EXPERT OPINION

Management of constipation in Parkinson's disease

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Introduction: Constipation is a frequent non-motor feature of Parkinson's disease (PD). It is the most common gastrointestinal symptom of the disease and it can precede motor symptoms by as much as 20 years. Constipation can produce discomfort and affect activities of daily living, productivity and quality of life, thus warranting early diagnosis and treatment.
Areas covered: In this review, the safety and efficacy of traditional and novel strategies for constipation management will be discussed. A treatment algorithm for constipation in PD will be presented.
Expert opinion: Polyethylene glycol and lubiprostone are first-line compounds recommended by evidence-based medicine guidelines for the treatment of constipation due to slow colonic transit in PD. Management of constipation secondary to defecatory dysfunction due to pelvic floor dyssynergia can be done by levodopa or apomorphine injections, botulinum toxin type A injection into the puborectalis muscle, and nonpharmacological interventions, like biofeedback therapy or functional magnetic stimulation, which showed some benefit in PD patients with constipation, but in general more extensive studies are warranted.

Keywords: algorithm, constipation, gastrointestinal, lubiprostone, Parkinson's disease, polyethylene glycol

Expert Opin. Pharmacother. [Early Online]

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder following Alzheimer's disease and involves dopaminergic and non-dopaminergic systems [1]. It is a progressive disease that leads to serious consequences on the function and quality of life of patients and their caregivers [2]. It is mainly recognized by its cardinal motor signs: bradykinesia, rigidity, rest tremor and postural instability, although other secondary motor features, such as hypomimia, dysarthria, dysphagia, micrographia, shuffling gait, festination, freezing and dystonia, are also common [3]. Non-motor symptoms are common during all stages of the disease, and frequently go under-recognized [4]. In many cases they develop before the onset of the cardinal motor features, which has been defined as the prodromal or premotor phase of PD and estimated to precede for about 5 – 20 years [5-7].

Gastrointestinal dysfunction is probably the most frequent non-motor feature of PD [8]. It was early identified and described in the monograph "An Essay on the Shaking Palsy," by James Parkinson in 1817 [9]. All parts of the gastrointestinal tract can potentially be compromised, producing for example, sialorrhea, dysphagia, gastroparesis, constipation and defecation disturbances, which may lead in many cases to weight loss and erratic absorption of drugs [10]. Constipation is the most common gastrointestinal disturbance in PD, with a prevalence lower than traditionally assumed (up to 60 – 70%), being currently estimated between 20 and 29% [11-13]. Epidemiological studies have shown that constipation can precede motor symptoms

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Article highlights.

- Constipation is a frequent and troublesome feature of Parkinson's disease (PD).
- Constipation in PD is related to slow colonic transit and defecatory dysfunction.
- Treatment of constipation due to reduced colonic transit should be initiated by nonpharmacological measures, including changes in lifestyle. Pharmacotherapy might include polyethylene glycol or lubiprostone. Rescue therapy by rectal laxatives might be necessary.
- Pharmacotherapy for defecatory dysfunction might include levodopa or apomorphine injections, botulinum toxin A injections into the puborectalis muscle and nonpharmacological interventions, like biofeedback therapy or functional magnetic stimulation.
- Trials for constipation in PD should be double-blind, randomized and placebo-controlled, should only including patients fulfilling ROME III criteria, should use frequency of stools as primary outcome endpoint, and should have a duration of at least 12 weeks.

This box summarizes key points contained in the article.

by as much as 20 years [14,15], with a relative risk of 2.34 (95% CI 1.55 – 3.53) of a later diagnosis of PD [16]. Constipation in PD arises from decreased bowel movement frequency (slow colonic transit) and/or defecatory dysfunction.

Constipation produces discomfort and in many patients it affects certain activities of daily living (e.g., work impairment) [17]. Moreover, serious and potentially life-threatening complications have been reported, such as intestinal pseudo-obstruction, volvulus, megacolon and bowel perforation [18]. Therefore, it should be readily diagnosed and treated.

In this article, after discussing the pathophysiology of constipation in PD, management of constipation will be reviewed, focusing on most efficacious traditional and novel treatments.

2. Search strategy

References for this review were identified through non-systematic electronic literature searches of MEDLINE (PubMed) from 1966 until April 2014, with the terms 'constipation,' 'gastrointestinal dysfunction,' 'slow colonic transit,' 'defecatory dysfunction,' 'anorectal,' 'treatment' and 'management' coupled with the term 'Parkinson's disease.' Papers with data of pathophysiology, clinical features and pharmacological and nonpharmacological measures of constipation in PD were selected. Only papers published in English were reviewed.

3. Pathophysiology of constipation in PD

The autonomic nervous system controls the gut, except the oropharyngeal and proximal esophageal musculature and the external anal sphincter, which receive somatic control. The dorsal motor nucleus of the vagus nerve derives parasympathetic innervations to the stomach, small intestine and proximal colon, whereas the middle and distal colon receive parasympathetic supply through sacral nerves. Sympathetic innervations arise from the intermediolateral column of the spinal cord from T5 to L3 levels and together with parasympathetic innervations, act on cholinergic neurons in the myenteric plexus of the enteric nervous system, which can also independently control by intrinsic circuits many features of gastrointestinal function [10]. A detailed neural control of the gastrointestinal tract can be found at the comprehensive review of Cersosimo and Benarroch [19]. According to ROME III diagnostic criteria for functional chronic constipation [20], normal bowel movements per week is three or more.

PD is not merely a motor disorder resulting from disturbed dopaminergic transmission as it also displays non-motor symptoms. Furthermore, their occurrence might be related to the involvement of other non-dopaminergic anatomical structures besides substantia nigra pars compacta. Several studies revealed that Lewy pathology is also localized in the lower brainstem and several nuclei of the peripheral nervous system [21]. Braak *et al.* proposed a staging system to predict a sequence of lesions starting in the dorsal motor nucleus of the glossopharyngeal and vagal nerves, anterior olfactory nucleus and peripheral autonomic ganglia, including enteric nervous system, which would spread following an ascending course to other brainstem and cortical structures [22,23].

Degeneration of autonomic and enteric nervous system might be the hallmark of gastrointestinal dysfunction in PD. Involvement of sympathetic and parasympathetic pathways is well documented [24], as is the presence of Lewy pathology or α-synuclein expression in the enteric nervous system, which may follow a rostrocaudal distribution in the colon and rectum [25-30]. Degeneration of the habitually scarce dopaminergic neurons in the enteric nervous system was also found [31]. Interestingly, α-synuclein accumulation in the gastrointestinal tract may occur in early untreated PD patients and also up to 8 years prior to the onset of motor symptoms [32,33]. Therefore, constipation in PD might be related to the degeneration of autonomic innervations coming either from central autonomic nuclei or from the enteric nervous system within the colon itself [34,35].

The pathophysiological correlate of intestinal neurodegeneration, particularly the affectation of parasympathetic innervations from the motor nucleus of the vagus nerve and the loss of cholinergic neurons and neurons containing vasoactive intestinal peptide in the myenteric plexus of the enteric nervous system, is an impairment of peristalsis, which manifests as slow colonic motility [19]. It has been demonstrated that slow colonic transit appears to be uniform along all sections of the colon in PD patients. Frequency of increased colon transit time was found to be 80%, with a mean duration that varied between 1.8 and 7 days and that was directly related to disease duration, but not to gender or age [36-39].

In addition to prolonged colonic transit time, defecatory dysfunction due to pelvic floor dyssynergia is another

mechanism associated to constipation in PD. It is characterized by decreased phasic rectal contraction, weak abdominal strain and paradoxical sphincter contraction on defecation. The underlying mechanism for outlet-type constipation in PD is still uncertain. An impaired supraspinal modulation of the sacral defecation reflex might paradoxically activate motoneurons in Onuf's nucleus during defecation [19]. Affectation of dopaminergic transmission might also play a role, as denoted by relief with apomorphine, as will be described afterwards. Frequency of outlet-type constipation was found to be as high as 66% and not restricted to late stages of the disease [11,40-43]. In some cases it may be a predominantly OFF-period non-motor manifestation [44,45].

Other secondary factors associated with constipation in PD might be poor bowel habits, and immobility, whereas decreased water intake correlated inversely with the severity of constipation in PD patients [46]. Systemic conditions, like hypercalcemia or hypokalemia, as well as organic colorectal diseases (e.g., inflammatory or neoplasm) may also cause constipation. Certain medications, like antacids with aluminum, opioids, calcium-channel blockers, anticholinergics, tricyclic antidepressants, antipsychotics or amantadine, are other potential factors associated with constipation in PD [11,47-49]. Dopaminergic medications and catechol-O-methyl transferase inhibitors do not appear to cause or aggravate constipation [50,51].

4. Management of functional constipation due to slow colonic transit in PD

4.1 Nonpharmacological measures

Chronic constipation is usually difficult to treat. Before starting any treatment, secondary causes of chronic constipation, like some disease processes or certain medications or their adverse events (AEs), as listed before, should be ruled out. Afterwards, a graded approach to treatment is suggested. First, nonpharmacological measures should be adopted, including simple lifestyle modifications, such as increasing fiber and fluid intake [52-56]. Non-intense aerobic physical activity or at least avoiding sedentarism should also be encouraged [57,58]. It should be kept in mind, however, that evidence supporting the efficacy of these measures is weak. A treatment algorithm is offered in **Figure 1**.

4.2 Oral laxatives: polyethylene glycol

Failure of nonpharmacological management may call for a pharmacological intervention (**Figure 1**). Oral laxatives, such as bulk-forming (e.g., psyllium or bran) or osmotic agents (e.g., polyethylene glycol, lactulose or milk of magnesia), are usually considered as first-line treatments in the general population [52]. Stimulant laxatives (e.g., bisacodyl, sodium picosulfate or Senna leaves) have been often reserved for patients who failed to achieve a response to osmotic laxatives and as a rescue alternative, but not for chronic use, as they may induce tolerance, electrolyte imbalance or absorption impairment [12,59].

Some laxatives have been tried in PD patients. In a small study involving seven PD patients with constipation, psyllium was found to increase stool frequency and weight ($p < 0.05$), but did not improve colon transit or anorectal function [60]. A double-blind randomized controlled trial (RCT) evaluated the efficacy and safety of polyethylene glycol in 57 PD patients for a period of 8 weeks [61]. Treatment efficacy was defined as complete relief of the symptom or a marked improvement of two of the following indicators: stool frequency, straining, stool consistency or use of rectal laxatives as a rescue therapy. After 8 weeks, 80% of patients were considered responders. The frequency of bowel movements and stool consistency were significantly improved with polyethylene glycol in 94 and 69% of the patients, respectively. None of those patients on active group needed rectal laxatives at final visit in contrast to 2 (12.5%) patients that received placebo. Polyethylene glycol was well tolerated, except for four patients (14%) that discontinued treatment due to AEs (nausea and diarrhea in two patients), and poor treatment compliance due to the taste or volume of preparation. The Movement Disorder Society evidence-based medicine review update on treatments for the non-motor symptoms of PD recommended polyethylene glycol as 'likely efficacious and possibly useful' for the management of constipation in PD [62]. Main characteristics of polyethylene glycol are summarized in **Table 1**. According to a recent Cochrane review, PD patients showed a statistically significant improvement in the number of bowel motions per week with psyllium (mean difference -2.2, 95% CI -3.3 to -1.4) or polyethylene glycol (mean difference -2.9, 95% CI 1.48 – 4.32) in comparison to placebo [63]. To date, no other laxatives, like lactulose, milk of magnesia, bisacodyl, glycerin and sorbitol, have been formally assessed in PD.

4.3 Secretagogues: lubiprostone

Lubiprostone is a novel compound for the management of constipation and has shown promising results for the management of chronic constipation, including PD patients. It was approved by the US FDA in 2006 for the treatment of chronic idiopathic constipation in adults and in 2008 for irritable bowel syndrome with constipation in adult women.

Lubiprostone, an intestinal chloride secretagogue, is an oral bicyclic fatty acid derived from prostaglandin E1 that selectively activates type 2 chloride channels (ClC-2) in the apical membrane of the gastrointestinal epithelium [64]. This enhances fluid secretion into the intestinal lumen without altering plasmatic sodium and potassium concentrations, which in turn facilitates the passage of softened stool through the gut [65,66]. Controversial results have been found in relation to the effect of lubiprostone on intestinal transit time, with most studies finding no positive effect [65,67-70]. Also, the exact mechanism of lubiprostone-induced fluid secretion is still a matter of debate [71-73]. Lubiprostone also protects and effectively repairs the intestinal epithelial barrier, which confers additional advantages for patients with compromised barrier

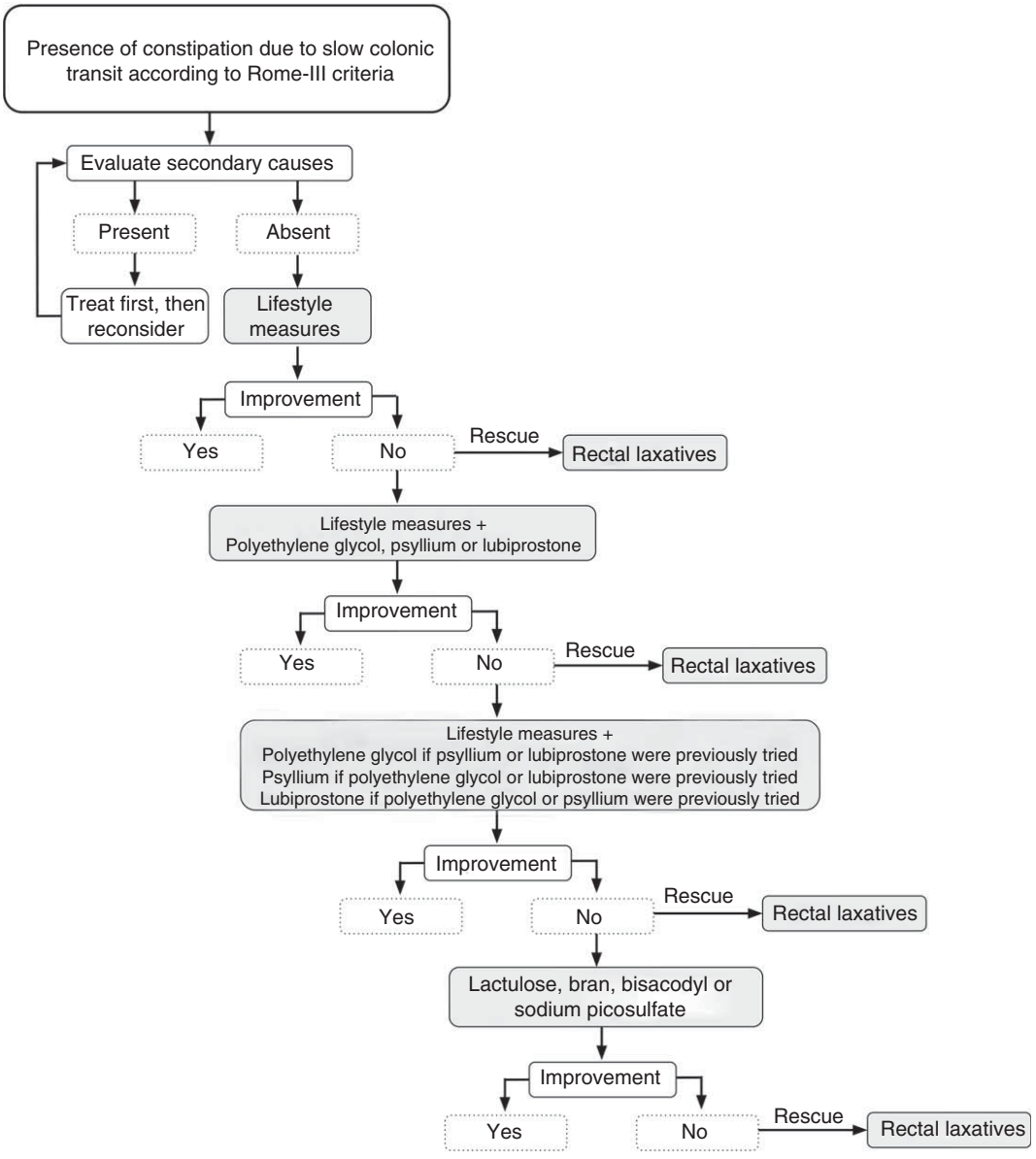

Figure 1. Treatment algorithm for functional constipation due to slow colonic treatment in PD.
PD: Parkinson's disease.

function, like those with irritable bowel syndrome [74]. It also shows prostaglandin-like actions on the small intestine, like stimulation of mucin release [75].

Lubiprostone is usually well tolerated in the general population, even up to 48 weeks of treatment. Most frequent treatment-related AEs found in two large clinical trials [76,77] included diarrhea (6.5 and 9.7%, respectively), nausea (6.3 and 18.8%, respectively), abdominal distension (3.7 and 6.9%, respectively), abdominal pain (2.9 and 5.2%, respectively), flatulence (2.1%), headache (1.5 and 6.9%, respectively), dizziness (1.3%) and vomiting (1.2%). Less than 6% of these AEs were reported as severe and no patient reported any treatment-related serious AE. The treatment-related diarrhea and nausea event rate were 0.35 and 0.34 per 1000 patient days, respectively.

According to a recent systematic review and meta-analysis, lubiprostone was found to be among the safest drugs for constipation-predominant irritable bowel syndrome (IBS-C) when compared to serotonin reuptake inhibitors, tricyclic antidepressants, alosetron and rifaximin, and showed insignificant harm in 2 concurrent Phase III trials involving 1171 patients [78,79].

The efficacy and safety of lubiprostone has been recently explored in PD by means of a double-blind, placebo-controlled, randomized clinical trial [80]. Fifty-four patients, with a mean duration of PD of 8 ± 5 years, without any

Table 1. Features of polyethylene glycol.

Indications	Short-term relief of chronic constipation. Bowel preparation before surgery or colonoscopy
Mechanism of action	Osmotic agent that causes water to be retained with the stool. This increases the number of bowel movements and softens the stool to allow an easier pass
Pharmacokinetic profile	It is unchanged along the intestinal tract. Absorption is rare and if it is absorbed, it is excreted in urine
Dosage	Different formulations and usually once daily
Route of administration	Oral or rectal for fecal impaction
Summary of clinical trials	Zangaglia *et al.* (2007) [61]: Double-blind RCT in 57 PD patients with constipation randomized to polyethylene glycol solution or placebo for 8 weeks. Treatment efficacy was defined as complete relief of constipation or a marked improvement of two of the following indicators: stool frequency, straining, stool consistency, use of rectal laxatives as a rescue therapy. Responders: 80%; p = 0.001. The frequency of bowel movements and stool consistency were significantly improved with polyethylene glycol in 94 and 69% of the patients, respectively. Rectal laxatives were still used by 2 patients on placebo (12.5%), but not on polyethylene glycol
Most frequent AEs	Nausea (7%) and diarrhea (7%)

AEs: Adverse events; PD: Parkinson's disease; RCT: Randomized controlled trial.

identifiable cause of constipation or use of constipating drugs were included. Patients were randomized to lubiprostone 24 mcg/twice daily or placebo for 4 weeks. Primary outcome was the frequency of spontaneous bowel movements. Compared with placebo, patients assigned to lubiprostone had increased stools frequency (0.75 ± 0.80 to 0.97 ± 0.88, respectively, for bowel movements/day for period before to after drug on treatment group vs 0.84 ± 0.76 to 0.83 ± 0.76 on placebo group; p = 0.001), improved global impression of change (z = 3.188; p = 0.001), visual analog scale score (51.4 ± 8.5 to 71.2 ± 16.6 for period before to after drug on treatment group vs 50.7 ± 5.9 to 56.8 ± 13.0 on placebo group; p < 0.001), and constipation questionnaires (p < 0.05). Main AEs were loose stools (48%), which were mild and self-limiting, followed by abdominal pain (1%). Curiously, no patient reported nausea, which is the most common AE in non-PD trials. Lubiprostone was found to be safe and effective for short-term treatment of constipation in PD. Further studies in larger samples and for longer follow-up periods are warranted [81]. A summary of the characteristics of lubiprostone is offered in **Table 2**.

4.4 Rectal laxatives

When oral medications have failed, a further step can be attempted with rectal laxatives (enemas) for occasional situations of acute episodes of severe constipation in chronically constipated patients [52]. To date, no studies compared oral laxatives against prokinetics or other medications used to treat constipation in PD patients. Large clinical trials of management of constipation in PD are warranted. Notwithstanding, it should be considered a rescue measure and thus used as the last resource in the management of constipation in PD.

4.5 Other traditional drugs

Pro-kinetic drugs have a minor role in the management of constipation in PD. Domperidone was not found to be useful for treatment of constipation in PD [82]. Metoclopramide should be avoided in PD patients, as it may worsen motor symptoms [83]. Cisapride was found to accelerate colon transit time by ~ 40% in most PD patients, but the therapeutic effect almost vanished after 1 year [38,84]. Similar positive results were also found with tegaserod, a partial 5HT-4 agonist that enhances peristalsis in an open-label report [85], but were not replicated in an RCT [86]. Moreover, cisapride and tegaserod have been withdrawn from the market, because of increased risk of cardiovascular AEs. Mosapride, a selective serotonin-4 receptor (5HT4) agonist and partial 5HT-3 antagonist, with no action on cardiovascular function, was found to be effective and well tolerated in a small open-label study involving seven PD patients with constipation during a 3-month trial period [87].

An approach with probiotics can be tried, as supported by RCTs involving patients with chronic constipation and a pilot study of milk fermented with the probiotic strain Lactobacillus Casei Shirota in 40 PD patients [88,89]. However, some doubts about the use of probiotics have been raised [90].

4.6 Emerging drugs

Some novel drugs are in the pipeline for IBS-C and chronic constipation treatment. Linaclotide is a new compound that activates the enzyme guanylate cyclase-C located in the luminal side of the intestinal epithelium and acts as a secretagogue, like lubiprostone. It showed superiority to placebo in reducing bowel and abdominal symptoms in Phase III studies. Safety profile showed to be similar to lubiprostone. Recommended doses of linaclotide are 290 µg once daily for IBS-C and 145 µg daily for chronic constipation [91]. Plecanatide, another guanylate cyclase-C enzyme activator under research, was found to be safe and well tolerated in healthy subjects, but requires further evaluation in patients with chronic constipation [92]. Novel highly selective 5HT-4 agonists, like prucalopride, velusetrag or naronapride, may be promising due to their efficacy and safety profile [93]. Elobixibat, an ileal bile acid transporter inhibitor, is another medication with an

Table 2. Features of lubiprostone.

Indications	Chronic constipation in adults and IBS-C in adult women
Mechanism of action	Selective activator of type 2 chloride channels
Pharmacokinetic profile*	Metabolizes to active metabolite M3 by carbonyl reductase enzymes in the stomach and jejunum. Peak M3 plasma levels in 1.14 h. Protein binding 94%. M3 $t_{1/2}$: 0.9 – 1.4 h. Elimination: 60% in urine, 30% in feces
Dosage	24 μg b.i.d. for CC and 8 μg b.i.d. for IBS-C
Route of administration	Oral
Summary of clinical trials	Drossman *et al.* (2009) [78]: Multicenter Phase-III double-blind RCT in 1171 IBS-C patients randomized to lubiprostone 8 mcg b.i.d. or placebo for 12 weeks. Completion rate: 76%. Responders: 17.9%; p = 0.001 Mean improvement from baseline in abdominal discomfort/pain was significantly greater in lubiprostone-treated patients compared with placebo-treated patients at month 3 (-0.45 vs -0.36, p = 0.028). Mean improvement in the lubiprostone group was significantly greater than the mean observed with placebo for abdominal bloating at month 2 (p = 0.044); bowel movements frequency at month 1 (p = 0.021); stool consistency at months 1, 2 and 3 (p ≤ 0.022); and degree of straining at months 1 and 2 (p ≤ 0.013) Lembo *et al.* (2011) [77]: Long-term efficacy multicenter, open-labeled trial in 248 patients with chronic constipation taking 24 μg b.i.d.. Completion rate: 51%. Mean reduction in constipation severity (p < 0.0015). Mean abdominal bloating scores were < 1.13 at all visits and < 1 for weeks 18 and 30 – 48, increasing to 1.15 at study end Mean abdominal discomfort scores were < 1 at every post-baseline assessment, with a score of 0.98 at study end. Improvements in both abdominal bloating and discomfort scores, at all time points post-baseline, were statistically significant (p ≤ 0.011). Efficacy lasted over 48 weeks of treatment Ondo *et al.* (2012) [80]: Double-blind RCT in 54 PD patients randomized to lubiprostone 24 μg b.i.d. or placebo for 4 weeks. Completion rate: 96%. Patients assigned to lubiprostone had increased stools frequency (p = 0.001), improved global impression of change (p = 0.001), visual analog scale score (p < 0.001), and constipation questionnaires (p < 0.05). AEs: loose stools (48%), abdominal pain (1%)
Most frequent AEs [76,77]	Diarrhea (6.5 and 9.7%, respectively), nausea (6.3 and 18.8%, respectively), abdominal distension (3.7 and 6.9%, respectively), abdominal pain (2.9 and 5.2%, respectively), flatulence (2.1%), headache (1.5 and 6.9%, respectively), dizziness (1.3%), vomiting (1.2%) and dyspnea (0.5%)

*Profile of the metabolite M3 after a single oral dose of 24 μg.

AEs: Adverse events; b.i.d.: Twice daily; IBS-C: Constipation-predominant irritable bowel syndrome; PD: Parkinson's disease; RCT: Randomized controlled trial.

original mechanism of action by blocking the absorption of bile acids, which in turn stimulate colonic secretions. It showed potential to treat chronic constipation [94]. A new class of medications, such as ghrelin agonist, is under research. No studies are available in PD.

5. Management of constipation due to defecatory dysfunction in PD

In general, treatment of outlet obstruction is challenging, but some measures are worthwhile to try. Levodopa or apomorphine injections have shown positive results, but were evaluated in small samples of patients [45,95]. Apomorphine normalized defecographic abnormalities in one out of three patients, by abolishing the paradoxical puborectalis contraction on strain, widened the anal canal and therefore improved evacuation. Repeated anorectal manometric parameters improved in all five patients that were evaluated [45]. Apomorphine needs to be used with caution because of adverse drug reactions involving the gastrointestinal (e.g., nausea and vomiting), cardiovascular (e.g., hypotension) and psychiatric (e.g., hallucinations, somnolence or impulse-control disorders) systems, especially in patients with advanced age.

Levodopa significantly lessened the first sensation during rectal filling (178.6 – 121.3 ml, p < 0.05), significantly reduced the amplitude in paradoxical sphincter contraction upon defecation (29.7 cmH_2O to -7.1 cmH_2O, p < 0.01) and lessened post-defecation residuals (142.2 – 53.9 ml, p < 0.05) in a quantitative lower-gastrointestinal autonomic test conducted in 18 constipated PD patients [95].

Biofeedback therapy, a manometric-assisted pelvic relaxation and stimulation defecation training, also showed to be effective in the short- and long-term management of dyssynergic defecation [96], and it might be useful in PD patients, although no results have been published yet. Functional magnetic stimulation showed some benefit in PD patients with constipation, but more extensive studies are warranted [97].

Lastly, botulinum toxin type A injection into the puborectalis muscle was tried with success in PD patients [98,99]. Albanese *et al.* injected 100 units of botulinum toxin type A in the puborectalis muscle under transrectal ultrasonographic guidance to 10 PD patients and found that anal tone during straining was reduced from 97.4 ± 19.6 mm Hg at baseline to 40.7 ± 11.5 mm Hg 1 month after treatment (p < 0.001), without any further change at 2 months of follow-up. The anorectal angle during straining increased from a mean of 99 ± 7.9° before treatment to 122.2 ± 15°, p = 0.0004) and

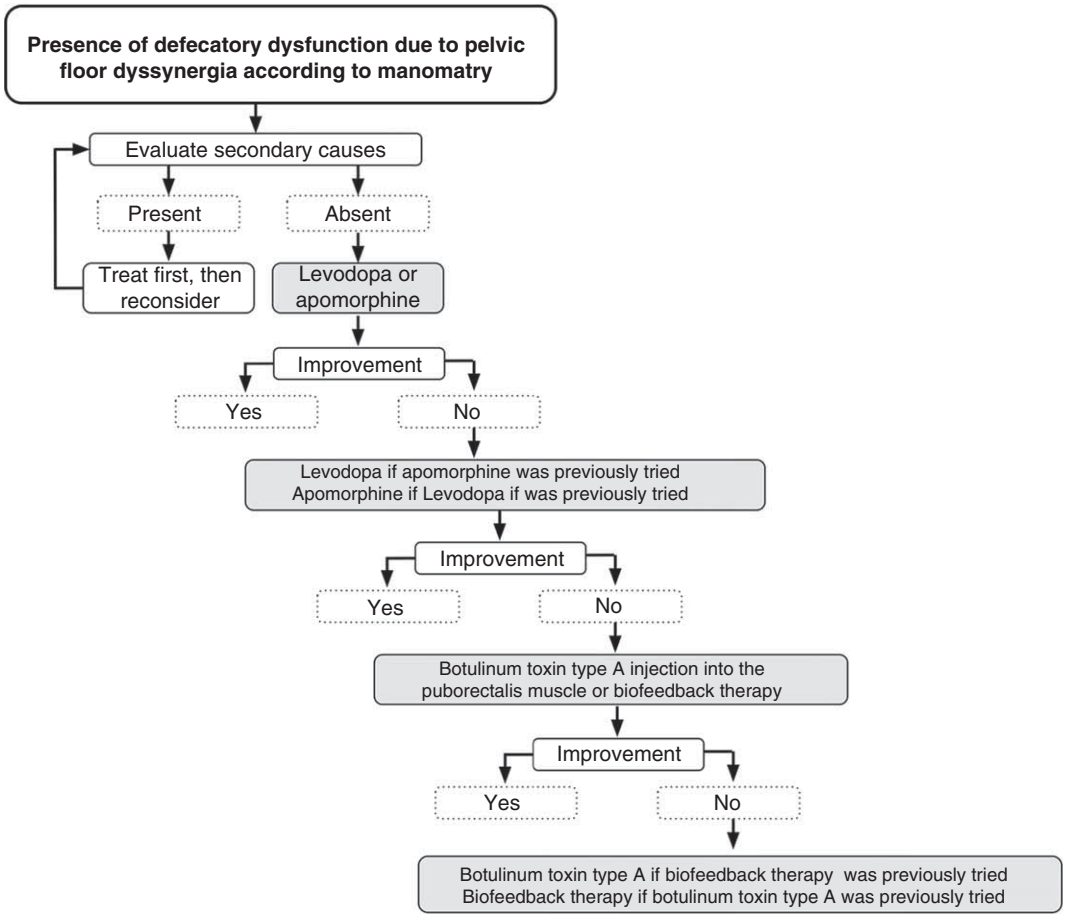

Figure 2. Treatment algorithm for constipation related to defecatory dysfunction due to pelvic floor dyssynergia.

nine patients (90%) evacuated without the need for laxatives or enemas [98].

A treatment algorithm for defecatory dysfunction in PD is depicted in **Figure 2**. It is important to acknowledge that treatments have been insufficiently studied in PD, and the algorithm representing the authors' expert opinion is based on the best available evidence.

6. Expert opinion

Constipation is a frequent non-motor feature of PD that usually causes concern, complaints and discomfort, affects activities of daily living and productivity and has a significant negative impact in health-related quality of life. Pathophysiology is related to central and peripheral degeneration of sympathetic and parasympathetic intestinal neurons, which causes slow colonic transit time and defecatory dysfunction due to pelvic floor dyssynergia. Other secondary factors associated with constipation in PD might be poor bowel habits, immobility, decreased water intake and certain medications, like antacids with aluminum, opioids, calcium-channel blockers, anticholinergics, tricyclic antidepressants, antipsychotics or amantadine. Difficulty in defecation may fluctuate as motor symptoms and tend to be more prominent and frequent during the OFF time.

Management of chronic constipation due to slow colonic transit should begin by implementing general measures, such as favoring exercise and increasing fiber intake and fluids, reducing OFF time. If they fail, then pharmacotherapy can be used. Exclusion of secondary causes of chronic constipation, like some disease processes or certain medications or their AEs, is mandatory.

Polyethylene glycol is one of the most effective and safe laxatives for management of chronic constipation in PD, and thus it can be regarded as a first-line treatment of constipation in PD. Novel compounds include lubiprostone, an activator of chloride channels in the apical membrane of the gastrointestinal epithelium. Such activation increases fluid secretion into the intestinal lumen and facilitates the passage of softened stool through the gut. Lubiprostone proved to be well tolerated, safe and long-term effective in reducing constipation in patients with chronic idiopathic functional constipation and constipated patients with PD. Given its efficacy, safety and tolerability, lubiprostone is a good option for the

management of constipation associated with PD. Further studies of lubiprostone with larger samples and longer follow-up periods are warranted [100]. Even if comparisons between polyethylene glycol, lubiprostone and other currently used agents are lacking, the evidence about their efficacy and safety obtained by double-blind RCT involving PD patients allows to recommend them as first-line compounds in treatment of constipation in PD due to slow colonic transit time.

There is a paucity of large and well-designed clinical trials to evaluate the efficacy of general measures or medications for management of constipation in PD. Studies comparing novel drugs with classical medications, like laxatives, are warranted, as well as long-term experience in PD patients. Future trials must be double-blind, randomized and placebo-controlled, should include PD patients fulfilling ROME III criteria, use frequency of stools as primary outcome endpoint, and have a duration of at least 12 weeks [81].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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