Clinical Drug Investigation
https://doi.org/10.1007/s40261-021-01064-z

ORIGINAL RESEARCH ARTICLE

The Impact of Non-dopaminergic Medication on Quality of Life in Parkinson's Disease

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Accepted: 15 July 2021

Abstract

Background and Objectives Quality of life (QoL) in Parkinson's disease (PD) depends on multiple factors. Due to PD treatment and accompanying, age-related or independent comorbidities, pill burden is often high. The relation of QoL and pharmacotherapy for comorbidities in PD has not been widely studied. This study investigated if and to what extent non-dopaminergic drugs are related to QoL in PD. Second, the impact of demographics and non-motor symptoms were evaluated. A better understanding of the impact of different non-dopaminergic drugs and polypharmacy on QoL will have added value in selecting appropriate (medication) interventions.

Methods In a cross-sectional analysis, medication prescription data of 209 PD patients were analyzed and grouped according to the Rx-Risk comorbidity index. QoL was measured using the PDQ-39 questionnaire. Non-motor symptoms were analyzed with the Non-Motor Symptoms questionnaire. Independent factors associated with a reduced QoL were identified with a multivariate linear regression analysis.

Results Non-dopaminergic drugs, subdivided into Rx-Risk comorbidity categories, were not associated with reduced QoL, except for the use of anti-epileptic drugs. However, using more daily non-dopaminergic drugs was also negatively associated with QoL, as well as female sex, increased PD severity, and more non-motor symptoms. Contraindicated non-dopaminergic medication was barely prescribed (0.4%).

Conclusion Non-dopaminergic drugs are frequently prescribed, and higher numbers are associated with impaired QoL in PD. However, when divided in drug types, only anti-epileptic drugs were negatively associated with QoL. In these patients, physicians might improve QoL by further optimizing the condition it was prescribed for (e.g., pain or anxiety), or managing of side effects.

Trial registration Netherlands Trial Register; NL4360.

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1 Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder, and is estimated to affect over 8.7 million patients worldwide by 2030 [1]. Next to the classical parkinsonian motor symptoms tremor, bradykinesia, rigidity, and postural instability, patients suffer from various non-motor symptoms, such as autonomic dysfunction and mental health disturbances [2]. All features adversely affect quality of life (QoL) [3, 4].

The mainstay of pharmacological treatment in PD consists of dopamine replacement therapy to control symptoms. With disease progression, medication schedules become

Published online: 10 August 2021

Key Points

In Parkinson's disease, higher numbers of non-dopaminergic drugs are associated with impaired quality of life (QoL).

Specifically, anti-epileptic drug use is associated with impaired QoL. Other non-dopaminergic drug types are not correlated with QoL.

Non-dopaminergic drugs, contraindicated in Parkinson's disease, were barely prescribed.

more complex. Additionally, concomitant drugs are often added to treat comorbidities [5]. Previous research reported the frequent occurrence of comorbidities and polypharmacy, contributing to cognitive and functional worsening, increased risk of drug related problems, and reduced medication adherence [6–8]. Treatment decisions in PD should therefore take a patient's total medication record into serious consideration.

Comorbidities in PD are often related to the wide spectrum of symptoms of PD itself and its complications [5, 6]. Leibson and colleagues [6] found that PD patients had an excess of comorbidities compared to matched controls, with a higher likelihood of being diagnosed with genitourinary, digestive, or neuropsychiatric disorders. Taking the frequent autonomic symptoms and higher prevalence of anxiety and depression in PD into consideration, these results are not surprising [3, 9]. Also, there was a higher risk of lower extremity fractures, likely explained as a complication of motor disability. Additionally, due to aging, the prevalence of other comorbidities increases, i.e., conditions concerning the circulatory system, as well as metabolic, endocrine, and nutritional diseases [7]. According to Santos Garcia et al. [7], the number of non-antiparkinsonian drugs is highly correlated to comorbidity, and a greater number of pills taken daily correlated with more advanced PD stage. However, the relationship between comorbid non-dopaminergic treatment and PD-related QoL have rarely been analyzed. This study aimed to investigate if and to what extent non-dopaminergic drugs are related to QoL in PD. A better understanding of the impact of different non-dopaminergic drugs will help in selecting the most appropriate future pharmacological interventions.

2 Methods

2.1 Study Design

We conducted a cross-sectional analysis of sociodemographic and baseline questionnaire data of PD patients enrolled in the Medication Review in Parkinson-trial [10]. In this multicenter, randomized, controlled trial, the effect of a structured medication review (SMR) by community pharmacists on QoL in PD patients was assessed. An SMR is defined as "a structured, critical examination of a patient's medicines aiming to reach an agreement with the patient about therapy, optimizing the impact of medication, minimizing the number of drug-related problems and reducing waste" [11]. When leading to optimization of a complex drug regimen and knowledge in PD patients, a better treatment effect might be achieved, which might improve PD symptoms [12]. Patients were enrolled from three Dutch neurology outpatient clinics. To be eligible for study participation, PD patients needed to take at least four different drugs and had a medication regimen with at least four drug-intake moments daily, irrespective of which drug was taken and when. Furthermore, patients had to live (semi-)independently and had to be able to administer their own medication. Half of the randomly assigned patients received an SMR from their community pharmacist after completing baseline measurements, while the other half received usual care from their pharmacist. Measurements at baseline and after 3 and 6 months comprised six questionnaires, with QoL, physical disability, and non-motor symptoms among them. Further details about the study design can be found in the published study protocol [10]. Written informed consent was obtained from all participants. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Medical Ethical Review Board Twente, the Netherlands (Netherlands Trial Register, NL4360).

2.2 Assessments and Outcome Measures

Information about drug use was obtained from patients and verified by prescription data from their pharmacists. Both total number of different daily drugs and daily drug intake moments were derived. We defined polypharmacy as the use of four or more drugs daily [13]. PD severity was measured by Hoehn and Yahr (HY) stage [14].

To group medicines for further analysis, we used the Rx-Risk comorbidity index, a tool for establishing comorbidities based on drug prescriptions [15]. It consists of 43 comorbidity categories, and the comorbidity score is presented as the sum of comorbidities (range 0–43). Although the index is validated to use as a comorbidity measure for predicting mortality, we used the individual categories for classifying medication rather than determining comorbidities, since the Rx-Risk comorbidity score is a proxy of comorbidities and definite diagnoses cannot be confirmed.

The Rx-Risk comorbidity "Parkinson's disease" was based on at least one prescription within Anatomical Therapeutic Chemical (ATC) code N04 (anti-Parkinson drugs), concerning anticholinergic agents (N04A), dopaminergic

agents (N04B), and other anti-Parkinson drugs (N04C). Since the number of prescribed N04A-drugs was small compared to the N04B-group, we merged these in the definition "dopaminergic drugs" in this study. An additional sensitivity analysis showed no difference in QoL in patients with or without the N04A-drug.

All included patients were diagnosed with PD according to the UK Brain Banking Criteria [16], and had been prescribed one or more dopaminergic anti-Parkinson drugs. The indication for which non-dopaminergic drugs are prescribed differs; either for comorbid conditions independent of PD, or for non-motor PD symptoms.

Information regarding contraindicated drugs in PD was obtained from the Royal Dutch Pharmacists Association [17].

All patients completed a set of validated questionnaires. For the current analyses the following were used:

1. The Parkinson's Disease Questionnaire-39 (PDQ-39), measuring disease-specific QoL [18]. Scores range from 0 to 100. Higher scores indicate worse PD-specific QoL.
2. The Non-Motor Symptoms Questionnaire (NMSQ), measuring non-motor symptoms [19]. Scores range from 0 to 30. Higher scores indicate more non-motor manifestations.

The primary outcome was the extent to which different non-dopaminergic drugs were related to QoL. Secondary outcomes were the influence of PD patient characteristics (sex, age, HY stage, PD duration, number of daily drugs, number of daily drug intake moments, comorbidity score) and number of non-motor symptoms on QoL. Furthermore, the number of contraindicated prescriptions in PD in the outpatient setting was quantified.

2.3 Statistical Analysis

Categorical variables were analyzed using Chi-square tests or Fisher's exact test, as appropriate, while continuous variables were analyzed using t-tests or a Mann-Whitney test, as appropriate. Normality of the data was visually inspected. Continuous data are presented as means with standard deviations (SD) in cases of normal distributions, or as medians with interquartile ranges (IQR) otherwise.

Univariate correlations were analyzed between PDQ-39 score and the Rx-Risk comorbidities that were present in at least 20 patients, to restrict the analyses to relevant variables only. Continuous variables were examined using Pearson's or Spearman's correlation coefficients, as appropriate. Correlation coefficient values ≤ 0.29 were considered not to be relevant, 0.30–0.49 weak, 0.50–0.69 moderate, and ≥ 0.70 strong. A multivariate linear regression analysis was subsequently performed, to determine independent predictors that best accounted for variance in QoL scores. In this model, all PD patient characteristics (e.g., sex, age, HY stage; see Table 1) were included, together with the Rx-Risk comorbidities that were univariately related to QoL. The model was reduced by excluding variables without significant association with PDQ-39 ($p > 0.05$). Data were analyzed using SPSS version 25. p values ≤ 0.05 were defined as statistically significant.

3 Results

Data of 209 patients were available. PD patient characteristics and questionnaire data are summarized in Table 1. All data were normally distributed, except for number of daily drug-intake moments. HY stages were grouped into a lower (HY 1–2.5) and a higher (HY 3–5) stage. The comorbidity score was on average 4.6 (range 1–10). Due to having PD, comorbidity scores were a minimum of 1.

3.1 Non-Dopaminergic Medication and Quality of Life (QoL)

Apart from PD, patients had 0–9 different Rx-Risk comorbidities (Fig. 1). The comorbidity gastroesophageal reflux disease (GERD) was present in 100 (47.8%) patients, defined by prescription of a proton pump inhibitor (PPI) ($n = 98$) or H_2-antagonist ($n = 2$). Also, cardiovascular comorbidities (defined by the use of medicines classified in the categories

Table 1 Parkinson's disease (PD) patient characteristics and questionnaire data ($n = 209$)

Characteristics	Value
Sex	
Male, *n* (%)	127 (60.8)
Female, *n* (%)	82 (39.2)
HY stage	
1–2.5, *n* (%)	143 (68.4)
3–5, *n* (%)	66 (31.6)
Age, y, mean ± SD	72.5 ± 7.5
PD duration, y, mean ± SD	6.7 ± 4.6
Number of different daily drugs, mean ± SD	7.4 ± 2.5
Dopaminergic	2.5 ± 1.2
Non-dopaminergic	4.9 ± 2.6
Number of daily-intake moments, median (IQR)	5 (4-6)
Comorbidity score (0–43), mean ± SD	4.6 ± 2.0
PDQ-39 (0–100), mean ± SD	36.0 ± 16.4
NMSQ (0–30), mean ± SD	10.2 ± 4.7

HY Hoehn & Yahr, *IQR* interquartile range, *NMSQ* non-motor symptoms questionnaire, *PDQ-39* Parkinson's Disease Questionnaire-39

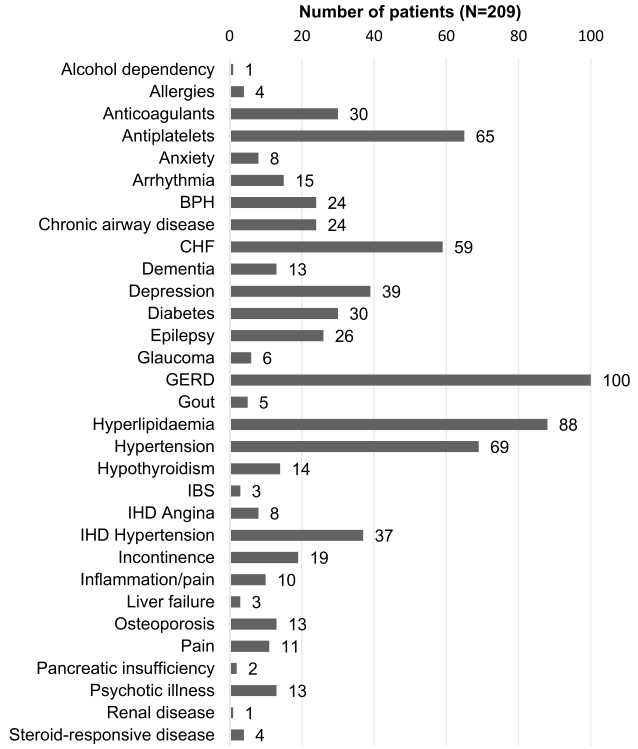

Fig. 1 Prevalence of comorbidities according to the Rx-Risk index. *BPH* benign prostatic hyperplasia, *CHF* congestive heart failure, *GERD* gastroesophageal reflux disease, *IBS* irritable bowel syndrome, *IHD* ischemic heart disease

hyperlipidemia, hypertension, and chronic heart failure) and antiplatelet usage were frequent.

The following Rx-Risk comorbidities were found to be significantly related to a reduced QoL in univariate analyses: depression (41.9; no depression: 34.6 [−13.0; −1.7]), epilepsy (44.9; no epilepsy: 34.7 [−16.9; −3.6]) and GERD (38.5; no GERD: 33.6 [−9.3; −0.4]). The presence of hypertension was related to better QoL (32.6; no hypertension: 37.6 [0.3; 9.7]).

3.2 Patient Characteristics and QoL

Table 2 shows the correlations between QoL and PD patient characteristics. Female sex and a higher HY stage were in univariate analyses significantly associated with worse QoL. We found a moderate correlation with the presence of more non-motor symptoms based on the NMSQ ($r = 0.51$; $p < 0.001$). A weak correlation was found between QoL and longer disease duration ($r = 0.30$; $p < 0.001$) and the use of more different daily drugs ($r = 0.36$; $p < 0.001$). When subdivided into dopaminergic and non-dopaminergic drugs, no relevant correlation was found. No relevant correlation between QoL and the number of Rx-Risk comorbidities (i.e., the total comorbidity score) was found ($r = 0.17$, $p < 0.013$).

Table 2 Univariate analysis of the association between PDQ-39 and patient characteristics

Characteristics	PDQ-39 (mean ± SD)	Correlation coefficient *r*	*p* value (95% CI)
Sex			
Male	32.1 ± 16.6		< 0.001 (−14.1; −5.6)
Female	42.0 ± 14.3		
HY stage			
1–2.5	30.5 ± 14.6		< 0.001 (−21.4; −13.0)
3–5	47.7 ± 13.9		
Age		0.15[a]	0.035
PD duration		0.30[a]	<0.001
Number of different daily drugs		0.36[a]	< 0.001
Dopaminergic		0.14[a]	0.037
Non-dopaminergic		0.28[a]	< 0.001
Number of daily-intake moments		0.16[b]	0.028
Comorbidity score		0.17[a]	0.013
NMSQ		0.51[a]	< 0.001

HY Hoehn & Yahr, *NMSQ* Non-Motor Symptoms Questionnaire, *PDQ-39* Parkinson's Disease Questionnaire-39

[a]Pearson's *R*

[b]Spearman's Rho

3.3 Regression Analysis

A multivariate linear regression analysis was executed, based on all PD patient characteristics presented in Table 2, and the Rx-Risk comorbidities that were univariately related to QoL (depression, epilepsy, GERD, and hypertension). In the final model exactly 50% of the variance in QoL was explained by five independent predictors (Table 3). Of all Rx-Risk categories, only epilepsy – defined as the use of anti-epileptic drugs – was independently associated with QoL.

3.4 Contraindicated Drug Use

Of 1551 prescriptions, only six (0.4%) should preferably be avoided, replaced, or need extra monitoring due to the possibility of worsening of PD symptoms; amiodarone ($n = 2$), valproic acid ($n = 2$), haloperidol ($n = 1$), and flunarizine ($n = 1$).

4 Discussion

The present study reports on the prevalence and impact of non-dopaminergic drugs in PD, subdivided in Rx-Risk comorbidity-categories. We found that the use of anti-epileptic drugs was negatively associated with QoL. The use of PPIs and antidepressants were significantly correlated with reduced QoL in univariate analyses, but not in a multivariate analysis when HY stage was also included. The use of more daily drugs, specifically non-dopaminergic drugs, significantly affected QoL. However, the total number of Rx-Risk comorbidities—into which all prescribed medication was subdivided—did not. Furthermore, female sex, HY stage ≥ 3, and the experience of more non-motor symptoms were independently associated with reduced QoL.

Non-dopaminergic drugs in PD could be prescribed for non-PD comorbidities, or PD-related non-motor symptoms. Although some comorbid conditions are well known non-motor PD symptoms (e.g., depression), this difference between being either or not PD related is not always crystal clear. However, it is relevant to realize that this article does not comprise an analysis about the impact of comorbid conditions, but about the impact of medication use for any of these conditions. For analyzing the effect of the different non-dopaminergic drugs, these were classified into categories. Individual drugs are less prevalent and the statistical power to show associations with QoL would be much less. We used the Rx-Risk comorbidity index, in which prescription data were grouped into comorbidities. It is important to keep in mind that this index is a proxy for comorbidities, and that the indication for prescribing might be different than the Rx-Risk comorbidity to which the specific drug is assigned.

Thus far, the link between comorbidities in PD and QoL has only rarely been evaluated, and different ways of defining comorbidities were used. Muslimovic et al. [4] found that a higher number of comorbidities contributed to worse QoL in PD, where comorbidities were assessed by the Cumulative Illness Rating Scale, an instrument assessing cumulative physical impairment in 13 organ systems [20]. Only one study specified comorbidity in further detail, and found that gastrointestinal symptoms, sleep disturbances, and depression were significantly associated with reduced QoL [21]. Seven self-reported chronic conditions were taken into account. According to the authors, an explanation why other medical conditions did not influence QoL might be that only a small number of accompanying disorders was analyzed, or that PD itself has a high impact on QoL. The same may apply to our study. Non-dopaminergic drugs subdivided into comorbidity groups were barely correlated with QoL. This might be explained by proper treatment of the specific health-related problem it was prescribed for, or by the fact that it is regarded as preventive medication, without major side effects. Nevertheless, it might be true that the burden of PD might be the biggest contributor to the substantially lower QoL, compared to the burden of accompanying comorbidities or symptoms [21, 22]. This is supported by the fact that both HY stage and the occurrence of more non-motor symptoms once again proved their burden on QoL. However, a control group of patients without PD is needed to verify this assumption.

The Rx-Risk comorbidity epilepsy—representing patients on anti-epileptic drugs—was the only category independently associated with worse QoL. Our prevalence of 12% was high compared to 1.2–2.6% reported in other studies [23, 24], presumably due to the spectrum of anti-epileptic drugs meeting the diagnosis "epilepsy" according to the Rx-Risk index. Of the 26 patients, 11 used gabapentin or pregabalin, and 11 used clonazepam, which are often prescribed for indications other than epilepsy, for example neuropathic pain, anxiety or sleep-related disorders. Pain, including neuropathic pain, is prevalent in PD and it is known to be

Table 3 Final model of the multivariate linear regression analysis for prediction of PDQ-39 (scale 0–100; higher scores indicate worse QoL)

Variable	Regression coefficient (95% CI)	*p* value
Female sex	8.43 (5.05–11.81)	< 0.001
HY stage (> 2.5)	10.80 (6.99–14.61)	< 0.001
Number of different daily non-dopaminergic drugs	0.74 (0.09–1.40)	0.026
NMSQ (range 0–30)	1.39 (1.03–1.76)	< 0.001
Use of anti-epileptic drugs (yes/no)	6.78 (1.69–11.86)	0.009

HY Hoehn & Yahr, *NMSQ* Non-Motor Symptoms Questionnaire

a strong determinant of impaired QoL [25]. The medical conditions for which the anti-epileptic drugs are prescribed, and the wide spectrum of side effects of these drugs, could plausibly worsen QoL. Physicians should therefore focus also on this "comorbidity," when optimizing treatment in PD patients.

Several other PD-related symptoms, associated with reduced QoL in previous research (e.g. GERD and depression) [9, 22], did not impact on QoL in our analyses. This might be explained by the different instruments used to assess comorbidities. The Rx-Risk index does not determine a formal diagnosis and is not related to experienced symptoms. GERD is remarkably prevalent in this cohort (48%), compared to Maeda et al. [26], who found a prevalence of 26.5% in PD, based on questionnaire data. The current definition of GERD is based on the presence of a PPI prescription, which does not necessarily mean that a patient has gastroesophageal reflux or dyspeptic manifestations. There might be asymptomatic prophylactic use of PPIs in combination with salicylic drugs or non-selective NSAIDs, justified by Dutch guidelines concerning dyspepsia [27]. Besides, if truly prescribed for dyspeptic complaints, symptoms might improve due to treatment. The same might apply to the Rx-Risk category depression, and its relation to QoL. Depression was in various studies found to be a major determinant of reduced health-related QoL in PD [9, 28]. Estimated prevalence varies widely between 2 and 70%, depending on the use of different criteria [29], with approximately 35% of PD patients suffering from clinically significant depressive symptoms [28]. In our study, 39 patients (19%) were treated with an antidepressive drug, confirming the Rx-Risk comorbidity depression. Antidepressant drugs, often in lower doses, might also be prescribed for indications other than depression [30], and misclassification of antidepressant prescriptions cannot be identified with the Rx-Risk scoring system. After additional analyses based on type and dose of prescribed antidepressant, we estimated that at most 8 out of 39 patients might rather be in pain than depressed. Together with the fact that depression is common in PD, it seems reasonable that the majority of patients with the comorbidity depression were appropriately classified. According to our data, we can only conclude that antidepressive drug use does not interfere with QoL. Presumably—again—when drug treatment is successful, an underlying depression, or other symptoms, do not necessarily affect QoL anymore.

Lastly, the prevalence of prescribed medicines for cardiovascular disease (CVD), divided into different categories, is worth mentioning: anticoagulant-use (14%), antiplatelet-use (30%), arrhythmia (7%), congestive heart failure (28%), diabetes (14%), hyperlipidemia (42%), hypertension (33%), ischemic heart disease/angina (4%), ischemic heart disease/hypertension (18%). A number of factors associated with PD share associations with CVD, for example male sex and older age. Also, physical activity and coffee consumption showed lower risks for both disorders [31]. On the contrary, high LDL cholesterol and smoking have contradictory associations [31]. This raises the question whether hyperlipidemia should be treated as strictly as in a non-PD population. However, until potential underlying pathophysiological links are better understood, CVD and its risk factors should not be treated differently in PD [31]. Furthermore, a causal relation between diabetes mellitus (DM) type II and PD is increasingly reported, together with a subsequent negative effect on motor function and cognition [32]. Again, underlying pathways still need further research. Nevertheless, it emphasizes the importance of adequate treatment. The prevalence rate of DM in our study is similar to others [5–7] and DM was not related to worse QoL.

All patients in our study used at least four different drugs daily. Polypharmacy is common in PD and drug-related problems and side effects are frequent consequences [5, 7]. We found that with more daily non-dopaminergic drugs, QoL is reduced. Decreasing the number of drugs might affect QoL positively, clearly when it improves interactions or side effects. However, healthcare professionals should carefully decide if ceasing a certain drug counterbalances its consequences. Prescriptions should also be checked with regard to drugs known to worsen clinical symptoms of PD. In these cases, the possibility to choose an alternative drug depends on the indication for prescribing and should therefore be evaluated individually. In case no alternative is available, extra monitoring is necessary. Fortunately, contraindicated drugs were rarely prescribed in our population.

Among the strengths of our research are the relatively large PD population with a complete overview of all used medicines. Furthermore, by using a validated index for grouping drugs, associations of drug categories with QoL could became visible. Nonetheless, one must be aware that the Rx-Risk comorbidity score is a proxy of comorbidities, and although validated, this way of addressing comorbidities does not confirm definite diagnoses. Therefore, the impact of actual comorbidities on QoL cannot be confirmed, and allocating drugs according to the Rx-Risk comorbidity index has some disadvantages. Not all medicines used are included in one of the 43 comorbidity categories. For example, the prevalence and effect of medication used for gastrointestinal symptoms other than GERD, such as constipation, could not be analyzed. Moreover, many of our patients had drugs, for example, laxatives, prescribed only as an "as-needed" prescription. These prescriptions were not included in our data, since we could not determine their actual use. Furthermore, over-the-counter medication was not included in the analysis. In spite of these limitations, knowledge of the way different kinds of medication do or do not impact on QoL is valuable in clinical practice.

5 Conclusion

Next to dopaminergic drug treatment for PD (motor) symptoms, a multitude of non-dopaminergic drugs are used by PD patients. Higher numbers of non-dopaminergic drugs were correlated with impaired QoL. However, when grouped into categories, only the use of anti-epileptic drugs had a negative association with QoL. Physicians should be aware that in PD patients on anti-epileptic drugs there is room for QoL improvement, for example by optimizing the condition it was prescribed for, or by the management of side effects.

Nevertheless, it is likely that the burden of PD itself is a big contributor to worse QoL, with both higher HY stage and more non-motor symptoms being negatively related. Therefore, improving treatment of symptoms regarding the PD spectrum remains of high importance for all healthcare professionals.

Declarations

Funding This work was supported by the Royal Dutch Pharmacists Association, The Hague, the Netherlands. This funding had no role in the analysis or interpretation of the results in this study.

Conflict of interest All authors declare that they have no conflicts of interest.

Ethics approval The study was performed in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study was provided by the Medical Ethical Review Board Twente, the Netherlands (reference number NL48661.044.14).

Consent to participate Written informed consent was obtained from all participants.

Consent for publication Not applicable

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable

Author contributions Study conception and design: NO, KM, JvdP, LD. Acquisition of data: NO, HWN, MvK, LD. Analysis and interpretation of data: NO, KM, JvdP, LD. Drafting of the manuscript: NO, KM, JvdP, LD. Critical revision: HWN, MvK.

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