Review Article

Evaluating the Scope of Gastrointestinal Symptoms of Parkinson’s Disease: A Review of the Evidence

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Abstract Gastrointestinal (GI) symptoms are among the most common nonmotor manifestations of Parkinson’s disease (PD), and they have many important consequences for patients. Virtually all parts of the gastrointestinal tract can be affected, in some cases early in the disease course or even predating clinical PD. The main focus of this review is a discussion of the clinical presentation, evaluation, treatment options, pathology, and etiology of individual GI symptoms in humans. Dysphagia can predispose individuals to aspiration. Gastro-esophageal reflux disease can result in nausea, vomiting, and bloating and lead to erratic absorption of levodopa. Slow colonic transit can lead to constipation and anorectal dysfunction leads to difficulty evacuating the bowel. GI symptoms in PD patients, among the most common of which are gastroparesis, constipation, and anorectal dysfunction leads to difficulty evacuating the bowel. These symptoms have many important consequences for patients. Virtually all parts of the GI system can be affected, in some cases early in the disease course or even predating clinical PD. The main focus of this review is a discussion of the clinical presentation, evaluation, treatment options, pathology, and etiology of individual GI symptoms in humans. Dysphagia can predispose individuals to aspiration. Gastro-esophageal reflux disease can result in nausea, vomiting, and bloating and lead to erratic absorption of levodopa. Slow colonic transit can lead to constipation and anorectal dysfunction leads to difficulty evacuating the bowel. GI symptoms in PD patients, among the most common of which are gastroparesis, constipation, and defecatory dysfunction. These symptoms have been shown to be much more prevalent than previously thought with much higher rates demonstrated when compared to healthy controls. Rapid fluctuations in clinical state (the “on-off” phenomenon) can occur while on levodopa treatment and become more apparent with disease progression. As time progresses, the effectiveness of levodopa treatment gradually declines [3]. Dopamine agonists are another potential treatment to be considered.

Keywords Parkinson’s disease; dysphagia; gastroparesis; constipation

1. Introduction

Parkinson’s disease (PD) is a progressive neurodegenerative disease of the central nervous system. PD is characterized by the presence of severe loss of dopamine-generating cells in the substantia nigra pars-compacta of the basal ganglia. Lewy bodies are the pathological hallmark of PD; they consist of aggregations of α-synuclein and are found in the spinal cord, brain stem, and cortical regions. The main risk factor for PD is age. The prevalence of PD rises steeply with age and it is predominantly a disease of an aging population. It is estimated that the lifetime risk of acquiring PD in a western country nears 1.5% [1], with a median age of onset of 60. Other risk factors include genetics, especially mutations in LRRK-2, α-synuclein, and parkin. The exact cause of death can be quite difficult to identify, but pneumonia is the most commonly cited certification.

The cardinal motor symptoms are bradykinesia, rigidity, resting tremor, and postural instability. The diagnosis is primarily clinical with imaging helping to rule out other differentials. Furthermore, PD leads to a variety of motor and nonmotor symptoms [1] but remains currently incurable; the mainstream of therapy concentrates on management of symptoms and dopamine replacement therapy. This is done using levodopa in combination with a peripheral dopa decarboxylase inhibitor. This is the single most effective treatment for PD since its introduction decades ago [2]. The majority of patients respond well with improvements seen in the motor symptoms within around three weeks. Levodopa is tolerated well but long-term use is linked to involuntary writhing movements (dyskinesia’s), which are linked to duration of treatment and occur in the majority of patients within two years. Rapid fluctuations in clinical state (the “on-off” phenomenon) can occur while on levodopa treatment and become more apparent with disease progression. As time progresses, the effectiveness of levodopa treatment gradually declines [3]. Dopamine agonists are another potential treatment to be considered.

There are a variety of nonmotor symptoms exhibited by PD patients, among the most common of which are gastrointestinal (GI) symptoms. In his original description of PD in “An essay into the shaking palsy,” James Parkinson clearly describes a variety of GI symptoms [4]. It is recognized today that abnormalities in function exist at virtually all levels of the GI system. The most common GI symptoms in PD are weight loss, sialorrhea, dysphagia, gastroparesis, constipation, and defecatory dysfunction. These symptoms have been shown to be much more prevalent than previously thought with much higher rates demonstrated when patients are directly questioned. The enteric nervous system (ENS) has been shown to be involved in the pathogenesis of PD with α-synuclein histopathology demonstrated in biopsies [2]. It has been suggested that the ENS may actually be the post of entry of the process that leads to PD [3]. This is known as the “Braak hypothesis.” The main focus of this review is a discussion of the clinical presentation, evaluation, treatment options, pathology, and etiology of individual GI symptoms in patients with PD.
2. Oral health status
PD patients suffer from a generalized increase in oral health problems, such as loss of teeth, chewing difficulty, and increased dental caries [5]. It is thought that difficulty with repetitive motions necessary for brushing and a jaw tremor and rigidity all contribute to the increased periodontal pathology seen in PD [6]. A variety of different problems have been described such as temporomandibular joint dysfunction [7] and increased prevalence of burning mouth syndrome [8]. No specific treatments have been properly evaluated, but increased regular assessment of dental status in PD is advised. The literature on this topic is quite conflicted with some studies concluding that PD patients have better oral health [9]. Further studies are required to elucidate the true role of PD on oral health.

3. Sialorrhea
Sialorrhea or the presence of excess saliva within the mouth is evident in many persons with PD. Survey studies indicate that drooling affects up to 78% of PD patients as compared to only 6% of controls [10,11]. Sialorrhea has a propensity to affect male [12] patients and those with clinical dysphagia [10]. The literature suggests that drooling in PD does not result from excess saliva production; on the contrary, saliva production is actually decreased in the setting of PD [13,14]. Drooling is instead a result of diminished frequency and reduced efficiency of swallowing [15]. It is probably worsened by stooped posture and the tendency for the mouth of PD patients to remain open [16].

In addition to being socially embarrassing, sialorrhea can lead to aspiration and subsequent pneumonia. There is also a link between drooling and a decreasing quality of life with up to 77% of patients stating that it affects their psychosocial wellbeing [17]. The link between increasing age and increasing prevalence of sialorrhea in PD is tenuous with mixed results [18].

3.1. Etiology of sialorrhea
There is prominent involvement of the submandibular gland in PD [19]. Biopsies show that the submandibular glands and cervical ganglion express Lewy bodies [20]. This may contribute to the mechanistic cause of sialorrhea in PD.

3.2. Diagnostics
Sialorrhea is defined as saliva beyond the margin of the lip. Quantification of salivary flow is difficult because many factors such as eating, talking, stress, and time of day change the flow rate. There is currently no gold standard diagnostic test for drooling. The most popular methods used are subjective questionnaires, but objective measure such as salivary gland cannulation [21,22], salivary gland scintigraphy [23], and spit collection [24] have also been used. The lack of standardization in the definition of drooling and measurements and tests used to quantify it has resulted in a large heterogeneity of results. Estimates for the prevalence range from 30% to 74% [21] and these are estimated using a variety of different methods. The different methodologies and study designs used make comparison between studies extremely difficult.

3.3. Treatment
Several treatment approaches may be employed in the management of reducing saliva accumulation. Both pharmacological and nonpharmacological measures are effective, although the focus of the literature tends to be pharmacological.

3.3.1. Pharmacological treatments
Systemic oral anticholinergic medications have proven effective [25]. Glycopyrrolate is the drug of choice due to its inability to cross the blood-brain barrier in significant amounts, making it less likely to cause central side effects [25]. Anticholinergics pose the risk of producing adverse effects such as constipation, urinary retention, and cognitive impairment. The side effect profile may be unacceptable to PD patients already suffering from constipation. Alternatively administration of topical anticholinergics such as sublingual atropine [26] or ipratropium bromide [27] may still provide benefit while diminishing systemic side effects. Botulinum toxin (A or B) injections into the salivary glands have been shown to reduce saliva production, although injections must be repeated periodically. There is neither a standard technique for injecting the salivary glands nor agreement on the optimal dose for treating sialorrhea [15].

3.3.2. Nonpharmacological treatments
The simple maneuver of chewing gum or hard candy can be used to encourage swallowing and reduce drooling in social situations [28]. This can be effective in some patients with mild symptoms, albeit it depends largely on patient self-motivation. It is also difficult to employ this treatment continuously.

Radiotherapy has been proposed as a possible treatment, this is largely due to its recognized side effect of causing a dry mouth when treating head and neck cancers. The initial results from using radiotherapy are largely positive with a 64% satisfactory response rate [29]. It is proposed that radiotherapy be reserved for patients in whom the risk of inducing neoplasm is less than the benefit of avoiding anticholinergic medication or surgery.

Surgical treatment options include tympanic neurectomy, which includes possible complications such as loss of taste over the anterior two-thirds of the tongue and hearing loss. The long-efficacy of these treatments has been questioned [30].
4. Dysphagia
Swallowing requires highly coordinated serial contractions and relaxation of numerous muscles in the mouth, pharynx, and esophagus. The prevalence of dysphagia varies drastically in the literature, from as low as 30% to as high as 100% [31,32]. All the stages of swallowing, oral, pharyngeal, and esophageal may be affected in PD. The oral phase is the most commonly affected and where the majority of the literature centers. In the oral phase rigidity, bradykinesia, and even tremor of the tongue and oral musculature may impede bolus formation and slow oral transit time [33]. In the pharyngeal phase, pharyngeal dysmotility, pharyngeal and vallecular stasis, and repetitive reflux from the vallecular and pyriform sinuses into the oral cavity can occur [34]. Esophageal abnormalities seen are represented by slowed esophageal transit, repetitive contraction, decreased lower esophageal sphincter (LES) pressure and esophageal dilation [35]. The majority of patients with early-stage PD actually show pharyngeal and esophageal dysfunction even before the clinical manifestation of dysphagia [31].

Physically dysphagia can lead to anorexia and may be a contributing factor to the weight loss seen in PD [36]. It may also lead to aspiration (accidental inhalation of food or liquid) and resultant pneumonia and death. Pneumonia is one of the main causes of death in PD patients [37], and the mean survival period once clinical dysphagia is present may be less than two years [38]. Frequencies of aspiration range widely from 15% to 66%. In terms of psychological burden, dysphagia is strongly linked to an increased risk of depressive states [39]. Therefore, dysphagia is a strong contributing factor to a deteriorating quality of life in PD.

Typically dysphagia presents after the diagnosis of PD by several years [38]. Early onset dysphagia in PD is atypical and should alert the clinician to an alternate diagnosis of the Parkinsonism [40]. It has even been suggested that the presentation of dysphagia within a year of diagnosis virtually excludes PD as a diagnosis [38]. There appears to be no correlation between the severity of PD and swallowing problems [41].

4.1. Etiology of dysphagia
Dysphagia in PD results from impairment of any of the three phases of deglutition, most typically there is impairment of the oropharyngeal phase, controlled primarily by the nucleus ambiguus. In PD, the nucleus ambiguus is spared, but the pedunculopontine tegmental nucleus and the dorsal motor nucleus of the vagus nerve are not [42]. The exact nature of dysphagia in PD is unclear, but it has been proposed that it may reflect impaired activity of suprabulbar motor pattern generators [43]. Lewy bodies have been discovered within the esophageal myenteric plexus. This finding suggests that some elements of esophageal dysphagia in PD result directly from damage to the enteric nervous system [44].

4.2. Diagnostics
Survey studies that measure subjective patient report are a poor indicator of the presence of dysphagia, with objective measures such as the modified barium swallow (MBS) consistently reporting a higher prevalence of dysphagia [45]. This is because a large number of patients with PD show silent aspiration but do not complain of dysphagia [46]. A meta-analysis of the literature shows that while 33% of patients may self-report dysphagia, 80% of patients actually show some objective degree of oropharyngeal dysphagia [47].

Patients with self-reported dysphagia but a normal MBS should undergo further investigations for esophageal dysphagia such as manometric studies or videofluoroscopic studies. These studies consistently demonstrate abnormalities within the esophagus such as a high incidence of esophageal dilation even within asymptomatic patients [48]. There is growing evidence that esophageal dysfunction predates most cases of clinical dysphagia [48].

4.3. Treatments
Dysphagia is difficult to treat in PD, with no universally effective treatment approach identified. This has resulted in a variety of different treatment approaches in the literature ranging from simple swallowing advice to surgical and pharmacological methods. The diverse outcome parameters employed makes it extremely problematic to directly compare different treatment methods [49].

There has been some interest in the use of dopaminergic medication with responsiveness demonstrated by some investigators in a minority of patients [50,51]. On the other hand, several studies have reported no response to treatment [34,52]. This lends credit to the theory that dysphagia in PD is not mediated solely by dopaminergic deficiency. Elucidating the factors eliciting response and quantification of the response is an area of future research.

Nonpharmacologic techniques such as swallowing maneuvers [53] or adopting a dysphagia diet may also be useful for some individuals. A Cochrane review has concluded that there is no evidence to support or refute the efficacy of nonpharmacological therapy. This is largely due to the absence of randomized control trials and methodological shortcoming within the literature [54].

Deep brain stimulation has received mixed results in the literature. While some articles directly state that it can itself worsen dysphagia [55], other articles advocate it as a viable treatment option [56]. To add to the confusion, other research has concluded that there is no effect from it on deglutition in PD [57]. The general uncertainty in the literature in regards to this topic has resulted in deep brain
stomach distension in PD. Gastroparesis can also cause other troublesome problems such as abdominal pain and weight loss. Even at an early stage of PD, signs of gastroparesis have been found [59]. It has even been proposed that signs and symptoms of gastroparesis can predate the neurological symptoms of PD [60].

Gastroparesis is widely prevalent in PD patients; the literature indicates that the rate for asymptomatic gastroparesis could be as high as 100% [61]. However, the prevalence of symptomatic gastroparesis is currently unknown. A problem encountered when elucidating the true prevalence in the literature of PD is the lack of a set definition of gastroparesis. The most widely accepted definition (from the National Institute of Diabetes and Digestive and Kidney Diseases Gastroparesis Clinical Research Consortium) is the presence of appropriate symptoms (including nausea, early satiety, and abdominal distension in PD). Gastroparesis can also cause other troublesome problems such as abdominal pain and weight loss. Even at an early stage of PD, signs of gastroparesis have been found [59]. It has even been proposed that signs and symptoms of gastroparesis can predate the neurological symptoms of PD [60].

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Gastroparesis in individuals with PD has profound pharmacokinetic implications. It has been shown to be one of the etiological causes of motor fluctuations in patients with PD. Delayed gastric emptying equates to a longer time spent in the stomach exposed to dopa decarboxylase, which can convert the levodopa to dopamine and render it unavailable for intestinal absorption. The main mechanism by which delayed gastric emptying contributes to motor fluctuations is by delaying or reducing the amount of levodopa transported to the jejunum—the site of levodopa absorption [64,65,66]. The clinical relevance of delayed gastric emptying in PD patients is difficult to establish. This is due to research demonstrating that gastric emptying does not differ between PD patients with and without motor fluctuations. This demonstrates that motor fluctuations in PD may not be influenced by gastric emptying [60].

5.1. Etiology of gastroparesis

While the exact pathophysiology of gastroparesis remains uncertain, the dorsal motor nucleus of the vagal nerve (DMV) is characteristically involved in PD [67]. Therefore, gastric dysmotility may reflect involvement of the DMV. Lewy bodies have been found in the myenteric and submucosal plexi of the stomach [68]. These might contribute to the GI pathology seen in patients with PD, but the precise contribution of any one of these findings to disease phenotype is very difficult to define.

5.2. Diagnostics

PD patients presenting with symptoms of gastroparesis are usually investigated using scintigraphic methods. These are the most frequently used methods for measuring gastric emptying [69]. Measurements by the 13C-sodium Octanoate breath test are also widespread in clinical practice due to their simplicity [70]. Other investigations, including ultrasonography and magnetic resonance imaging have been used [62].

A variety of different problems have been encountered in the diagnostics of gastroparesis. Firstly, there is no unified definition of gastroparesis, and although the aforementioned one is the most widely used definition, different researchers have adopted different parameters in their definition. Secondly, it is extremely difficult to compare results obtained with different techniques. This may explain why such a wide prevalence rate of gastroparesis exists. Furthermore, the interpretation of data generated with each technique is subject to variation depending on the nature of the test meal ingested. In conclusion, greater standardization is needed within the literature.

5.3. Treatment options

Several approaches to the treatment of gastroparesis in PD have been investigated. Initially treatment should be conservative focusing on dietary changes. The aims of dietary changes are to reduce symptoms and improve quality of life. It focuses on increasing the speed of gastric emptying through simple measures such as having smaller meals, avoidance of foods high in fat and fiber, and increasing fluid intake. Unlike solids, the gastric emptying of fluids is thought to be near normal [61]. To the knowledge of the authors, the gastroparesis diet has been designed using knowledge of the physiology of normal gastric emptying and has never been formally tested in a study.
Eradication of *Helicobacter pylori* (*H. pylori*) has been recommended in the setting of gastroparesis in a patient with PD. This is because it has been linked as a contributing factor to cachexia in PD and its eradication has been shown to improve nutritional status [71]. Furthermore, eradication of *H. pylori* has been shown to improve levodopa absorption [72]. Therefore eradication of *H. pylori* should be considered in the management of gastroparesis in PD.

When pharmacologic treatments are required, a variety of approaches have been investigated in an effort to accelerate gastric emptying. The mainstay are drugs that block dopamine receptors, these accelerate gastric emptying via an effect on gastric dopamine receptors [73]. The drug of choice is Domperidone, which blocks dopamine receptors but does not cross the blood-brain barrier and therefore does not exacerbate the extrapyramidal symptoms of PD, unlike Metoclopramide. Domperidone has been shown to improve both gastric emptying and symptoms of gastroparesis [74]. Prokinetic agents, such as Cisapride and Mosapride, are Serotonin 5-HT4 receptor agonist. These stimulate acetylcholine release and thus increase gastric motility. Both Cisapride and Mosapride have been shown to improve gastric emptying in patients with PD [75, 76]. Further studies have elucidated the fact that these medications help increase the plasma concentration of levodopa [77] and reduce levodopa dose failures [75]. Concerns regarding the potential side effect of cardiotoxicity have hampered widespread use of both medications.

There has been recent interest in the use of Botulinum toxin injections directly into the pyloric sphincter. The early results showed promise [78,79], but a recent systemic review has concluded there is no evidence that this is an effective treatment [80]. Further research is needed into the topic before conclusions can be reached. There are a host of other treatments that have proven effective in gastroparesis. These are all viable areas of future research. These include, but are not limited to, Erythromycin [81], which acts as a motilin agonist and gastric pacemakers [82].

Other avenues of treatment have attempted to combat the effect of delayed gastric emptying on levodopa absorption. This approach does not attempt to combat the symptoms of gastroparesis itself, but aims to improve the rate of motor fluctuations in PD. Levodopa ethylester is a levodopa prodrug that leaves the stomach more rapidly because it is more soluble. Patients treated with levodopa ethylester demonstrate a shorter time to “on” and a decrease in motor fluctuations as compared to a control group [83]. Another option is the use of continuous duodenal levodopa infusion with the aims of giving a continuous dose optimized for the patients’ therapeutic window. This is achieved either through a nasoduodenal or jejunostomy tube, and clinical evidence indicates that there is a marked reduction in motor fluctuations [84]. The widespread use of this treatment may be hampered by the technical difficulties in setting it up. Some argue that the main aim of pharmacological therapy should be on correcting the delayed gastric emptying in an effort to combat motor fluctuations, rather than focusing on the symptoms of gastroparesis. Finally, it has been demonstrated that subthalamic deep brain stimulation can improve PD gastroparesis by possibly altering the neural system that controls GI function [85].

6. Small bowel dysfunction

The literature suggests that patients have a propensity to have abnormal small intestine motor patterns on manometric studies [86]. The small intestine has been reported to be dilated in PD [87]. These abnormalities may explain the significantly higher incidence of small intestinal bacterial overgrowth (SIBO) in PD [88]. Patients with SIBO have been shown to have longer off time daily and more episodes of delayed-on and no-on. Eradication therapy has been shown to result in an improvement in motor fluctuations.

Overall, very little research has been done on the pathology of the small intestine in PD. This is due to difficulties investigating the small intestine role and difficulty identifying the clinical correlates of these changes.

7. Colonic problems

7.1. Constipation

Diminished frequency of bowel movements is considered the most common manifestation of autonomic dysfunction, and was described by James Parkinson in his original essay [4]. The actual frequency of this problem, however, is not entirely clear. It is estimated to occur in around 20% to 89% of PD patients [33]. Several studies have indicated that the severity of constipation correlates with disease severity [89]. It has been noted that severe constipation can predate the cardinal motor symptoms of PD, sometimes by many years [90,91,92]. In a further twist, a large scale epidemiological study of men has revealed an association between frequency of bowel movements and future risk of developing PD. It was found that men who had less than one bowel movement a day have a 400% increased risk of PD as compared to men having two or more. Further to this, postmortem biopsies of asymptomatic patients with late life constipation has shown incidental Lewy bodies in the substantia nigra as well as decreased neuron density [90,93]. These clinical and pathologic findings may be interpreted as showing that late life constipation may represent asymptomatic PD. It has also been suggested that constipation may be an early manifestation of PD.

The mechanism proposed to lead to constipation in PD is impairment of colonic motility leading to a slowed colonic transit time. It has been demonstrated that even in asymptomatic individuals colonic transit time is reduced [94].
Colonic transit time has been shown to be twice as long in PD patients as compared to controls [95,96]. In most people constipation produces simple discomfort, but it can also produce more serious complications. Megacolon [87,97], pseudo-obstruction and volvulus and even malignant syndrome [10,98,99,100] have all been known to occur in the setting of PD-related constipation. Colonic perforation has also been described [97]. The constipating effects of antiparkinsonian medication will be discussed in Section 8.

7.2. Etiology

The term “slow transit” constipation refers to a clinical syndrome attributable to ineffective colonic propulsion. In constipation, there is a reduction in high-amplitude propagated contractions [101]. It has been proposed that loss of neurons in the myenteric plexus in PD is the pathognomonic underlying mechanism of constipation [102]. Thus, reduced colonic transit most likely reflects involvement of myenteric neurons in PD. PD medications are also well known for causing constipation. This is discussed in further detail in Section 8.

7.3. Diagnostics

The most fundamental step in diagnosis is a thorough history taking followed by a physical examination. Questions are aimed at trying to find an underlying cause for the constipation such as medications (i.e., anticholinergics, antidepressants) and attempting to differentiate between problems defecating and those of colonic transit. Healthcare professionals need to be proactive in identifying patients with PD suffering with constipation, as many patients may not discuss their concerns [103]. Currently the most widely accepted and used criteria for constipation is the Rome III criteria shown in Table 1 [104]. There are also a variety of questionnaires and other diagnostic criteria that can be used [89]. Depending on the definition used, the prevalence of constipation in the community varies widely from 2% to 25% and averages around 15% [105].

Slow transit constipation can be distinguished from other causes of constipation using a variety of investigations, the most popular of which are marker studies of colonic transit. Marker studies involve the patient swallowing a specified number of radio-opaque capsules and abdominal X-rays are obtained at specified time periods after ingestion. The operator judges the speed of movement of the markers against the norm and this can be used to decide if the patient has slow transit constipation [96]. Scintigraphic techniques can also be used to assess slow transit constipation. In this, a radioisotope \(^{(111}\text{In DTPA})\) is ingested and dissolved in the distal ileum, releasing the radioisotope in the ascending colon. The distribution of the radioisotope is then measured using scans and can be used to identify slow transit constipation [106]. There is a reasonable correlation between radiopaque markers and scintigraphic measurements [107]. There are also a variety of other investigations that can be used, and these include anorectal manometry [108] and electromyography [109]. Other procedures, such as a barium enema, or colonoscopy, may be performed to exclude other causes of constipation in patients with PD.

The apparent lack on standardization of the criteria and diagnostic tools in investigating constipation has led to the massive prevalence range mentioned previously. It is evident that further international consensus within the literature is needed.

7.4. Treatment

There are a variety of treatment options for constipation in PD. This section will focus specifically on the management of slow transit constipation in association with PD. Treatment should begin with conservative, nonpharmacologic options and progress through gradually more complex treatment measures. Medications known to cause or exacerbate constipation should be discontinued if possible. Simple measures such as increasing dietary fiber [110] and fluid intake are usually tried first. It has been shown that daily fiber intake is deficient in many patients with PD [111]. Fiber supplementation, such as psyllium can be used next [92]. These have been shown to increase stool frequency and even motor function slightly [92]. The mechanism by which psyllium improves motor function has not been explained. A stool softener such as docosate may also be beneficial. This can be used in combination with fiber and psyllium, or by itself. These measures are efficient in patients with mild constipation in PD, but most patients require further pharmacological treatment.

The addition of laxatives, typically osmotic laxatives, is usually the first pharmacological choice. Polyethylene glycol (Macrogol) is an osmotic laxative that has been specifically studied for PD and found to be highly effective. It has been shown to increase frequency of bowel movements and stool consistency [112,113]. Enemas may be necessary at times but should not be used routinely.

Table 1: Rome III criteria for functional constipation adapted from [103].

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<th>Rome III criteria for functional constipation [104]</th>
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<td>They must include two or more of the following:</td>
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<tr>
<td>• Infrequent passage of stools (&lt; 3 defecations/week)</td>
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<tr>
<td>• Lumpy or hard stools*</td>
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<tr>
<td>• Straining*</td>
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<tr>
<td>• Sensation of incomplete evacuation*</td>
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<tr>
<td>• Sensation of anorectal obstruction/blockage*</td>
</tr>
<tr>
<td>• Manual maneuvers to facilitate defecation (e.g., digital evacuation, support of the pelvic floor)*</td>
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Symptoms must be present for 12 weeks.
*Present in = 25% of defecations.
The role of prokinetic agents in the treatment of PD associated constipation has been investigated. Domperidone and 5-HT4 receptor agonists such as Tegaserod, Mosapride, and Cisapride have been investigated. Domperidone’s prokinetic effects appear confined to the upper intestinal tract and have failed to show any efficacy in the management of constipation [114]. While the 5-HT4 receptor agonists have shown efficacy [115,116,117,118], their propensity to cause cardiotoxicity has limited their use severely. Nizatidine (an H2 receptor antagonist) has demonstrated some promise [119]. Furthermore, beta-blockers have been proven effective in reducing constipation [120]. Novel treatment options such as probiotics have been shown to increase stool consistency and bowel frequency in PD [111]. Lubiprostone is currently under investigation as a potential treatment option, and the initial results appear promising in improving the symptoms of constipation [121,122]. There are a variety of potential treatment avenues to be investigated in the future in relation to constipation in PD. These treatments have all shown promise in the treatment of constipation in a variety of studies, but have not been specifically investigated in PD. These include biofeedback and rectal irrigation techniques. In addition, Linaclootide, Prucalopride, and sacral nerve stimulation need formal investigation in relation to PD.

Surgical treatment is indicated in the management of rare complications such as megacolon or volvulus [97,98].

7.5. Anorectal dysfunction

Difficulty defecating is a much more prevalent form of bowel dysfunction in PD than constipation. Defecatory dysfunction is characterized by pain, excessive straining, and a feeling of incomplete evacuation during defecation [11]. This can occur very early in the course of PD [35] and affects up to 67% of patients with PD [11]. In order for effective anorectal function to occur, several muscles need to contract in a coordinated fashion. Defecatory dysfunction in PD results from dysfunction of the rectal muscles. It has been shown that there is a paradoxical contraction of the voluntary sphincters during defecation leading to marked difficulties in rectal evacuation [123]. A variety of other sphincter abnormalities have also been recorded in PD patient including lower basal sphincter pressure, difficulty in sustaining sphincter pressure, and unusual phasic contractions of the sphincter during voluntary contractions [124, 125]. Anorectal dysfunction was originally described as a form of focal dystonia [123], and this hypothesis has been supported by several pieces of work [126,127].

7.6. Etiology of defecatory dysfunction

As with many of the GI symptoms of PD, the exact pathophysiology of defecatory problems are not fully understood, and are likely to be multifactorial. However, aggregations of alpha-synuclein have been found in the sacral parasympathetic nucleus and the pelvic ganglia [128,129]. Impaired defecation may reflect the disturbance cause by these inclusions.

7.7. Diagnostics

There are no routine studies or guidelines in the investigation of anorectal dysfunction. There are a variety of investigations used such as anorectal manometry, anal sphincter electromyography, and fluoroscopic defecography. None of these investigations are routinely available or used due to their complexity.

Anorectal manometry consists of a series of measurements that include the assessment of the anal sphincter function, cough reflex, rectal sensation, recto-anal inhibitory reflexes, and rectal compliance [130]. Three types of abnormalities can be recognized: paradoxical anal contraction (i.e., paradoxical elevation of the resting anal pressure), impaired anal relaxation (i.e. unchanged resting anal pressure), or both [131]. Defecography is used for visualization of the anal canal and rectum. This test provides useful information on the anatomical and functional changes of the anorectum [132]. Electromyography studies can provide information on the electrical activities during straining at stool. There are also a variety of other techniques such as magnetic resonance defecography and high-resolution anorectal manometry. These may enable more specific investigations of anorectal dysfunction [133].

7.8. Treatment

Management of defecatory dysfunction has proven more challenging than slow transit constipation. This is due to the fact that no specific treatment has been extensively studied or proven to be unequivocally effective. The use of routine laxatives and stool softeners has not been shown to be effective and can actually worsen the problem [134]. Dopaminergic medication might be of some benefit as improvement has been noted manometrically during “on” periods [124]. Apomorphine is a dopamine agonist that has received considerable interest as a treatment option. Subcutaneous Apomorphine injections have been proven to improve defecatory dysfunction in PD significantly [123,135]. The role of biofeedback in the treatment of defecatory dysfunction in PD has not been investigated. Levodopa itself has been demonstrated to augment rectal contraction and lessen paradoxical sphincter contraction, thereby helping ameliorate anorectal constipation in PD patients [136].

Botulinum toxin injections into the puborectalis muscle under ultrasound have produced positive results [137]. It reversibly weakens the external sphincter and facilitates rectal emptying. The main disadvantages of this treatment are that results typically last several months [138] before needing to be repeated, that the procedure itself is technically difficult, and that treated patients have an increased
rate of fecal incontinence. More effective and practical treatments for defecatory dysfunction are needed. There are a variety of treatments that have proven effective in anorectal dysfunction, but have not been specifically trialled for anorectal dysfunction in PD. These include sacral nerve stimulation, rectal irrigation, and various pharmacological options. These are potential avenues of future research.

8. Gastrointestinal side effect profile of antiparkinsonian medications

Almost all PD medication have been described as causing or worsening constipation [139], the worst and most infamous offenders are anticholinergic medications and levodopa itself [140]. Anticholinergics are used in PD in the management of sialorrhea, but the ability of anticholinergics to potentiate constipation in PD is a definitive drawback. Healthcare professionals have to effectively communicate with patients and balance the benefits of alleviating the drooling as compared to the potential to worsen the constipation [141].

Nausea and vomiting are very common side effects of dopaminergic medication, which can make it difficult to differentiate between the symptoms of gastroparesis and the medication itself. Dopaminergic medication has also been shown to inhibit upper gastrointestinal motility [142], and therefore may worsen the underlying symptoms of gastroparesis. The effect of dopaminergic medication and deep brain stimulation on dysphagia is controversial and was discussed in Section 4. Finally, deep brain stimulation has been linked to increased body weight [143].

9. Conclusion

Gastrointestinal manifestations of PD are highly prevalent and problematic for patients. They are often underreported and undertreated, and present the patient with considerable morbidity. More research is needed to elucidate the underlying etiology and best management guidelines for these symptoms. In recent years, there have been several excellent reviews in the literature on the GI manifestations of PD [33, 134, 141, 144].

Conflict of interest  The authors declare that they have no conflict of interest.

References


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