5.3%), and loss of follow-up (N = 1; 0.2%). In the group who discontinued the DAT (N = 101), the frequency of discontinuation due to a direct decision of the patient and/or principal caregiver was similar in both sexes, 20% in men vs. 19.6% in women, but discontinuation due to any complication related to the therapy had a trend

to be significantly higher in women than in men (58.7% vs. 36.4%; $p = 0.085$). Ten patients (1.6%) died for different reasons (two with infection with sepsis; two with cancer; one with intestinal perforation; one with gastrointestinal bleeding; four with no reported cause), all of them being men except one woman.

## 4. Discussion

The present study observed relevant differences in the management of advanced PD concerning the treatment with a DAT in a Spanish cohort of more than 600 PwP in relation to sex. Specifically, women were less frequently treated with a DAT, which is very noticeable in the case of DBS (less than one in four patients), and when they were treated, they were older, more frequently had cognitive impairment and a worse health-related QoL, and had lesser AADL. Of note, this study analyzing differences in DATs by sex has the largest sample size to date and includes for the first time recently emerged therapies, fLD/fCD and LECIG. Furthermore, and in line with recent studies [24], fLD/fCD treatment was the most used DAT in both sexes, accounting for almost half of all the cases, while enteral therapies only accounted for 13%, which reinforces the idea that subcutaneous therapies could be the first choice in many cases due to their lower cost, invasiveness, and complexity of implantation.

Previously published data indicate that there are sex differences in many features of PD [27–33]. A recent meta-analysis study found, using pooled data of 4352 PD patients (58% men), that women showed higher symptom severity in mood/cognition, whereas higher severity in the sexual domain was found in men, highlighting the need for a specific sex-related approach in PD [32]. In agreement with the literature, a study conducted in Spanish PwP (N = 681) showed that symptoms such as depression, fatigue, and pain were more frequent and/or severe in women, whereas other symptoms, such as hypomimia, speech problems, rigidity, and hypersexuality, were more noted in men [33]. However, sex differences appear to exist in access to DATs as well, with differences about the indication and management of the DAT being poorly studied [3–5], and particularly, without previously published data in Spain. The findings observed in this study are consistent with the idea that women receive a DAT for PD significantly less frequently than men. In a large Medicare study, women were less likely to receive any DAT compared to men, even after controlling for disease severity [34]. Different studies have found a male predominance for DBS and LCIG [3–5,34–42]. In our cohort, the greatest difference was observed in DBS, being 73% of PWP-treated men. Women represent only 27–30% of DBS recipients despite comprising approximately 40% of the PD population [35,36]. This underrepresentation persists across multiple countries and healthcare systems [37,38]. Women are referred less frequently for DBS evaluation (relative risk 0.72) and have a 26% lower overall likelihood of undergoing DBS treatment [36]. However, when referred, women are more likely to be approved for DBS than men (relative risk 1.17), suggesting the primary barrier is at the referral stage rather than candidacy. While men may tend to have a decision-making process driven by their own initiative, women tend to hesitate and wait, being more anxious and appearing more fearful about complications [8]. LCIG shows less sex disparity than DBS, with men comprising about 55–65% of LCIG recipients across multiple studies [38,41,42], but more disparity than CSAI, where women approached or exceeded parity with men [38,43,44]. Several factors may contribute to the more balanced sex distribution with CSAI, such as less invasive and simpler initiation than DBS and LCIG, pharmacokinetic equivalence, and smaller sample sizes in published studies, which may limit the generalizability of these findings. However, our findings, with 52.3% men out of 128 patients receiving CSAI, support these data. Although there is less evidence on the use of the new therapies, fLD/fCD and LECIG, data from some studies may suggest a men predominance similar to LCIG [11–14].

However, comparison by sex continues to be largely ignored, to the point that some recent observational studies of fLD/fCD do not provide even any information on the sex/gender variable [45,46]. In this cohort, and contrary to other observational studies [13,14], LECIG was the only DAT with more women treated than men. Another factor that could influence the decision is whether there is a principal caregiver and who he/she is. In this study, the difference between groups in the caregiver, with men more frequently having a caregiver who was their spouse, could have also influenced the decision, although this is something that was not explored as such. Previous studies observed that male patients may receive more intensive caregiving than women patients [47]. Data from a larger number of patients from this registry [16] will give us more certainty in the future about the frequency of use of DATs according to sex. Furthermore, to know for sure whether more men than women are treated with a DAT, a population study would be necessary that specifically analyzes the number of cases of each sex treated with respect to the total number of patients of each sex with PD in that area.

An essential point is that women referred for DATs present with more advanced disease compared to men, suggesting the women may be referred later in their disease course, potentially missing the optimal therapeutic window [38,39]. However, studies investigating sex disparity in the access to fLD/fCD, CSAI, LCIG, and LECIG are lacking, with only a few focusing on DBS [3,5,8,34–37]. At the time of DBS evaluation, women demonstrate significantly longer disease duration, worse motor symptoms (higher UPDRS-III off-medication scores), and lower QoL scores despite receiving lower LEDD [3,5,8,34–37]. These findings agree with ours for this cohort, in which all DATs are considered as a whole. On the contrary, in 2024 Maccarrone et al. reported, in a study in which PwP treated with DBS, CSAI, LCIG, and MrgFUS thalamotomy were included, no differences in age, disease duration, H&Y and the previous LEDD between men and women [38]. Large observational studies of LCIG have included both men and women but generally have not reported sex-disaggregated outcomes. For example, the TANDEM study included 55% men among 159 patients and demonstrated significant improvements in motor scores and complications, but did not analyze outcomes by sex [48]. Similarly, the GREENFIELD study and COSMOS long-term follow-up studies included mixed-sex cohorts but did not report sex-specific efficacy or safety data [49,50]. This same circumstance occurs in the case of CSAI and the new fLD/fCD and LECIG therapies. In the present study, women showed at baseline a greater affectation in dyskinesia, representing this sex difference as one of the most clinically important disparities in PD treatment complications [27,28,51]. Furthermore, both groups (men and women) improved in dyskinesia, but this improvement was reduced in women, as has been previously reported with DBS in some studies [52]. In future analyses in this cohort, it will be of interest to analyze the differences in dyskinesias between men and women according to each DAT and the influence of important variables such as weight, LEDD, sex differences in levodopa pharmacokinetics, and higher baseline dyskinesia severity in women. OFF time, MS and NMS burden, and health-related QoL improved after 6 months with a DAT in each group (men and women) similarly to what has been reported in the literature in general populations of PwP, but again, there is a lack of studies on sex differences [5,8,14,37–46,48–51]. Specifically, regarding QoL, women were more affected before treatment, as in other studies [3,36], and both men and women improved, but no percentage differences were detected between the two groups. A 2024 systematic review [8] concluded that, regarding QoL, the evidence for DBS seems to be inconsistent, with activities of daily living improving in both sexes but conflicting data on overall QoL measures. Again, no published studies have performed sex-stratified analyses of QoL outcomes with fLD/fCD, CSAI, LCIG, and LECIG. In this context, it is absolutely

necessary to conduct studies analyzing the differences by sex in the selection of candidates for a DAT as well as the response and outcome, including the analysis individually by DAT.

This study observes that in clinical practice there are sex differences in the indication of DATs in patients with PD. From a practical standpoint, it would be advisable to investigate the causes of these findings and attempt to correct them if they result in inequity in decision making. For example, it is important to invest time in explaining to the patient the realistic goals of a possible benefit with the DAT and also the possible complications if, for example, the fear of a side effect may be a more frequent reason for rejection in one sex than the other. In other words, it is not only important to analyze the differences [38] but also their causes and to propose strategies to improve management. A study specifically designed to analyze this on a large scale would be of utmost interest.

The present study has some limitations. First, although the overall sample size is relatively large for a study with this type of treatment (i.e., DATs), it varies between groups, resulting in a small sample size for enteral therapies. Second, the analysis of differences by sex has been carried out considering all DATs as a whole, without going into detail on the differences by sex in each of them. Third, the follow-up period is short, making it necessary to observe medium- to long-term outcomes. Fourth, this study did not analyze the complications experienced by patients or the specific management of DATs and other treatments for PD. This will be addressed in a second subsequent analysis. Fifth, although some validated scales and/or questionnaires were used (H&Y, UPDRS, ADLS, PDQ-39, etc.), some scores defined to measure other symptoms [16,24] lack validation. Moreover, information about a specific cognitive test score was not provided. Sixth, there are all of the limitations inherent to the methodology used, which is the extraction of data from a registry, such as not completing all variables in all cases. Finally, despite the indication of consecutive inclusion of PwP treated with a DAT in the hospitals participating from Spain, this was not fulfilled, and there is an inclusion bias. For all of these reasons, the results should be interpreted with extreme caution and await corroboration in other well-planned studies.

In conclusion, we report here the first study to date in which the differences by sex in the characteristics of PwP selected to be treated with a DAT, as well as their response at 6 months, were analyzed. Women were less frequently treated with a DAT than men, especially in the case of DBS with a higher percentage of men (>70%) than the known prevalence ratio of approximately 60 vs. 40% (men vs. women). When PD patients are treated with a DAT, women are more affected by PD. Despite this, OFF time, MS and NMS burden, and health-related QoL improve in both groups. There is a striking lack of evidence on this topic and more studies are needed.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medsci14020217/s1, Table S1: Supplementary Material. MSs and NMSs used for this study.

**Author Contributions:** Research project: (1) Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique, C., Approval of the final version. D.S.G.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B, 3C. Á.S.V.: 1C, 3B, and 3C. Rest of the authors: 1B, 1C, 3B, and 3C. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the ICH Good Clinical Practice version 6 Revision 2 standard, the fundamental ethical principles established

in the Declaration of Helsinki and the Oviedo Convention, as well as the Spanish legal requirements for biomedical research (Biomedical Research Law 14/2007). The study was approved on 02/APR/2024 by the IRB "Comité de Ética de la Investigación Clínica de Galicia from Spain" with code number 2024/109.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The protocol, statistical analysis plan and unidentified participant data will be available on request.

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## Abbreviations

AADL, autonomy for activities of daily living; CSAI, continuous subcutaneous apomorphine infusion; DATs, device-aided therapies; DBS, deep brain stimulation; fLD/fCD, foslevodopa/foscarbidopa; LCIG, levodopa–carbidopa intestinal gel infusion; LECIG, levodopa–carbidopa–entacapone intestinal gel; LEDD, levodopa equivalent daily dose; MS, motor symptoms; MSs, motor symptoms score; NMS, non-motor symptoms; NMSs, non-motor symptoms score; PDQ-39, 39-item Parkinson's Disease Questionnaire; PD, Parkinson's disease; PwP, people with PD; UPDRS, Unified Parkinson's Disease Rated Scale.

## Appendix A

DATs-PD GETM Spanish Registry STUDY GROUP (only members who participated with available data for this analysis are here included)

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