Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Characterization of Gastrointestinal Symptom Type and Severity in Parkinson's Disease: A Case–Control Study in an Australian Cohort

Jade E. Kenna, BSc (Hons),[1,2,3,*] Megan C. Bakeberg, BBSc (Hons),[1,2] Anastazja M. Gorecki, BSc (Hons),[1,4] Alfred Chin Yen Tay, PhD,[4,5] Samantha Winter, PhD,[1,6] Frank L. Mastaglia, MD, FRACP FRCP (Lond),[1,2] and Ryan S. Anderton, PhD[1,2,6]

ABSTRACT: Background: While constipation is a well-known non-motor symptom which may precede the onset of the classical motor symptoms of PD, there have been few comprehensive studies of gastrointestinal (GI) symptoms in people with PD (PwP).

Objectives: To investigate the spectrum of GI symptoms in an Australian PwP cohort and their relationship to use of anti-parkinsonian medications dietary habits and smoking.

Methods: The prevalence and severity of GI symptoms were compared in a group of 163 PwP and 113 healthy control subjects using the Gastrointestinal Symptom Rating Scale (GSRS). Corrected linear regression models were used to determine differences between PwP and controls, and to investigate the influence of different classes of anti-Parkinsonian medications.

Results: PwP reported a greater frequency of constipation and GI-associated illnesses when compared to healthy controls. Total GSRS scores ($P < 0.0001$), upper GI symptoms ($P < 0.0001$), and hypoactive GI Symptoms ($P < 0.0001$) were all significantly greater in the PD cohort than controls. Further analyses revealed a positive association between the use of anti-Parkinsonian medications and total GSRS scores ($P < 0.001$), as well as upper GI symptoms ($P < 0.001$) and hypoactive GI function ($P < 0.001$).

Conclusions: This study illustrates the frequency and array of GI symptoms in a large PD cohort. The findings indicate that anti-parkinsonian medications play an important role in the presentation and development of GI symptoms.

Parkinson's disease (PD) has gained recognition as a heterogenous disease with a wide variety of non-motor symptoms (NMS), in addition to the classical motor disturbances. Non-motor manifestations include cognitive impairment, autonomic dysfunction, neuropsychiatric disorders and sleep disturbances, as well as a variety of gastrointestinal (GI) symptoms, which have recently been included in standardized NMS questionnaires.[1–4] GI symptoms, including constipation and nausea, are reported to be among the earliest symptoms in individuals with Parkinson's disease, emerging up to two decades prior to clinically defining motor symptoms.[5,6] Although GI symptoms are ubiquitously expressed within cohorts of people with Parkinson's disease (PwP), the literature has focused largely on constipation,[5,7–12] and there have been few comprehensive studies of other GI symptoms.[13–19] While some GI symptoms such as constipation, nausea and swallowing difficulties are included in current NMS questionnaires routinely used in patient assessments, these do not adequately assess all GI symptoms. As such, some symptoms may

[1]Perron Institute for Neurological and Translational Science, Nedlands, Western Australia, Australia; [2]Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Perth, Western Australia, Australia; [3]Centre for Clinical Neurosciences and Neurological Research, St. Vincent's Hospital Melbourne, Melbourne, Australia; [4]School of Biological Sciences, University of Western Australia, Perth, Australia; [5]Marshall Centre for Infectious Diseases Research and Training, Nedlands, Western Australia, Australia; [6]Institute for Health Research and School of Health Sciences, University of Notre Dame Australia, Fremantle, Western Australia, Australia

***Correspondence to:** Miss Jade E. Kenna, Perron Institute for Neurological and Translational Science, 1st Floor, 8 Verdun Street, Nedlands, WA 6148, Australia; E-mail: jade.kenna@research.uwa.edu.au
Keywords: Parkinson's disease, gastrointestinal symptoms, anti-parkinsonian medications, non-motor symptoms.
Received 13 September 2020; revised 19 November 2020; accepted 2 December 2020.
Published online 5 January 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13134

remain undisclosed and, therefore, untreated,[20] which adversely affects clinical care and quality of life.[21]

Despite increasing research supporting the prodromal nature of GI symptoms in PD, current diagnosis and treatment methods are still largely based on the cardinal motor symptoms of tremor, bradykinesia, rigidity and postural instability. However, with the extent of dopaminergic degeneration reaching up to 70% before the first motor symptoms emerge,[22] this severely limits therapeutic options to slow, stop or reverse the underlying neurodegenerative process. Furthermore, it is thought that assessments do not comprehensively cover GI symptoms, and as PwP are believed to be less likely to report GI symptoms when not directly probed, this means that these symptoms are often overlooked,[7] which was demonstrated in a recent study where they reported a discrepancy of 76% in objective versus subjective GI dysfunction measures in a cohort of PwP.[8] Moreover, NMS in PD have a greater impact on quality of life measures than motor symptoms,[20] likely arising from their lack of acknowledgement and paucity of effective treatments. Given the difficulties associated with the lack of connection between PD and GI symptoms (especially those other than constipation), their role in PD is still unclear. Therefore, there is an important need to develop more comprehensive protocols to aid in the detection and further investigation of GI symptoms in patients with PD, in order to facilitate the development of more effective therapies to improve symptom management, as well as disease-modifying therapies particularly for patients with early or prodromal disease.[23] In addition, in view of the known geographic influences on the gut microflora, comparative studies of the spectrum of GI symptoms in different populations are of interest.

In the present case–control study, we investigated the prevalence and severity of GI symptoms in an Australian PD cohort using the comprehensive Gastrointestinal Symptom Rating Scale (GSRS), assessing the influence of different classes of antiparkinsonian medications, as well as dietary and lifestyle factors such as smoking on different GI symptom domains.

Methods

Participants

Participants diagnosed with idiopathic PD (n = 163) and healthy controls (n = 113) were recruited from Movement Disorders Clinics at the Perron Institute for Neurological and Translational Science (Perth, WA) and St Vincent's Hospital (Melbourne, VIC) and assessed at respective clinics in Perth and Melbourne between 24th of May 2018 and 18th of March 2019 by the same clinically trained and certified researcher (JK) to mitigate potential bias. Controls were generally the spouse or carer of the PwP. All participants were ambulant and exclusion criteria included: dementia or inability to complete the GSRS questionnaire, other neurological disorders or debilitating medical or psychiatric conditions, and use of antibiotics within the previous 3 months. A detailed history of prior gastrointestinal and other medical disorders; diet content; and pharmacological treatments including antibiotic, probiotic, prebiotic, antacid or constipation treatment use within the past year was obtained from all participants at the initial interview through a checklist as well as specific questions: 'Have you previously been diagnosed with irritable bowel syndrome, inflammatory bowel disease, peptic ulcer? Do you have a history of any other gastrointestinal issues?". All PD participants were previously examined and diagnosed by a movement disorders neurologist for verification of the diagnosis in accordance with the UK Brain Bank Criteria for idiopathic PD.[24] Prior to inclusion in the study, all participants were required to provide written informed consent and participants were free to withdraw from the study at any time. The study was approved by the Human Research Ethics Committees of the University of Western Australia (RA/4/20/4470) and St Vincent's Hospital, Melbourne (LRR137/18).

Assessment of Gastrointestinal Symptoms

PwP and controls completed a 15-question Gastrointestinal Symptom Rating Scale (GSRS) to evaluate the frequency and severity of gastrointestinal symptoms during the previous 3 months. The GSRS has previously been widely used to assess GI health in various conditions and in healthy populations.[11,25–37] Each symptom was rated on a 4-point Likert-type scale, with 0 being "normal, none or transient", and 3 representing "frequent, continuous or most severe symptoms".[34,36] For purposes of analysis, symptoms were classified into the following four categories: (1) upper GI (heartburn, acid reflux, sucking sensation, nausea and vomiting, increased eructation); (2) general GI (abdominal pain, borborygmus, abdominal distention, increased flatus); (3) hyperactive GI symptoms (increased passage of stools, urgent need for defecation, soft stools); (4) hypoactive GI symptoms (decreased passage of stools, hard stools, feeling of incomplete evacuation).

Clinical Assessments

All PwP were assessed in the "ON" state using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I–IV, with a higher score representing greater disease severity. Non-motor and motor experiences of daily living were evaluated by MDS-UPDRS parts I and II, respectively. Severity of motor symptoms, and motor complications were evaluated by MDS-UPDRS parts III and IV, respectively, and disease severity was rated using the Hoehn and Yahr scale. PD medications were categorized into six main medication classes: levodopa (L-DOPA), dopamine agonists (DA), catechol-O-methyl transferase inhibitors (COMT-I), monoamine oxidase inhibitors (MAO-I), anticholinergics, and amantadine, and reported daily dosages were converted into a levodopa equivalent daily dosage (LEDD), as previously described.[38]

Statistical Analysis

Data were analyzed using IBM-SPSS (v. 25, IBM Corporation). Case–control differences in demographic, clinical and GSRS scores were determined using chi squared or Mann Whitney-U tests, with Generalized Linear Models (GLMs) used to correct for covariates. To identify associations between GSRS scores, disease associated variables and lifestyle factors, GLMs were utilized. Similarly, to analyze associations between medications and GSRS scores, GLMs correcting for significant covariates were constructed. β-coefficients were calculated to express the size and direction of associations. A nominal *P*-value <0.05 was regarded as being statistically significant.

Results

Cohort Demographic and Clinical Data

Demographic and clinical assessment details in the PD and control groups are presented in Table 1. A higher proportion of PwP than controls reported a history of gastrointestinal illnesses, but the differences were not significant: (irritable bowel syndrome PD 10.4% vs. Control 5.3% (n.s.); inflammatory bowel disease PD 1.8% vs. Control 1.0% (n.s.); coeliac disease PD 0.6% vs. Control 0% (n.s.); Helicobacter pylori/peptic ulcer PD 1.8% vs. Controls 0.9% (n.s.)), antacid use (PD: 22.7% vs. Control: 4.4%; $P < 0.001$); and use of constipation medications (PD: 41.1 vs. Control: 8.8%; $P < 0.001$). Within the PD cohort, participants had a mean MDS-UPDRS III motor score of 25.44 (SD = 19.66) and ranged from 1–5 on the Hoehn and Yahr Scale, with the majority being stage 2 (51.9%). The majority of PwP were taking medications to treat PD with 31% taking more than one medication, and 3% being unmedicated. There was an approximately 6-year difference in mean age between the PD and control groups, and subsequent analyses therefore corrected for age as a confounding factor.

Gastrointestinal Symptoms Are More Prevalent in PwP Than Controls

Gastrointestinal symptoms, as measured by the GSRS, were significantly more frequent in the PD cohort compared to the healthy controls ($P < 0.0001$; Table 2). PwP reported significantly higher scores in 8/15 individual GI symptoms evaluated in the GSRS assessment, when compared to controls. Univariate

TABLE 1 Demographic and clinical characteristics of PD and control cohorts

Measure		PD (n = 163) *Mean (SD) or n (%)*	Controls (n = 113) *Mean (SD) or n (%)*	*P*-Value*
Age (yrs)		66.26 (9.1)	59.91 (8.7)	**<0.001**
Gender	Male	103 (63.2%)	61 (54.0%)	0.080
History of diabetes		4 (2.5%)	6 (5.3%)	0.198
History of GI illness		27 (16.6%)	8 (7.1%)	**0.020**
	IBS	19 (11.7%)	7 (6.2%)	0.127
	IBD	3 (1.8%)	1 (0.9%)	0.514
	Coeliac d.	1 (0.6%)	0 (0%)	0.404
	H. Pylori/PU	3 (1.8%)	1 (0.9%)	0.514
Currently smoking		0	3 (2.7%)	0.072
Consume coffee		120 (73.6%)	95 (84.1%)	0.078
Consume alcohol		115 (70.6%)	100 (85.5%)	**0.001**
Pro- or prebiotic use		23 (14.1%)	13 (11.5%)	0.329
Antacid use		37 (22.7%)	5 (4.4%)	**<0.001**
Constipation medication		67 (41.1%)	10 (8.8%)	**<0.001**
Disease duration (yrs)		9.5 (6.7)	–	–
Age of onset (yrs)		56.7 (10.59)	–	–
LEDD (mg)		876.4 (662.3)	–	–
PD medications	L-DOPA	134 (82.2%)	–	–
	DA	77 (47.2%)	–	–
	COMT-I	44 (27.0%)	–	–
	MAO-I	37 (22.7%)	–	–
	Amantadine	23 (14.1%)	–	–
	Anticholinergics	0 (0%)	–	–
	Unmedicated	5 (3.1%)	–	–
MDS-UPDRS score	Part I	11.48 (7.7)	–	–
	Part III	25.51 (19.8)	–	
Motor fluctuations		53 (32.5%)	–	–
Hoehn & Yahr stage		2.23 (.97)	–	–

*P values were determined through Independent Samples test, Mann Whitney U test or Spearman's Chi Square test. Significant *P* values are highlighted in bold.

PD, Parkinson's disease; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; PU, peptic ulcer; SD, Standard deviation; GI, Gastrointestinal; LEDD, Levodopa equivalent daily dosage; L-DOPA, Levodopa; DA, Dopamine Agonists; COMT-I, Catechol-O-methyltransferase Inhibitors; MAO-I, Monoamine Oxidase Inhibitors; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale.

TABLE 2 Mean comparisons between sub-domains of the GSRS in PD and control cohorts

	PD Mean (SD)	Control Mean (SD)	Corrected *P value*
General GI Symptoms			
Abdominal Pain	.25 (.56)	.18 (.47)	0.395
Borborygmus	.36 (.68)	.16 (.41)	**0.010**
Abdominal Distention	.53 (.79)	.50 (.70)	0.690
Increased Flatus	.83 (.94)	.50 (.72)	**0.015**
Total	2.0 (2.1)	1.4 (1.4)	**0.018**
Upper GI Symptoms			
Heartburn	.45 (.66)	.21 (.43)	**0.001**
Acid Reflux	.58 (.76)	.24 (.52)	**0.001**
Sucking Sensation	.01 (.08)	.01 (.09)	0.774
Nausea and Vomiting	.20 (.46)	.04 (.23)	**<0.001**
Increased Eructation	.23 (.58)	.19 (.44)	0.981
Total	1.5 (1.5)	.69 (1.1)	**<0.001**
Hypoactive GI Symptoms			
Decreased Passage of Stools	.47 (.69)	.15 (.52)	**<0.001**
Hard Stools	.99 (.99)	.54 (.76)	**<0.001**
Feeling of Incomplete Evacuation	.92 (.98)	.31 (.52)	**<0.001**
Total	2.4 (1.9)	1.00 (1.2)	**<0.001**
Hyperactive GI Symptoms			
Increased Passage of Stools	.08 (.28)	.09 (.29)	0.580
Urgent Need for Defecation	.36 (.61)	.27 (.56)	0.292
Soft Stools	.21 (.560)	.26 (.624)	0.662
Total	.66 (1.011)	.62 (1.055)	0.839
GSRS Total Scores	6.19 (4.068)	3.65 (2.987)	**<0.001**

PD, Parkinson's disease; SD, Standard deviation; GI, Gastrointestinal; GSRS, Gastrointestinal Symptom Rating Scale. GLMs were corrected for significantly different covariables identified in Table 1: age, history of GI illness, alcohol consumption, use of antacid or constipation medication. *P* values were corrected using a Bonferroni correction for multiple comparisons. Significant *P* values are highlighted in bold.

analysis revealed significant differences in age, history of GI illness, alcohol consumption, and use of antacid or constipation medications, as such these factors were incorporated as covariates into future models. Significant differences remained for heartburn ($P = 0.001$), acid reflux ($P = 0.001$), nausea and vomiting ($P < 0.0001$), borborygmus ($P = 0.014$), increased flatus ($P = 0.018$), decreased passage of stools ($P < 0.0001$), feeling of incomplete evacuation/constipation ($P < 0.0001$), and hard stools ($P < 0.0001$). When individual GI symptom questions were grouped into domains, analysis revealed that the PD cohort had significantly higher scores in upper GI symptoms ($P < 0.0001$), general GI symptoms ($P = 0.018$), and hypoactive GI symptoms ($P < 0.0001$), but was not significantly associated with hyperactive GI symptoms (Table 2).

Disease Factors Associated with GSRS Total and Subdomains

To further examine variability in GSRS scores, lifestyle and disease-associated factors were investigated. As shown in Table 3, all GSRS scores were significantly correlated with an increase in severity of motor symptoms (MDS-UPDRS III). Age of onset significantly correlated with decreased upper GI symptoms ($P = 0.006$, β-co = −.001) and decreased hypoactive GI symptoms ($P = 0.047$, β-co = −.030). Disease duration significantly correlated with increased GSRS total score ($P = 0.006$, β-co = .041), decreased upper GI symptoms ($P < 0.001$, β-co = −.010) and increased hypoactive GI symptoms ($P = 0.001$, β-co = .131). MDS-UPDRS I (which measures non-motor activities of daily living; $P = 0.001$, β-co = .073) and Hoehn & Yahr ($P = 0.001$, β-co = .589) also significantly associated with increased hypoactive GI function scores, whereas caffeine intake ($P = 0.008$, β-co = −1.003) and water consumption ($P = 0.008$, β-co = −.505) associated with significantly decreasing hypoactive GI function score.

Influence of Anti-Parkinsonian Medications on GI Symptom Domains

As anti-parkinsonian medications are a major differentiating factor between the control and PD groups, we next examined if disease-associated medication contributed to greater GSRS scores in PwP (Table 4). All four GI symptom domains were first tested for associations with age, gender, age of onset and duration of PD. Age of disease onset ($P = 0.047$) and duration of PD ($P < 0.001$) were associated with hypoactive GI function scores, and therefore remaining analyses involving hypoactive GI function scores controlled for these covariates. All four GI symptom domains were found to be significantly, positively affected by total levodopa equivalent daily dosage (LEDD; total medication dose; $P < 0.001$). General GI symptom scores were also significantly decreased by MAO-I medications ($P = 0.022$, β-co = −.878), hypoactive GI function scores significantly decreased by COMT-I medications ($P = 0.021$, β-co = −8.46), and GSRS total scores significantly decreased by amantadine ($P = 0.012$, β-co = −2.23), while there was no significant association with dopamine agonists, and no patients were on anticholinergics. These findings therefore indicate that all four symptom

TABLE 3 Analysis of associations between total and sub-domain GSRS scores and disease or demographic measures in PD subjects

	GSRS Total Score		General GI Symptoms		Upper GI Symptoms		Hypoactive GI Symptoms		Hyperactive GI Symptoms	
	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value
Age	−.016	0.652	.012	0.521	−.005	0.672	.019	0.283	−.006	0.536
Gender	.912	0.164	.574	0.094	.237	0.328	.008	0.982	.278	0.097
Age of onset	−.027	0.368	−.004	0.799	−.001	**0.006**	−.030	**0.047**	.001	0.852
Disease duration	.041	**0.006**	.039	0.149	−.010	**<0.001**	.131	**<0.001**	−.017	0.208
MDS-UPDRS I	.043	0.304	.036	0.125	.005	0.484	.073	**0.001**	.012	0.295
MDS-UPDRS III	.006	**<0.001**	.005	**0.038**	.008	**0.001**	.021	**0.017**	.005	**<0.001**
Hoehn & Yahr stage	−.260	0.429	−.034	0.858	.095	0.478	.589	**0.001**	−.044	0.638
Caffeine (Yes/no)	−1.01	0.177	−.344	0.390	.184	0.513	−1.003	**0.008**	.094	0.632
Alcohol (Yes/no)	.669	0.351	−.137	0.720	−.017	0.950	.603	0.099	.109	0.560
Water consumption	−.493	0.189	−.026	0.897	−.126	0.373	−.505	**0.008**	.144	0.139
Junk food	.296	0.423	.123	0.532	−.003	0.981	.151	0.424	−.021	0.826

P values and β-coefficients were generated using naïve GLMs. The size and direction of associations are indicated by the positive or negative β-coefficients. A nominal *P* value of 0.05 was employed and significant *P* values are highlighted in bold.
GSRS, Gastrointestinal Symptom Rating Scale; PD, Parkinson's disease; GI, Gastrointestinal; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale.

TABLE 4 Analysis of associations between use of anti-parkinsonian medications and GSRS scores in PD subjects

	Total GSRS Score		General GI Symptoms		Upper GI Symptoms		Hypoactive GI Symptoms		Hyperactive GI Symptoms	
	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value	β-Co	*P* value
LEDD (mg)	−.001	**<0.001**	.800	**<0.001**	.060	**<0.001**	.001	**<0.001**	.003	**<0.001**
L-DOPA	−1.49	0.103	−.531	0.281	.112	0.745	−.314	0.476	−.019	0.937
DA	.302	0.673	.162	0.629	.002	0.991	.061	0.839	.285	0.082
COMT-I	−1.01	0.154	.011	0.977	−.164	0.528	−.846	**0.021**	.298	0.102
MAO-I	−.867	0.247	−.878	**0.022**	−.080	0.768	.429	0.211	−.155	0.416
Amantadine	−2.23	**0.012**	−.509	0.273	−.132	0.683	−.843	0.052	.377	0.097

P values and β-coefficients were generated using GLMs. Hypoactive GI symptom tests were corrected for significant interactions with disease duration and age of onset by including these as covariates on the models. A nominal *P* value of 0.05 was employed and significant *P* values are highlighted in bold. Direction of associations are indicated as a positive or negative β-coefficient.
GSRS, Gastrointestinal Symptom Rating Scale; PD, Parkinson's disease; GI, Gastrointestinal; LEDD, Levodopa equivalent daily dosage; L-DOPA, Levodopa; DA, Dopamine Agonists; COMT-I, Catechol-O-methyltransferase Inhibitors; MAO-I, Monoamine Oxidase Inhibitors.

domains are medication dependent. However, in the case of hypoactive GI symptoms (such as constipation), which were significantly associated with use of COMT-1 inhibitors, it is likely that they are primarily disease-related, given the strong association with disease duration and severity as shown in Table 3.

Discussion

Previous studies of GI symptoms in PD have focused largely on the presence of constipation, and few have assessed the broader spectrum of GI symptoms experienced by PwP. In this case–control study we utilized the comprehensive Gastrointestinal Symptom Rating Scale (GSRS), which has been used to evaluate the frequency and severity of GI symptoms in various clinical settings, to examine a large cohort of patients with idiopathic PD which has only previously been done in one comprehensive study with a cohort comprised of mainly later-staged PwP.[19] Our findings confirm that GI symptoms occur more frequently in PwP than in non-affected individuals, with specific domains of upper, lower, and hypoactive GI symptoms all being greater in PwP.

The most common GI symptoms reported by PwP in this study were hard stools, difficulty defecating with straining resulting in the feeling of incomplete evacuation, and increased flatus, respectively. These symptoms can all be related to constipation, which is a particularly troublesome NMS, and a well-studied symptom of prodromal PD.[5,7–11] Constipation in PD is reported to involve a dysfunctional colonic musculature which causes slowed movement of bowl contents through the colon, and prolonged transit time has been reported previously in PwP.[8,39,40] In addition, there is an outlet type obstruction and difficulty with rectal expulsion. Furthermore, excessive straining and a feeling of incomplete evacuation may be caused by dyssynergic uncoordinated action of the muscles involved with completing a bowel movement.[10,40] A number of factors may contribute to the high frequency of upper GI symptoms in the PD subjects, including delayed gastric emptying,[41,42] which is associated with multiple upper GI symptoms such as nausea, acid reflux and vomiting (Pfeiffer et al. 2020). Infection with *helicobacter pylori*, which has been reported to occur with greater frequency in PD,[43] could also be a contributory factor to increased GI symptoms in some patients. Moreover, as enteric dopamine is known to regulate GI transit and contraction,[44]

reduced dopamine levels in the enteric nervous system in PD[45] may result in slowing of gut motility and constipation.

We next asked whether GI symptom variability was associated with aspects of the disease. Disease severity measured by MDS-UPDRS III significantly associated with all total and domain GSRS scores. Interestingly, disease duration also significantly associated with GSRS total, upper GI symptom and hypoactive GI symptom scores. This suggests that as the disease progresses, GI symptoms are more likely to be present and more severe. Despite previous findings of caffeine being protective in PD,[46] our study found that coffee intake was associated with more severe and frequent hypoactive GI symptoms, which was unpredicted as hypoactive GI symptoms are frequently associated with constipation, and coffee is associated with the opposite effect in healthy controls.[47]

Our study also evaluated previous medical history that may have contributed to the increased severity and frequency of GI symptoms found in individuals with PD when compared to healthy controls, and we found that a higher proportion of PwP than controls had a history of a previous GI illness, such as irritable bowel syndrome or inflammatory bowel disease, although the differences were not statistically significant. Because of variable findings in different studies there is still debate as to whether inflammatory bowel disease is a risk factor for the development of PD.[48,49] In addition, within this cohort there was a significantly higher use of antacid and constipation medications within the PwP when compared to controls. However, it remains to be seen whether such reports are associated with a greater risk of developing PD, or whether they are a consequence of the disease and the associated use of PD medications.

To date, there are limited comprehensive studies that have evaluated the effects of different classes of anti-parkinsonian medications on GI symptom presentations. In the present study, generalized linear modeling demonstrated that total daily medication dose (LEDD) was significantly associated with increasing all four GI symptom domain scores, and more specifically that COMT-inhibitors were associated with significantly decreasing hypoactive GI scores, MAO-inhibitors with significantly decreasing general GI symptoms, and amantadine with significantly decreasing the total GSRS score. In the case of MAO-inhibitors and amantadine it is likely that the iatrogenic GI side effects are related to the increase in dopamine bioavailability.[50] With regard to the COMT-inhibitors, the finding of an association with a reduction in hypoactive bowel symptoms can be explained, given that COMT-inhibitors can also cause diarrhea, which has been attributed to inhibition of 5-HT metabolism.[51] These findings underscore the impact of anti-parkinsonian medications on GI symptom presentations and are a reminder that these symptoms are not necessarily a product of the underlying disease. They also point to basic differences in the GI side-effect profiles of the different classes of anti-parkinsonian medication.

In addition to their direct effect on wellbeing, GI dysfunction has been reported to dampen medication responses and trigger response fluctuations in PwP.[52] Such fluctuations result in temporary or premature re-emergence of symptoms, commonly referred to as "OFF" periods, which themselves are strongly associated with reduced quality of life.[53] In the current study, PwP reported elevated nausea, vomiting, bloating or heartburn in the current study, all which are symptomatic presentations of delayed gastric emptying and increased colonic transit time. These forms of GI dysfunction can inhibit medication absorption, with studies reporting lower peak plasma levels and increased "OFF" periods.[41,42,54] Furthermore, it has similarly been proposed that Small Intestinal Bacterial Overgrowth (SIBO; a form of gut microbial dysbiosis) could be associated with worsening 'ON' state motor scores and more severe motor fluctuations due to downstream inflammatory effects that reduce medication absorption.[55,56] Thus, further investigating the foundations of increased GI symptoms in PwP could potentially improve medication absorption, improve symptom severity, and reduce medication resistance.

The gut microbiome is one of the most important determining factors for GI health, and a dysbiotic microbiome is widely acknowledged to manifest symptomatically with GI symptoms such as nausea, vomiting, constipation, bloating, reflux, heartburn, or increased flatulence. A number of animal and human studies suggest that a reduced diversity of gut microbiota and altered metabolic products, as well as predicted effects on metabolic pathways may initiate an inflammatory process within the gut which may trigger the onset and spread of PD pathophysiology.[57–63] However, little consideration has been given to the impact that medications, as well as dietary and lifestyle factors, have on this process or wide-spread GI symptoms in PD.[23] Future studies investigating the composition and diversity of the microbiota, with careful consideration of antiparkinsonian medications, will be crucial to further understand the trigger for the increased GI symptoms observed in this cohort of PwP.

Lastly, under reporting of GI symptoms is a problem that may be skewing documented reported symptoms in PwP and is undeniably generating a gap in literature. An international study reported that 62% of non-motor symptoms, such as GI symptoms, are not reported by PwP due to embarrassment or not realizing they are related to PD.[64,65] Furthermore, a more recent study reported that although 66%–79% of the studied cohort demonstrated objective evidence of GI dysfunction, only 3%–38% reported subjective constipation.[8] The GI symptom assessment used in our study, the GSRS, asks study participants to think about their specific GI symptoms, not just their PD related symptoms, and so is more likely to capture information regarding GI symptoms in PD. Thus, more research into the relationship of GI symptoms with PD could mitigate this established stigma and lack of recognition surrounding these symptoms in PwP.

Limitations

A number of limitations of the current study must be noted. Firstly, home-based PwP were recruited from two different Movement Disorders Clinics across Australia, which may have resulted in exclusion of more severe cases who were unable to travel to a clinic, thereby skewing GSRS scores. Secondly, although we did not have access to a complete medical history of previously diagnosed illnesses for all participants, they were

asked for a verbal recollection of their past gastrointestinal diagnoses at the time of assessment. Thirdly, in spite of its comprehensive nature, the GSRS assessment relies on participant recollection and judgment, and it is therefore still likely that GI symptom frequency and severity were under reported.[8,64] Finally, the cross-sectional nature of the study limits conclusions regarding causal relationships, so the present findings would benefit from confirmation in longitudinal studies.

Conclusions

Our study ranks as one of the most comprehensive case–control studies of GI symptoms in PwP and their association with treatment and lifestyle factors to date. PwP reported significantly higher instances of GI symptoms, particularly upper GI symptoms and hypoactive GI function, which correlated with disease duration and severity. However, these symptom domains as well as GSRS total score were also shown to be significantly influenced by total daily medication dose (LEDD), while specific classes of anti-parkinsonian medications had differential effects on symptom subdomains. To this end, the presented results highlight the role of anti-parkinsonian medications in GI symptom presentation and severity in PwP, whereas dietary or lifestyle factors appear to be of lesser importance. As GI symptoms are among the first to present in PD, this comprehensive but short and easily employed GI assessment shows potential to identify bothersome symptoms in PwP, to identify medications that need altering, and to possibly identify individuals at risk of PD prior to motor symptom onset. All in all, comprehensive screening of GI symptoms in PwP shows great promise to facilitate improved personalized healthcare for PD.

Acknowledgments

We thank Professor Soumya Ghosh and Associate Professor Rick Stell for providing access to patients through the Perron Movement Disorders Clinic; and Ms Sue Walters and the Perron Clinic Team for providing assessment training and logistical support. We would also like to thank Professor Malcolm Horne and Ms Sarah Osborne for making it possible to recruit patients through the St Vincent's Hospital Movement Disorders Clinic and for their generous support. Finally, we would like to thank all of the individuals who participated in this study for their time and enthusiasm.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

J.K.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
M.B.: 1C, 2C, 3B
A.G.: 2C, 3B
A.T.: 1B, 3B
S.W.: 3B
F.M.: 1A, 2C, 3A, 3B
R.A.: 1A, 1B, 2A, 2B, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Human Research Ethics Committees of the University of Western Australia (RA/4/20/4470) and St Vincent's Hospital Melbourne (LRR137/18). Prior to inclusion in the study, all participants (patient and controls) were required to provide written informed consent. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This study was funded by Parkinson's WA Zrinski Research Grant 2019, Perron Institute of Neurological and Translational Science, and The University of Notre Dame Australia. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: The authors declare that there are no additional disclosures to report. ■

References

1. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord* 2007;22(13):1901–1911.
2. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* 2006;21(7):916–923.
3. Martinez-Martin P, Schrag A, Weintraub D, IPMDS Non Motor PD Study Group. Pilot study of the International Parkinson and Movement Disorder Society-sponsored non-motor rating scale (MDS-NMS). *Mov Disord Clin Pract* 2019;6(3):227–234.
4. Chaudhuri KR, Schrag A, Weintraub D, et al. The movement disorder society nonmotor rating scale: initial validation study. *Mov Disord* 2020; 35(1):116–133.
5. Adams-Carr KL, Bestwick JP, Shribman S, Lees A, Schrag A, Noyce AJ, et al. Constipation preceding Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87(7):710–716.
6. Cersosimo MG, Raina GB, Pecci C, et al. Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms. *J Neurol* 2013;260(5):1332–1338.
7. Kaye J, Gage H, Kimber A, Storey L, Trend P. Excess burden of constipation in Parkinson's disease: a pilot study. *Mov Disord* 2006;21(8): 1270–1273.
8. Knudsen K, Fedorova TD, Bekker AC, Iversen P, Østergaard K, Krogh K, Borghammer P. Objective colonic dysfunction is far more prevalent than subjective constipation in Parkinson's disease: a colon transit and volume study. *J Parkinsons Dis* 2017;7(2):359–367.
9. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2014;20(12):1371–1375.
10. Mathers SE, Kempster PA, Swash M, Lees AJ. Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? *J Neurol Neurosurg Psychiatry* 1988;51(12): 1503–1507.

11. Ueki A, Otsuka M. Life style risks of Parkinson's disease: association between decreased water intake and constipation. *J Neurol* 2004;251 (Suppl 7):vII18–vII23.

12. Cirstea MS, Yu AC, Golz E, et al. Microbiota composition and metabolism are associated with gut function in Parkinson's disease. *Mov Disord* 2020;35(7):1208–1217.

13. Eadie MJ, Tyrer JH. Alimentary disorder in parkinsonism. *Australas Ann Med* 1965;14:13–22.

14. Edwards L, Quigley EM, Hofman R, et al. Gastrointestinal symptoms in Parkinson disease: 18-month follow-up study. *Mov Disord* 1993;8(1): 83–86.

15. Edwards LL, Pfeiffer RF, Quigley EM, et al. Gastrointestinal symptoms in Parkinson's disease. *Mov Disord* 1991;6(2):151–156.

16. Qin X, Li X, Xin Z, et al. Gastrointestinal dysfunction in Chinese patients with Parkinson's disease. *Parkinsons Dis* 2019;2019:3897315.

17. Siddiqui MF, Rast S, Lynn MJ, Auchus AP, Pfeiffer RF. Autonomic dysfunction in Parkinson's disease: a comprehensive symptom survey. *Parkinsonism Relat Disord* 2002;8(4):277–284.

18. Sung HY, Park JW, Kim JS. The frequency and severity of gastrointestinal symptoms in patients with early Parkinson's disease. *J Mov Disord* 2014;7(1):7–12.

19. Lubomski M, Davis RL, Sue CM. Gastrointestinal dysfunction in Parkinson's disease. *J Neurol* 2020;267(5):1377–1388.

20. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord* 2010;25(15):2493–2500.

21. Sauerbier A, Ray Chaudhuri K. Non-motor symptoms: the core of multi-morbid Parkinson's disease. *Br J Hosp Med* 2014;75(1):18–24.

22. Hayes MW, Fung VS, Kimber TE, O'Sullivan JD. Current concepts in the management of Parkinson disease. *Med J Aust* 2010;192(3):144–149.

23. Bullich C, Keshavarzian A, Garssen J, Kraneveld A, Perez-Pardo P. Gut vibes in Parkinson's disease: the microbiota-gut-brain Axis. *Mov Disord Clin Pract* 2019;6(8):639–651.

24. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55(3):181–184.

25. Dimenas E, Carlsson G, Glise H, et al. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. *Scand J Gastroenterol Suppl* 1996;221:8–13.

26. Dimenas E, Glise H, Hallerback B, et al. Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer. *Scand J Gastroenterol* 1995;30(11):1046–1052.

27. Karling P, Maripuu M, Wikgren M, Adolfsson R, Norrback KF. Association between gastrointestinal symptoms and affectivity in patients with bipolar disorder. *World J Gastroenterol* 2016;22(38):8540–8548.

28. Khanna D, Nagaraja V, Gladue H, Chey W, Pimentel M, Frech T Measuring response in the gastrointestinal tract in systemic sclerosis. *Curr Opin Rheumatol* 2013;25(6):700–706.

29. Kleinman L, Kilburg A, Machnicki G, et al. Using GI-specific patient outcome measures in renal transplant patients: validation of the GSRS and GIQLI. *Qual Life Res* 2006;15(7):1223–1232.

30. Kulich KR, Calabrese C, Pacini F, et al. Psychometric validation of the Italian translation of the gastrointestinal symptom-rating scale and quality of life in reflux and dyspepsia questionnaire in patients with gastro-oesophageal reflux disease. *Clin Drug Investig* 2004;24(4):205–215.

31. Kulich KR, Madisch A, Pacini F, et al. Reliability and validity of the gastrointestinal symptom rating scale (GSRS) and quality of life in reflux and dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. *Health Qual Life Outcomes* 2008;6:12.

32. Ljotsson B, Jones M, Talley NJ, et al. Discriminant and convergent validity of the GSRS-IBS symptom severity measure for irritable bowel syndrome: a population study. *United Eur Gastroenterol J* 2020;8(3):284–292.

33. Miller MA, Tong W, Fan X, et al. 2012 Global summit on regulatory science (GSRS-2012)—modernizing toxicology. *Toxicol Sci* 2013;131 (1):9–12.

34. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. *Qual Life Res* 1998;7(1):75–83.

35. Souza GS, Sarda FA, Giuntini EB, et al. Translation and validation of the Brazilian Portuguese version of the gastrointestinal symptom rating scale (Gsrs) questionnaire. *Arq Gastroenterol* 2016;53(3):146–151.

36. Svedlund J, Sjodin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988;33(2):129–134.

37. Tornatore C, Amjad F. Attenuation of dimethyl Fumerate-related gastrointestinal symptoms with Montelukast. *Neurology* 2014;82:7.

38. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25(15):2649–2653.

39. Knudsen K, Haase AM, Fedorova TD, Bekker AC, Østergaard K, Krogh K, Borghammer P. Gastrointestinal transit time in Parkinson's disease using a magnetic tracking system. *J Parkinsons Dis* 2017;7(3): 471–479.

40. Coletto E, Dolan JS, Pritchard S, et al. Contractile dysfunction and nitrergic dysregulation in small intestine of a primate model of Parkinson's disease. *NPJ Parkinsons Dis* 2019;5:10.

41. Hardoff R, Sula M, Tamir A, et al. Gastric emptying time and gastric motility in patients with Parkinson's disease. *Mov Disord* 2001;16(6): 1041–1047.

42. Marrinan S, Emmanuel AV, Burn DJ. Delayed gastric emptying in Parkinson's disease. *Mov Disord* 2014;29(1):23–32.

43. Camci G, Oguz S. Association between Parkinson's disease and helicobacter pylori. *J Clin Neurol* 2016;12(2):147–150.

44. Poirier AA, Aube B, Cote M, et al. Gastrointestinal dysfunctions in Parkinson's disease: symptoms and treatments. *Parkinsons Dis* 2016;2016: 6762528.

45. Ohlsson B, Englund E. Atrophic myenteric and submucosal neurons are observed in Parkinson's disease. *Parkinsons Dis* 2019;2019:7935820.

46. Hernan MA, Takkouche B, Caamano-Isorna F, et al. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002;52(3):276–284.

47. Papakonstantinou E, Kechribari I, Sotirakoglou K, et al. Acute effects of coffee consumption on self-reported gastrointestinal symptoms, blood pressure and stress indices in healthy individuals. *Nutr J* 2016;15:26.

48. Camacho-Soto A, Gross A, Searles Nielsen S, Dey N, Racette BA. Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries. *Parkinsonism Relat Disord* 2018;50:23–28.

49. Zhu F, Li C, Gong J, Zhu W, Gu L, Li N. The risk of Parkinson's disease in inflammatory bowel disease: a systematic review and meta-analysis. *Dig Liver Dis* 2019;51(1):38–42.

50. Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: the critical modulators regulating gut-brain Axis. *J Cell Physiol* 2017;232(9):2359–2372.

51. Kaakkola S. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. *Drugs* 2000;59(6):1233–1250.

52. Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clin Interv Aging* 2010;5:229–238.

53. Rastgardani T, Armstrong MJ, Gagliardi AR, Marras C. Understanding, impact, and communication of "off" periods in Parkinson's disease: a scoping review. *Mov Disord Clin Pract* 2018;5(5):461–470.

54. Doi H, Sakakibara R, Sato M, et al. Plasma levodopa peak delay and impaired gastric emptying in Parkinson's disease. *J Neurol Sci* 2012;319 (1–2):86–88.

55. Fasano A, Bove F, Gabrielli M, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* 2013;28(9):1241–1249.

56. Gabrielli M, Bonazzi P, Scarpellini E, et al. Prevalence of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* 2011;26(5): 889–892.

57. Heintz-Buschart A, Pandey U, Wicke T, et al. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. *Mov Disord* 2018;33(1):88–98.

58. Hill-Burns EM, Debelius JW, Morton JT, et al. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Mov Disord* 2017;32(5):739–749.

59. Keshavarzian A, Green SJ, Engen PA, et al. Colonic bacterial composition in Parkinson's disease. *Mov Disord* 2015;30(10):1351–1360.

60. Li W, Wu X, Hu X, Wang T, Liang S, Duan Y, Jin F, Qin B Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. *Sci China Life Sci* 2017;60(11):1223–1233.

61. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord* 2015;30(3): 350–358.

62. Gorecki AM, Preskey L, Bakeberg MC, et al. Altered gut microbiome in Parkinson's disease and the influence of lipopolysaccharide in a human alpha-Synuclein over-expressing mouse model. *Front Neurosci* 2019;13:839.

63. Kenna JE, Anderton RS. The Role of the Gastrointestinal System and Gut Microbiota in Parkinson's Disease. *The Neuroscience of Parkinson's Disease: Genetics, Neurology, Behaviour, and Diet*. Amsterdam: Elsevier; 2020. https://www.elsevier.com/books/genetics-neurology-behavior-and-diet-in-parkinsons-disease/martin/978-0-12-815950-7.

64. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord* 2010;25(6):704–709.

65. Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009;8 (5):464–474.