Parkinson Disease and the Gut: A Primer for Gastroenterologists

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Parkinson disease (PD) is a chronic, progressive movement disorder and the fastest growing neurological condition worldwide, affecting over 6 million individuals. In 2017, the economic burden of PD in the United States alone reached $52 billion. Gastrointestinal symptoms and dysfunction such as constipation, gastroparesis, and dysphagia are common in PD, are difficult to manage, and negatively affect quality of life. In addition, constipation often precedes motor symptoms by decades, perhaps suggesting that a disrupted bidirectional microbiota-gut-brain axis is present early in PD. Data from mechanistic studies in rodent models and observational human studies demonstrate that gut-microbiota dysbiosis, intestinal hyperpermeability, and gut inflammation may promote neuroinflammation and α-synuclein aggregation, inciting loss of dopaminergic neurons. Studies also indicate that the intestinal milieu may influence symptom severity and response to PD treatments. These findings underscore the potential role of the gut as (i) a site of early diagnosis and risk stratification for populations at high risk of PD and (ii) a potentially disease-modifying treatment approach. This review summarizes the current knowledge on the role of the gut-brain axis in PD pathogenesis, clinical disease course, prodromal gastrointestinal symptoms, and their underlying mechanisms and stresses current knowledge gaps and future directions.

KEYWORDS: Parkinson disease; microbiota; gut-brain axis; gastroparesis; constipation; inflammatory bowel disease

Am J Gastroenterol 2025;00:1–10. https://doi.org/10.14309/ajg.0000000000003508

INTRODUCTION

Parkinson disease (PD) is the fastest growing of all neurological disorders and a leading cause of disability (1), affecting over 6 million people globally (2). One million Americans are currently diagnosed with PD, and the global impact of PD reaches both high and low-socioeconomic index countries (3). These data underscore the urgent need for strategies to address PD prevention, early diagnosis, disease-modifying treatment, and management.

The onset of motor symptoms, when PD is typically diagnosed, is associated with loss of approximately 70%–80% of nigrostriatal dopaminergic neurons (4). Dopamine-replacement therapy is the cornerstone treatment for the management of PD symptoms, but it does not influence disease progression and also fails to address troublesome nonmotor gastrointestinal (GI) and other systemic symptoms. Evidence indicates that a disrupted microbiota-gut-brain axis may be a critical initial biological process contributing to the pathogenesis of PD and may play a role throughout the disease even into its late stages. Better understanding of the mechanism by which disrupted microbiota-gut-brain axis contributes to PD pathogenesis and disease progression underlies the search for GI-based biomarkers, especially for early diagnosis and stratification for PD risk within the general population with the hope of disease prevention or disease-modifying treatment development.

Longitudinal studies have shown that GI symptoms, including constipation, can precede motor symptoms by years or even decades in at least a subset of patients with PD (5–8). This observation has led to hypotheses that gut dysfunction initiates or accelerates PD progression through mechanisms such as altered intestinal permeability, gut microbiota dysbiosis, and α-synuclein misfolding and aggregation within the enteric nervous system. Variability in symptom presentation, however, indicates that PD is heterogeneous and that GI symptoms are early manifestations in some PD phenotypes (gut-first PD) but may also occur only after motor symptoms develop (brain-first PD). In both instances, the association of GI and neurological symptoms in PD suggests a bidirectionality of the gut-brain axis throughout the disease.

Severe, difficult-to-manage GI symptoms and the potential of gut-directed therapeutic strategies to modify the disease course have led neurologists to partner with gastroenterologists in multidisciplinary clinics and in research endeavors. The aims of this review article are to understand GI-associated PD risk factors, to define what is known and unknown about the role of the gut in PD pathogenesis and onset, to review the prior challenges and

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Received September 4, 2024; accepted April 1, 2025; published online April 29, 2025

explore the future potential role of endoscopy in PD screening, and to discuss the current approach to a GI consult of constipation in the patient with PD.

GI-ASSOCIATED RISK FACTORS AND PATHWAYS IN PD

PD is influenced by a multifaceted interplay of demographic, genetic, environmental, and systemic factors (Figure 1). Insights into these factors and their role in PD (and prodromal PD (9)) continue to evolve.

Demographic and genetic risk factors

Age and sex are factors that strongly influence PD risk. Advanced age is a risk factor in many diseases, but after the age of 65, there is a dramatic rise in PD incidence (45). Furthermore, PD is 1.4 times more frequent in men than women (3). Genetics are important, and certain populations are associated with high risk (Ashkenazi Jewish, Spanish Basque, North African Berber) (10). Autosomal dominant mutations in leucine-rich repeat kinase 2 (*LRRK2)* and synuclein alpha, as well as recessive mutations in *PARK2*, are implicated in familial PD. Among risk variants, *GBA1* mutations are most prevalent in idiopathic PD worldwide, while *LRRK2* (the G20119S variant) is the second most common and associated with both familial and sporadic PD (10). Women with autosomal dominant PD often have mutations in the *LRRK2* gene (10,46). In preclinical and early clinical studies in PD, LRRK2 kinase inhibitors have demonstrated safety, tolerability, and promise (47). However, it is important to note that increased PD genetic susceptibility does not ensure development. This underscores the complex interplay between genotype, phenotype, and the environment and the need for further studies to untangle these relationships.

Intestinal inflammation and disease

Chronic intestinal inflammation, as seen in inflammatory bowel disease (IBD), is associated with a 20%–90% higher relative risk of PD, potentially mediated by gut microbiota dysbiosis and dysregulated immune activation (48–52). However, in a meta-analysis of 354,792 patients with IBD, the absolute risk remains low at approximately 0.26%, (53). Patients with PD have a 15% lower risk of developing IBD than the general population, stressing the need for further investigation to distinguish correlation from causation (54). The interplay between intestinal inflammation and dysbiosis is complex, and compelling evidence demonstrates that reducing intestinal inflammation in general and specifically in IBD mitigates PD risk: (i) Patients with IBD who take 5-aminosalicylic acid for the treatment of their disease have a 25% lower risk of PD (55), (ii) azathioprine and corticosteroid use also reduces PD risk (56), and (iii) anti-tumor necrosis factor agents confer a 78% risk reduction for PD (49). Reducing gut inflammation associated with IBD seems to reduce risk of PD.

GI motility and functional bowel disorders

Constipation, oropharyngeal (transfer) dysphagia, bloating, and nausea are common in patients with PD. One-third of patients with PD have at least mild dysphagia that increases in frequency and severity in the more advanced stages of PD (57,58); 80% of patients exhibit oropharyngeal delay due to impairment of pharyngeal muscles (57). Dysphagia in PD can also result in excessive drooling and can be associated with aspiration pneumonia (59).

Nausea occurs in one-quarter of patients with PD, and more than 70% have delayed gastric emptying (60–62), the latter complicating medication management such as with levodopa that requires predictable, time-sensitive duodenal delivery. In addition, some data indicate that dopaminergic medications delay gastric emptying (63).

Irritable bowel syndrome (IBS) is associated with a 45%–50% increased risk of PD above age 65 (64–67). In a recent study, 4 GI conditions (dysphagia, gastroparesis, constipation, and IBS) were found to increase the risk of developing PD in the subsequent 5 years (67). This increased risk is specific to PD over other neurological conditions, such as Alzheimer disease and cerebrovascular disease. Delayed gastric emptying (i.e., gastroparesis) was found to have the highest relative risk of PD compared with dysphagia, constipation, and IBS. However, it is plausible that at least a subset of patients with an IBS diagnosis have unrecognized prodromal PD with GI symptoms.

Diabetes, the gut, and PD

Patients with young-onset diabetes carry a higher risk of early-onset PD (21–23). Coexisting type 2 diabetes is associated with severe symptoms, postural instability, gait disturbance, loss of independence, cognitive impairment, and higher rates of depression in PD (68–70). Diabetes can potentially worsen coexisting GI symptoms including constipation, dyssynergic defecation, and nausea (23).

Management of diabetes with medications lowers PD risk: (i) Glitazones have a 20% lower risk (24) and dipeptidyl peptidase-4 inhibitors a 50% lower risk (24). Multivariate analysis demonstrates a 30%–60% risk reduction with dipeptidyl peptidase-4 inhibitors and glucagon-like peptide (GLP-1) agonists, independent of glycemic control and weight loss. Exenatide, an injectable GLP-1 agonist, for 48 months improved motor symptoms in an early-stage, randomized, placebo-controlled PD trial (71) and also improved nonmotor symptoms (72). However, a multicenter, placebo-controlled, phase III randomized clinical trial (RCT) of exenatide in patients with PD without type 2 diabetes found no benefit in the primary end point of motor symptoms or secondary end points, including improvement in nonmotor symptoms (73).

Metabolic syndrome, characterized by chronic low-grade inflammation, may also contribute to PD risk through systemic and neuroinflammatory pathways. The benefits of GLP-1 agonists could be multifactorial: neuroprotective against mitochondrial injury (74), reversal of low-grade inflammation associated with metabolic syndrome, and reversal of diminished GLP-1 secretion seen in patients with PD (75). GLP-1 agonists may delay gastric emptying; however, the anti-inflammatory and neuroprotective effects of GLP-1 agonists may eclipse their impact on GI motility. Neuroendocrine cells, key sensory cells in the intestinal epithelial layer that relay luminal factors (including bacteria products) to the mucosal immune system and enteric nervous system, also mediate gut-brain communication through hormones such as GLP-1 and through the vagus nerve to affect neuroinflammation, α-synuclein aggregation, and dopamine loss (76). These observations underscore the need for better understanding of the complex relationship between metabolic syndrome and PD. Other factors such as head injury and environmental toxicants are also associated with increased risk (Figure 1).

MICROBIOTA-GUT-BRAIN AXIS AND PD PATHOGENESIS

PD pathogenesis involves a complex interplay of genetic and environmental factors. PD is part of a spectrum of Lewy body

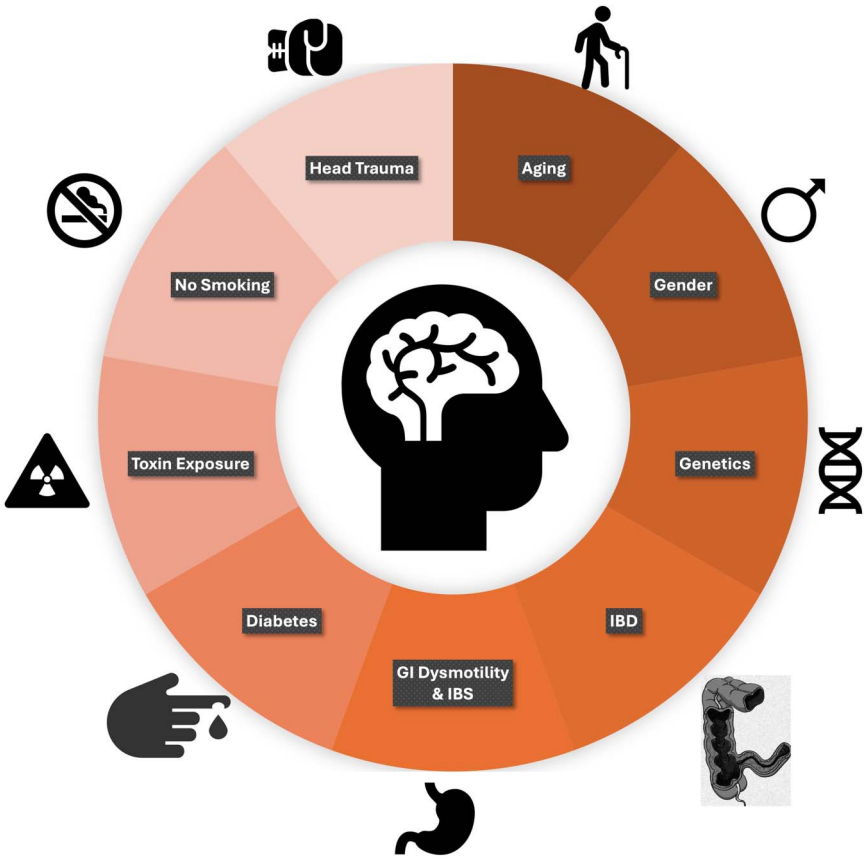

Figure 1. Risk factors of developing Parkinson disease (PD). PD risk is shaped by a complex interplay of factors, including gastrointestinal (GI) conditions and gut inflammation. PD incidence increases with age with a dramatic rise after 65. PD is 1.4 times more frequent in men than women. Disease-relevant genetic variants are found in 13.4% of people with Parkinson disease (PwP) in North America. *GBA1* mutations are most prevalent genetic variants in idiopathic PD worldwide, while *LRRK2* (the G20119S variant) is the second most common and associated with both familial and sporadic PD (10). Inflammatory bowel disease (IBD), dysphagia, gastroparesis, constipation, irritable bowel syndrome (IBS), diabetes, and head trauma are all associated with increased risk of PD. *LRRK2* gene mutations also affect the risk of developing Crohn's disease (e.g., N2081D variant vs N551K variant) (11). Higher levels of LRRK2 are found in inflamed colonic tissue in Crohn's disease (12), and LRRK2 is also involved in regulation of gut microbiota and microbe-host interactions (13). In addition to the overlap of genetic susceptibility between IBD and PD, smoking is a common environmental factor that affects susceptibility to both diseases and promotes gut inflammation. Smoking has been associated with a reduced risk of PD, potentially because of nicotine's anti-inflammatory neuroprotective effects on dopaminergic neurons (14,15). Smokers have a 40% decrease in the risk of PD (16). Smoking has a dose-dependent relationship with current heavy smokers (greater than 30 pack-year) having the greatest protection (17,18). Declining rates of smoking in the United States are estimated to contribute to a 10% rise in incidence by 2040 (19). Epidemiological studies have shown smoking to also be protective for the development of ulcerative colitis (20). By contrast, smoking increases the risk of Crohn's disease (20). It remains undetermined whether smoking affects the risk of PD in patients with IBD. Patients with diabetes diagnosed at a younger age are at higher risk of early-onset PD (21–23). Antidiabetic medications are associated with deceased risk of developing PD (24). Head injury as a risk factor of PD gained significant recognition after Muhammad Ali was diagnosed with early-onset disease at the age of 42 (25). A history of head injury that results in loss of consciousness confers a higher risk of PD (26). Head injury can trigger neuroinflammation, disruption of the blood-brain barrier, leukocyte infiltration, and microglial activation (27). Head injury can also result in mitochondrial dysfunction and glutamate excitotoxicity, common features of PD (28–30). Environmental toxins, such as pesticides (paraquat, rotenone) and industrial solvents (trichloroethylene, perchloroethylene) are associated with increased PD risk (31–36). Paraquat, rotenone, and trichloroethylene promote oxidative stress, mitochondrial dysfunction, and dopaminergic neuronal loss (37,38). Rotenone was withdrawn from use in the Europe in 2007, and most of its use in the United States has voluntarily ceased (39). However, paraquat remains the most widely used pesticides in the world. Trichloroethylene, a widely used industrial solvent, was recently linked to PD in the United States marines stationed at Camp Lejeune in North Carolina between 1975 and 1985 (40). Manganese concentrations in urban air vary based on location, season, and source (41). During occupational exposure, acute manganese results in dopaminergic neurotoxicity and parkinsonism (42). Emissions from industrial processes such as ferroalloy production, iron and steel foundries, and coke ovens are a major source of manganese. If gasoline contains methycly-clopentadienyl manganese tricarbonyl, manganese can also be dispersed from gasoline engine combustion (43). Both traffic-related and environmental manganese air pollution confer an increased risk of PD (43,44).

disorders (LBDs) that also include Parkinson disease dementia and dementia with Lewy bodies (77,78). Incidental Lewy body disease, often considered a prodromal stage of PD, provides valuable insights into early pathogenesis through histopathological findings. Multiple system atrophy, although associated with α-synuclein pathology, is excluded from LBDs because of its distinct glial cytoplasmic inclusions rather than neuronal Lewy bodies (79). This section explores critical

mechanisms underpinning LBDs, integrating insights and addressing ongoing controversies.

Evidence from human studies

Two prominent staging models of PD progression exist. The Braak hypothesis posits that α-synuclein pathology begins in peripheral sites, such as the nasal cavity or the enteric nervous system (80,81) and then gradually and linearly spreads to the brain. The body-first vs brain-first model expands upon this framework, proposing alternative propagation routes and allowing for nonlinear spread of pathology, to account for heterogeneity in clinical presentations (81). It is estimated that one-third of patients exhibit an amygdala-centered or brain-first distribution with pathology in the amygdala, entorhinal cortex, and substantia nigra originating from the olfactory bulb through the nose (82). The remaining two-thirds are proposed to exhibit a body-first phenotype with prominent pathology in the sacral spinal cord, thoracic interomediolateral column, or dorsal motor nucleus of vagus, which emanates from the gut (Figure 2) (8,81,83,84).

In patients with brain-first PD, the central PD pathology affects the amygdala and central autonomic network to affect gut function and the gut microbiome downstream (Figure 2). Subsequent progression of PD pathology to the dorsal motor nucleus of the vagus nerve further augments gut dysfunction.

In body-first PD, the vagus nerve can promote spread of pathology from the enteric nervous system to the central nervous system (CNS). A 15% reduction in PD risk is observed during a 5-year follow-up period after vagotomy supports the vagal route (85). However, when this cohort was examined 16 years later, no significant protection from PD was found 20 years after vagotomy (86). This later observation was also seen in a Swedish registry, which also did not observe protection against PD after vagotomy (87).

Spinal nerve pathways are less appreciated as gut-to-brain transmission of pathology in body-first patients. Both branches of the autonomic nervous system, sympathetic and parasympathetic, are affected by PD. Interestingly, there are cases of PD with pathology only in the sympathetic ganglia without pathological involvement of the vagus nerve or CNS (88,89). These observations indicate that spinal nerves may also serve as an alternative route to the vagus nerve for neuron-to-neuron gut-brain transmission (8,81).

Importantly, there is a bidirectional disruption in communication in PD, involving both gut-to-brain and brain-to-gut

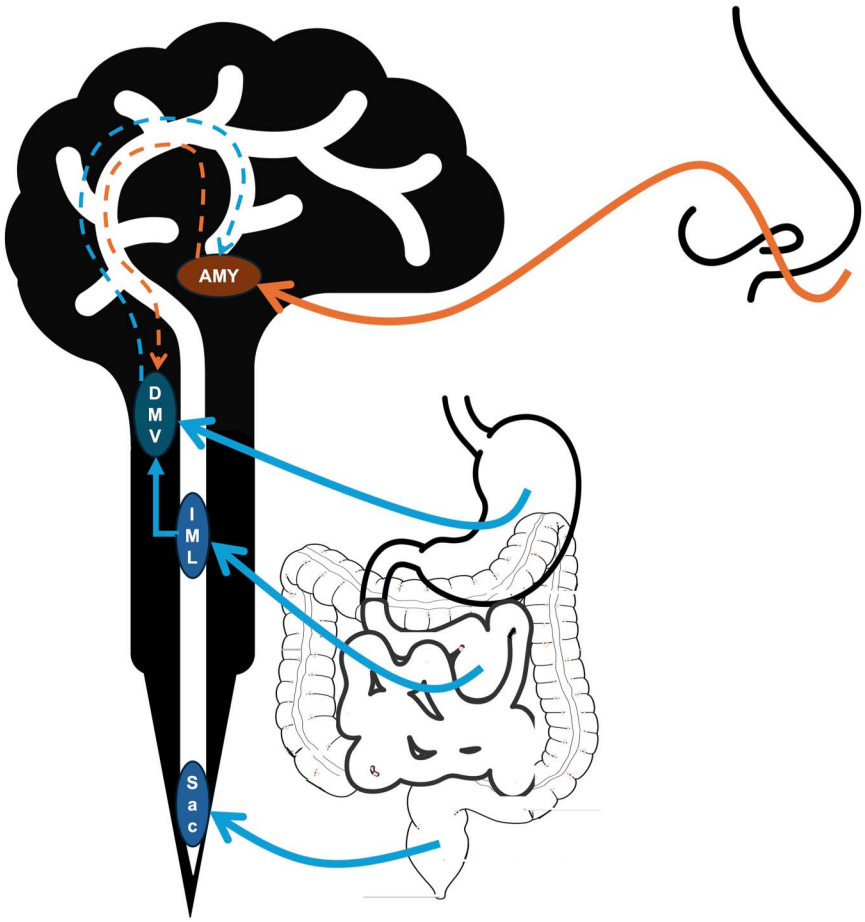

Figure 2. Neuron-to-neuron pathogenesis: Body-first and brain-first patterns of Lewy body distribution in Parkinson disease. Two-thirds of patients demonstrate a body-first pattern with more pathology in the sacral spinal cord, thoracic interomediolateral (IML) column, or dorsal motor nucleus of the vagus (DMV), which emanates from the gut. The remaining one-third of patients exhibit an amygdala-centered or brain-first distribution with more pathology in the amygdala, entorhinal cortex, and substantia nigra that is believed to originate from the nose.

aberrations that could involve promotion of pathology by non-neuronal mediators. Gut dysbiosis is a key feature of PD; the proinflammatory profile in PD is not unique to PD but the PD-associated microbiota profile is consistently characterized by low relative abundance of short-chain fatty acid (SCFA)-producing taxa and increased relative abundance of proinflammatory pathobionts that can promote neuroinflammation and neurodegeneration (90). Several niches of gut microbiota, including luminal (i.e., stool) and mucosa-associated, are altered in PD (91). Exact localization of these pathobionts promoting inflammation is important (91–93). The decreased abundance of SCFA-producing taxa and associated low SCFA levels may contribute to disruption of intestinal and blood-brain barrier, promoting both systemic and neuroinflammation (92–101).

Recent early studies of microbiota-directed interventions are beginning to demonstrate a causal link between microbiota dysbiosis and PD pathogenesis. Beneficial changes in the intestinal microbiome and improved intestinal barrier function were associated with reduced inflammation and PD symptom improvement (102). Another small study found that probiotics (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus royi*, and *Limosilactobacillus fermentum*) positively affected oxidative stress and PD motor function (103). In an open-label, proof-of-concept study of small sample size, prebiotic supplementation was associated with improved gut barrier integrity, reduced gut and systemic inflammation, and improved GI and motor symptoms (102). Several studies have attempted to improve dysbiosis through fecal microbiota transplantation (FMT). Colonization of patients with PD with non-PD stool microbiota community improves motor symptoms. Healthy donor stool administered to patients with early-stage PD (Hoehn and Yahr stage 2) using a nasojejunal tube improved motor symptoms off medications after 12 months in a single-center RCT (104). However, FMT of healthy donor stool administered by colonoscopy failed to improve motor symptoms in patients with mild-to-moderate PD (Hoehn & Yahr stages 1–3), with bowel cleansing having potentially confounded this study (105). Orally administered, lyophilized stool with repeated administration twice weekly for 12 weeks from healthy donors improved diversity of microbiome and gut transit in patients with mild-to-moderate PD and constipation in a small RCT (106).

Neuromodulation approaches may also be useful. Stimulation of the abdominal vagal fibers and amygdalar-vagal-glandular circuit could trigger Brunner glands in the duodenal submucosa to modulate the intestinal microbiome (107). Vagal nerve stimulation also activates cholinergic anti-inflammatory pathways (108). High-frequency transauricular vagal nerve stimulation, which involves surface electrodes placed near the ear (i.e., cymba concha) to stimulate the auricular branch of the vagus, improves gait and anxiety in early-phase studies of PD (109–111). Thoracic neuromodulation, a promising treatment of diabetic gastroparesis that uses repetitive magnetic stimulation targeting the spinal nerves, may also hold promise for GI symptoms in PD (112).

In summary, human studies demonstrate a strong link between gut microbiome dysbiosis and PD progression. Interventions such as probiotics, prebiotics, and FMT show promise in improving PD symptoms by modulating the microbiome. In addition, neuromodulation offers further therapeutic avenues.

Evidence from animal studies

Multiple rodent microbiota-directed interventional studies support the microbiota's role in PD. For example, an α-synuclein transgenic mouse model of PD that exhibits decreased PD-like pathology after treatment with antibiotics displays PD pathology when the mice are colonized with stool from patients with PD (90). Other studies also show that reduction of the microbial burden by antibiotics or change in microbiota community with probiotics or prebiotics influences PD-like outcomes. In addition, stress associated with microbiota dysbiosis and intestinal barrier dysfunction promotes parkinsonism induced by the pesticide rotenone, possibly through a mechanism including increased systemic and neuroinflammation (99). The parkinsonism associated with rotenone can be reversed by colonizing mice with stool specimens without rotenone exposure (113), consistent with observations that the microbiota can either potentiate or mitigate PD at least in part because of the Toll-like receptor 4 receptor (114). Data from several animal studies also show that modifying the microbiota by probiotics, prebiotics, or FMT can affect PD-like outcomes in mouse models (115–117). Taken together, rodent studies consistently demonstrate that gut microbiota significantly influences PD-like pathology and PD-like outcomes.

LIMITATIONS OF GI-BASED PD SCREENING

Colonoscopy and endoscopy cannot screen for prodromal or early PD with sufficient accuracy to be clinically useful. First, the body-first vs brain-first concept suggests many individuals do not have primary GI disease. Second, although α-synuclein staining in gastrointestinal biopsies has shown promise to identify early PD-like pathology (118–120), fundamental issues concerning the inability of mucosal biopsies to sample enteric neurons, ganglia, or supporting cellular structures and challenges associated with distinguishing physiologic vs pathological α-synuclein prevent standard GI-based evaluations for diagnosing PD or prodromal PD (121–126). Seed amplification assays may be promising tools to refine PD staging by detecting pathological α-synuclein in cerebrospinal fluid, although these techniques are not yet integrated into standard staging models (127). Future studies to evaluate the sensitivity/specificity of seed amplification assays of endoscopically obtained intestinal mucosa samples are required to determine whether a gut-based biomarker has a promise for early PD diagnosis and risk stratification.

CURBSIDE CONSULT: THE PD PATIENT WITH CONSTIPATION

Constipation affects 60%–70% of patients with PD, with more than a third frequently expressing significant concern about this symptom (5,8,128). As one of the earliest nonmotor symptoms, constipation may precede motor symptoms by 20 years with higher risk of PD development associated with increasing severity of constipation (6,7,129). However, its high prevalence and nonspecific nature limit its predictive utility in clinical settings. Constipation in PD is associated with multiple physiological abnormalities, including slow colonic transit, a lack of anorectal coordination (i.e., dyssynergic defecation), and rectal hyposensitivity (130,131). These factors collectively present a challenging clinical scenario, particularly because management strategies are often constrained by the absence of robust placebo-controlled, RCTs. Existing studies assessing mechanism of GI symptoms/dysfunction in PD are hindered by less than optimal and accepted enrollment criteria, heterogeneous methodologies, and inconsistent outcome measures, which may contribute to mixed results (Table 1) (132–139). For example, RCTs evaluating probiotics are plagued by use of unvalidated questionnaires (137),

Table 1. Summary of Randomized Controlled Trials evaluating interventions for constipation in Parkinson disease

Citation	Intervention	Constipation inclusion criteria	Sample size	Outcome measures	Results	Lead-in period	Study duration	Adverse effects
Hatano et al 2024 (135)	Elobixibat	Rome IV criteria	Elobixibat group n = 38 Placebo group n = 39	# SBMs/wk on stool diary	Did not meet 1° end point ΔSBMs/wk Elobixibat: +1.7; placebo: +0.8	2 wk	4 wk	Diarrhea and abdominal pain (55.3%)
Camilleri et al 2022 (136)	ENT-01, squalamine phosphate that inhibits α-synuclein aggregation	Rome IV criteria AND <3 CSBMs/wk	ENT-01 group n = 93 Placebo group n = 57	# CSBMs/wk on stool diary	Met 1° end point ΔCSBMs/wk ENT-01: +2.5; placebo: +0.5	2 wk	6 wk	Nausea (34.4%); Diarrhea (19.4%)
The Parkinson's study group 2017 (134)	Relamorelin	Rome III criteria AND less than 3 bowel movements per wk	Did not meet recruitment goal of 56 Relamorelin sc inj daily n = 10 Placebo n = 18	# SBMs/wk on stool diary	Did not meet 1° end point ΔSBMs/wk Relamorelin: +0.2 Placebo: +0.1	2 wk	2 wk	Headache (20%)
Ibrahim et al 2020 (137)	Multistrain probiotic (Hexbio)	Rome III criteria	Probiotic group n = 22 Placebo group n = 26	Garrigues questionnaire	Met 1° end point Mean weekly bowel opening frequency Probiotic: +2.11 Placebo: +0.85	2 wk	8 wk	Bloating, dizziness (14.8%)
Tan et al 2021 (138)	Multistrain probiotic	Rome IV criteria AND < 3 CSBMs/wk	Probiotic group n = 34 Placebo group n = 38	# SBMs/wk on stool diary	Met 1° end point ΔSBMs/wk during last 2 wk Probiotic: +1.0 Placebo: 0.3	2 wk	4 wk	Lethargy (2.9%)
Du et al 2022 (139)	Multistrain probiotic	Rome III criteria	Probiotic group n = 34 Placebo group n = 38	# CSBMs/wk based on patient recall during clinical evaluation	Met 1° end point ΔSBMs/wk during last 2 wk Probiotic: +1.09 Placebo: +0.04	2 wk	12 wk	Lethargy (2.9%)
Zangaglia et al 2007 (132)	Isosmotic Macrogol Electrolyte Solution (MC-ES)	Rome II criteria	MC-ES n-29 Placebo n = 28	Responder rate Responder = >marked improvement of predominant symptom AND at least one other Rome II criteria	Met 1° end point Responder rate MC-ES: 80.0% Placebo: 30.4%	Length not reported	8 wk	Nausea, diarrhea (6.9%)
Ondo et al 2012 (133)	Lubiprostone	Rome II criteria AND constipation rating Scale >10	Lubiprostone n = 27 Placebo n = 27	% Marked or very marked clinical global improvement	Met 1° end point >Marked clinical global improvement Lubiprostone: 64% Placebo: 18.5%	2 wk	4 wk	Loose stools (48%)

CSBMs, complete spontaneous bowel movements; inj, injection; SBMs, spontaneous bowel movements; sc, subcutaneous.

suboptimal end points such as number of spontaneous bowel movements instead of complete spontaneous bowel movements per week (138), or flawed by recall bias (139). Small intestinal bacterial overgrowth (SIBO), defined by hydrogen breath tests and associated clinical symptoms of bloating and abdominal discomfort, has a high prevalence in PD; however, studies defining SIBO prevalence using the gold standard of jejunal aspirates are lacking (140–144). SIBO in PD is often characterized by frequent relapses after treatment, necessitating a comprehensive, multifaceted management approach. The bacterial composition of SIBO in PD also may mirror PD dysbiotic microbiota with increased abundance of *Lactobacillus* and *Enterococcus fecalis*. These bacteria contain the enzyme tyrosine decarboxylase, which can metabolize levodopa to dopamine, compromising its absorption from the intestine (145). Dopamine, unlike levodopa, cannot pass through the blood-brain barrier, and therefore, dopamine decarboxylase inhibitors such as carbidopa are coadministered with levodopa to optimize absorption. However, dopamine decarboxylase inhibitors are unable to inhibit bacterial tyrosine decarboxylase. In addition to improvement of abdominal symptoms, effective treatment of SIBO may reduce bacterial abundance and also improve levodopa CNS delivery. Furthermore, the use of *Lactobacillus* probiotics should be cautioned in the absence of supporting data from robust RCTs showing any beneficial effects on PD disease course. Other agents, including those outlined in society guidelines for chronic idiopathic constipation or IBS with constipation, may be considered in clinical practice (146,147). For patients with coexisting upper GI symptoms, such as nausea, prucalopride, a serotoninergic, panenteric, promotility agent, may provide added benefit for foregut symptoms. Importantly, metoclopramide, a dopamine antagonist with promotility properties, is contraindicated in PD because of its potential to exacerbate motor symptoms (143). In cases where abdominal pain and bloating predominate, secretagogues, such as linaclotide and plecanatide, or the sodium/hydrogen exchanger inhibitor tenapanor may be effective (148–151). Elderly and frail patients with PD need special attention, because coexisting fecal incontinence may complicate the clinical picture and require tailored interventions (152,153). Dyssynergic defecation, present in 90% of PD constipation, calls for specialized management (130,154). Expertise in biofeedback or pelvic floor physical therapy should be sought. Although these interventions have been studied for urinary symptoms in PD, they remain uninvestigated in this cohort (155). A personalized, symptom-directed approach that considers the full spectrum of GI dysfunction is critical in optimizing the management of constipation in PD and can be achieved by coordinating care between neurologists and gastroenterologists.

CONFLICTS OF INTEREST

Guarantor of the article: Amol Sharma, MD, MS, FACG.

Specific author contributions: A.S. contributed to the conception and design of the work (equal), extensive literature review (lead), initial draft of the manuscript (lead), and critical review for intellectual content (equal). R.M.V., C.G.G., and A.K. contributed to the conception and design of the work (equal) and critical review for intellectual content [equal]. All authors have approved the final version of the manuscript submitted.

Financial support: The authors (A.S., R.M.V., C.G.G., A.K.) are supported by NIDDK U01-DK140923. R.M.V. is supported by NIA R01-AG056653. The Rush Parkinson's Disease Program is a designated Parkinson's Foun dation Center of Clinical Excellence.

Potential competing interests: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. A.K. is a co-owner of RiteCarbs LLC that developed SCFA promoting prebiotic fiber mixture used in a PD study quoted in this review.

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