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REVIEW ARTICLE

Gastrointestinal barriers to levodopa transport and absorption in Parkinson's disease

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Abstract

Levodopa is the gold standard for the symptomatic treatment of Parkinson's disease (PD). There are well documented motor and non-motor fluctuations, however, that occur almost inevitably once levodopa is started after a variable period in people with PD. Whilst brain neurodegenerative processes play a part in the pathogenesis of these fluctuations, a range of barriers across the gastrointestinal (GI) tract can alter levodopa pharmacokinetics, ultimately contributing to non-optimal levodopa response and symptoms fluctuations. GI barriers to levodopa transport and absorption include dysphagia, delayed gastric emptying, constipation, *Helicobacter pylori* infection, small intestinal bacterial overgrowth and gut dysbiosis. In addition, a protein-rich diet and concomitant medication intake can further alter levodopa pharmacokinetics. This can result in unpredictable or sub-optimal levodopa response, 'delayed on' or 'no on' phenomena. In this narrative review, we provided an overview on the plethora of GI obstacles to levodopa transport and absorption

in PD and their implications on levodopa pharmacokinetics and development of motor fluctuations. In addition, management strategies to address GI dysfunction in PD are highlighted, including use of non-oral therapies to bypass the GI tract.

KEYWORDS
absorption, constipation, delayed gastric emptying, diet, dysphagia, levodopa, medication, microbiota, Parkinson's disease, pharmacokinetics, transport

INTRODUCTION

Seven decades after its introduction in clinical practice, levodopa still represents the gold standard for the symptomatic treatment of Parkinson's disease (PD), despite being far from a perfect drug [1]. Levodopa, the precursor of the neurotransmitter dopamine, is a large neutral amino acid (LNAA) that can bypass the blood–brain barrier and is converted into dopamine in the central nervous system (CNS) [2]. However, the limited oral bioavailability combined with the extremely short half-life make levodopa one of the most challenging molecules to control therapeutically. Referred to as the 'pharmacologist's nightmare', levodopa peripheral pharmacokinetics are complicated by (1) an extensive pre-systemic metabolism to dopamine in the gastrointestinal (GI) tract mediated by the enzymes L-amino acid decarboxylase (AADC) and catechol-O-methyltransferase (COMT); (2) an absorption site limited to a short segment of the small intestine (duodenum and jejunum) and mediated by a transport system shared with and competed for by other LNAAs; (3) a fast metabolization in the blood stream to dopamine or 3-O-methyldopa (3-OMD) by AADC or COMT enzymes [2]. Additional factors related to the GI tract morphology and functionality have emerged as possible negative influencers of levodopa transport and absorption. The latter is particularly relevant amongst people with PD (PwP), since this population often presents with concomitant GI dysfunction related to the disease itself (see Figure 1) [3].

Virtually the whole GI tract can be affected in PD, from the mouth to the rectum, and GI dysfunction is one of the most prominent aspects of PD at every disease stage, from prodromal to advanced [3,4]. Constipation, for instance, is one of the prodromal features of PD, preceding the onset of motor symptoms by up to 20 years, and is a risk factor for in life-manifest PD [5–7]. In addition, constipation is often a troublesome clinical manifestation which complicates management in all phases of the disease [8]. Recent studies have also highlighted the presence of alterations in the gut microbiota composition of PwP, although the clinical relevance needs to be further elucidated [9].

Together with the ongoing neurodegenerative processes, a range of barriers across the GI tract can play a role in the pathogenesis of motor and non-motor fluctuations in PwP [10,11], which occur almost inevitably once levodopa is started. Whilst the role of delayed gastric emptying in levodopa absorption has been reported by many researchers, a comprehensive review on how GI dysfunction, diet, comorbidity and medication intake can influence levodopa pharmacokinetics and contribute to the development of non-optimal levodopa response and fluctuations is lacking, and we aimed to address this in this narrative review. In addition, management strategies to address GI dysfunction in PD are highlighted, including the use of non-oral therapies to bypass the dysfunctional GI tract.

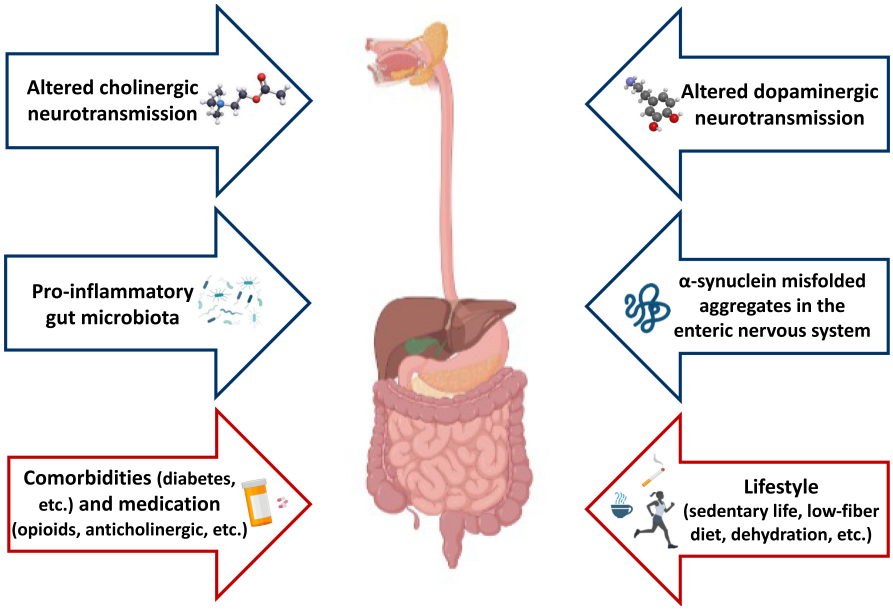

FIGURE 1 Postulated pathophysiological mechanisms underpinning gastrointestinal dysfunction in Parkinson's disease. Whilst some mechanisms are intrinsic to Parkinson's disease (blue arrows), others are extrinsic and not related to Parkinson's disease *per se* (red arrows).

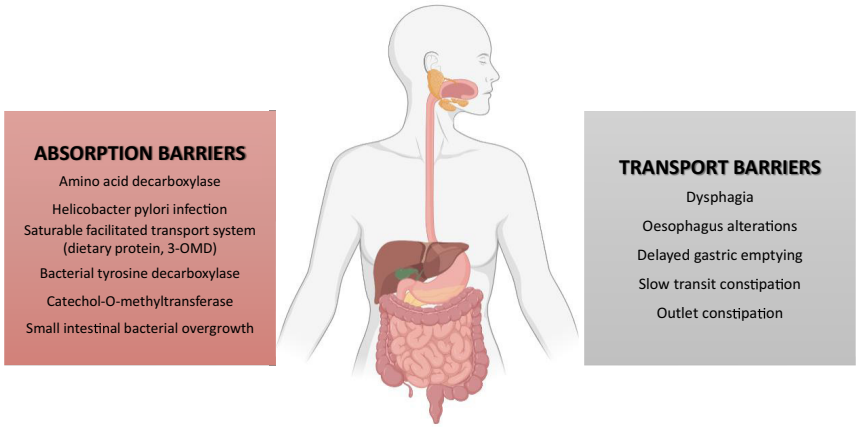

FIGURE 2 Barriers to levodopa transport and absorption in the gastrointestinal tract. The figure shows barriers to levodopa pharmacokinetics categorised as absorption barriers (factors which affect levodopa absorption in the small intestine primarily) and transport barriers (factors which affect levodopa transport through the gastrointestinal tract primarily). Of note, transport barriers can ultimately alter levodopa absorption. 3-OMD, 3-O-methyldopa.

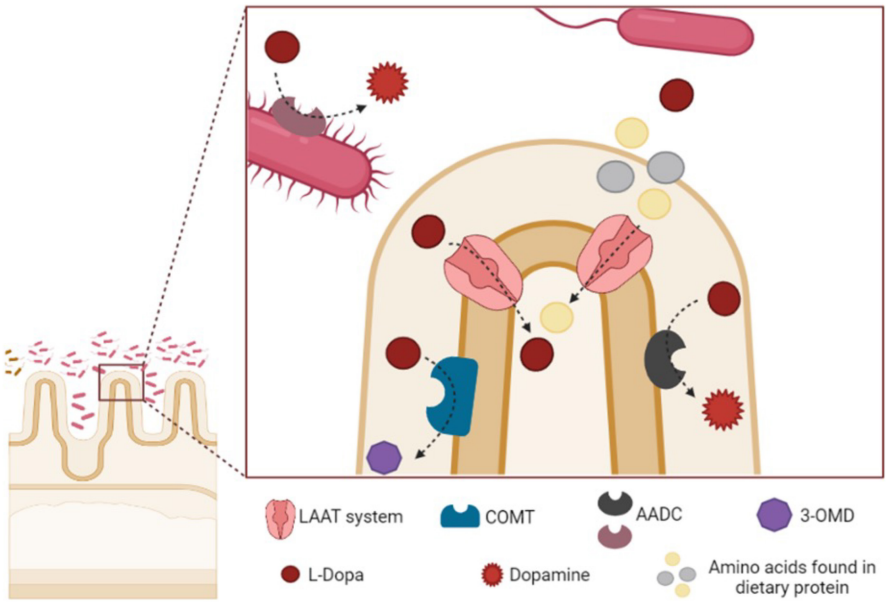

FIGURE 3 Absorption-related gastrointestinal obstacles. The figure shows the small intestine (lumen in white and villi in yellow) which is the site of oral levodopa absorption. A variety of barriers to levodopa absorption are illustrated including (1) human (1A) and bacterial (1B) AADC which prematurely decarboxylates levodopa to dopamine in the gastrointestinal tract; (2) COMT enzyme which metabolizes levodopa to 3-OMD in the gastrointestinal tract preventing its conversion to dopamine; (3) the potentially saturable LAAT system SLC7A9–SLC3A1 where levodopa competes with the amino acids arginine and leucine found in dietary protein. Whilst 3-OMD, which derives from levodopa metabolisation by COMT enzyme, competes with levodopa for transport at the level of the blood–brain barrier, its role as a competitor at the level of the gastrointestinal tract is unclear. 3-OMD, 3-O-methyldopa; AADC, L-amino acid decarboxylase; COMT, catechol-O-methyltransferase; LAAT, large amino acid transporter.

The barriers: an overview

An oral levodopa tablet can encounter numerous challenges in the GI tract that can interfere with its transport, absorption or both (see Figure 2).

Transport-related obstacles

The transport of oral levodopa depends on several mechanisms, which can be disturbed in different segments of the GI tract. If taken as a tablet or capsule, levodopa must be transported through the mouth and swallowed after initiating the swallowing reflex. The oral, pharyngeal and oesophageal parts of the swallowing process can be altered in PD [12]. In addition, delayed gastric emptying can slow the transport of levodopa from the oesophagus to the small intestine [13]. Within the intestine, impaired colonic motility can also prolong transportation time, causing 'slow transit' constipation and even resulting in faecal impaction [14–17]. Further, 'outlet' constipation, caused by anorectal dysfunction with defaecatory problems, occurs in up to twothirds of PwP and may amplify slow transit constipation and indirectly delay the transport of levodopa [3,18]. Prolonged transit time of levodopa from the mouth to the small intestine can also facilitate the premature metabolisation of levodopa in the GI tract, ultimately resulting in impaired absorption.

Absorption-related obstacles

Oral levodopa is administered combined with an AADC inhibitor (carbidopa or benserazide) to improve its efficacy and reduce peripheral side effects (e.g., nausea and vomiting). AADC is an enzyme distributed throughout the body that decarboxylates levodopa to dopamine in the brain and during its transportation through the GI tract and bloodstream (see Figure 3). The stomach can decarboxylate levodopa but has a limited capacity to absorb it [2], as the bulk of levodopa absorption occurs in the proximal small intestine [2]. Therefore, impaired gastric emptying delays levodopa delivery to the intestinal absorption sites, possibly increasing pre-systemic peripheral decarboxylation and resulting in reduced levodopa absorption [2]. In addition, recent evidence suggests that carbidopa or benserazide inhibit human AADC only, whilst bacterial forms of AADC are resistant to their effect [19]. As such, bacterial strains expressing AADC in the GI tract can further contribute to the premature metabolisation of levodopa to dopamine in the intestinal lumen, which might also contribute to peripheral side effects.

Since levodopa is an LNAA, it shares its transport system with other LNAAs [20]. Physiologically, levodopa is absorbed rapidly in the proximal small intestine by a potentially saturable facilitated transport system. However, this is not the major LNAA transporter (LAAT) (SLC6A19), which seems to mediate levodopa transport from the plasma to the brain at the level of the blood–brain barrier, but a more restricted transporter system (SLC7A9–SLC3A1) with leucine and arginine as competitors [21,22]. Thus, the type and quantity of food and timing of meals can interfere with levodopa absorption (see Figure 3).

The COMT enzyme also plays an important part in levodopa pharmacokinetics and the latter is translated to clinical therapy with the use of COMT inhibitors (see Figure 3). COMT metabolises levodopa to 3-OMD, blocking its conversion to dopamine. There are two forms of COMT, which are expressed in the brain and other tissues of the body: (1) soluble COMT in the cytoplasm and (2) membrane-bound COMT, which is anchored to the inner side of the cell plasma membrane [23]. After oral levodopa administration, COMT activity in the GI tract converts a significant fraction of levodopa to 3-OMD, reducing the amount of levodopa available to the CNS. In addition, 3-OMD contributes to the total amount of LNAA, and competes with levodopa for absorption and transportation by the LAAT in the blood–brain barrier [24,25]. The amount of COMT activity varies between individuals based on different factors, including sex, race and various gene polymorphisms *COMT* [26–28]. Both peripherally acting COMT inhibitors (i.e., entacapone, opicapone) and CNS-active COMT inhibitors (i.e., tolcapone) are commercially available as oral tablets and are used for PD treatment [29] to prolong levodopa half-life and, subsequently, its bioavailability [30,31].

DYSPHAGIA

Dysphagia is often overlooked in PD and is common across all stages of the disease (prevalence varying from 18% to 100%) [3,32]. Both dopaminergic and non-dopaminergic mechanisms contribute to the development of dysphagia [33] and disease severity, dementia, low body weight and drooling are all associated with swallowing disturbances in PD [34–36].

Dysphagia can affect the transport of oral levodopa tablets and contribute to the development of motor complications. Sato and colleagues described the case of a 69-year-old man with PD experiencing dysphagia as well as 'delayed on' and 'no on' phenomena [37]. Video fluorographic examination of swallowing during an 'off' episode revealed tongue hypokinesia with tablets retained in the epiglottic vallecula, which was associated with reduced levels of levodopa plasma concentration and a 'no on' phenomenon. After undergoing a 1-week tongue resistance exercise training regimen, the authors observed increased tongue mobility, faster tablet swallowing time, increased levels of levodopa plasma concentration, and reaching an 'on state' within 30 min after tablet intake. This initial observation was further supported by a retrospective case study of 20 PwP. Flexible endoscopic evaluation of swallowing showed that residual drug in the pharynx was more likely in patients with 'delayed on' phenomenon (odds ratio [OR] 42.7, 95% confidence interval [CI] 1.89–962.9) [38]. A recent study assessed 66 PwP using flexible endoscopic evaluation of swallowing to detect dysphagia for medication, including the swallowing of two tablets and capsules of different sizes. A two-dimensional and graduated classification of dysphagia for medication was applied differentiating swallowing efficiency and swallowing safety. According to this classification, dysphagia for medication was present in nearly 70% of PwP and predicted motor complications according to the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part IV in a linear regression model (beta coefficient 0.5; $p = 0.006$). Capsules tended to be swallowed more efficiently compared to tablets, irrespective of size [39]. Further prospective and controlled studies are needed to confirm the role of dysphagia in levodopa transport and absorption.

Delayed gastric emptying

Delayed gastric emptying (DGE), or gastroparesis, is frequently observed in PwP, with an overall prevalence ranging from 35% to 100% [40]. Multifactorial in origin, DGE can be an intrinsic manifestation of PD or secondary to another medical comorbidity (e.g., diabetes mellitus, amyloidosis etc.), as well as iatrogenic (see Figure S1) [40,41]. Interestingly, levodopa itself can also induce DGE by binding gastric dopaminergic receptors in a dose-dependent manner [42–44].

Also, DGE is associated with delayed small bowel transit. In 65 PwP and various gastrointestinal symptoms, 35% exhibited gastroparesis by the wireless motility capsule study, 20% small bowel transit delay, whilst 8% had combined transit abnormalities suggestive of overlapping gastric and small bowel dysmotility [45].

Since levodopa is absorbed only in a small portion of the proximal intestine, DGE interferes with levodopa pharmacokinetics by prolonging the time that levodopa remains in the stomach and thus increasing the chance of AADC metabolising levodopa to dopamine

prematurely. Activation of gastric dopamine receptors promotes stomach relaxation and inhibits gastric motility. A standard levodopa/carbidopa tablet resides in the stomach for a relatively long period of time where it can be decarboxylated to form dopamine that could inhibit gastric motility. Differences in the pH and solidity of tablets may play a role for a more rapid and predictable transit of levodopa to the jejunum [46].

Some of the first evidences suggesting that DGE can interfere with levodopa absorption comes from a study of 11 PwP without unpredictable motor fluctuations who underwent a ^{13}C-octanoate breath test to measure gastric emptying and blood sampling to assess levodopa pharmacokinetics [47]. All PwP presented with DGE compared to controls (half gastric emptying time: PD 161 ± 37 min vs. controls 107 ± 10 min). Furthermore, lower levodopa absorption was observed in the PwP with slower gastric emptying [47]. This was further supported by Doi et al. in their case study of 31 PwP, where DGE, measured using the methods described above, was associated with delayed levodopa peak plasma concentration, with potential implications on levodopa delivery to the brain and motor response [48]. Djaldetti et al. showed that DGE, as measured by gastric scintigraphy, is more severe in PwP with motor fluctuations ('delayed on' or 'no on' phenomena) compared to those without fluctuations (gastric retention after 1 h: PD with fluctuations 77.4% ± 15.5% vs. PD without fluctuations 64.0% ± 14.3%) [49].

Therefore, DGE negatively influences levodopa transport and absorption and contributes to the development of motor complications, such as 'delayed on' or 'dose failure' and potentially to medication overload.

Helicobacter pylori infection

Helicobacter pylori (HP) is a Gram-negative, microaerophilic bacterium that frequently infects the human GI tract, with a global prevalence ranging from 24% to 79% [50]. Recent metanalyses confirmed that PwP have a higher prevalence of HP infection compared to persons without PD (OR 1.47, 95% CI 1.27–1.70) [51]. Furthermore, individuals with HP infection are more likely to develop PD compared to those without the infection (OR 1.59, 95% CI 1.37–1.85), suggesting a potential role for the infection in the pathogenesis of PD [52].

HP infection may represent an obstacle to levodopa transport and absorption due to a variety of mechanisms summarised in Figure S2.

According to a recent metanalysis, PwP and HP infection have higher levodopa equivalent daily dose, worse motor symptoms severity, longer time to 'on' and reduced 'on' duration compared with those without HP [53]. Pierantozzi and colleagues were the first to demonstrate that HP infection can negatively impact levodopa pharmacokinetics in randomised controlled trials of PwP and motor complications [54–56] and showed that both the area under the curve of levodopa plasma concentration and the duration of clinical benefit can be augmented at 2 and 12 weeks after HP eradication (Table 1) [56]. However, no statistically significant differences in levodopa absorption were observed in a case–control, cross-sectional study comparing levodopa pharmacokinetics-related outcomes in PwP with and without HP infection [57]. The results of this study suggest that changes in levodopa absorption after HP treatment could result from factors other than bacteria elimination, including reduced GI inflammation and use of antibiotics with prokinetic effect (i.e., macrolides) as part of the eradication therapy regimen [57]. Despite the unclear underlying mechanisms of action, a variety of open-label, case–control studies have shown the beneficial effect of HP eradication in PD on motor symptoms severity, time to 'on' and 'on' duration at up to 1 year after HP eradication. However, a recent single centre randomised, double-blind, placebo-controlled trial of PwP with HP infection failed to show reduction of motor symptoms severity and improved quality of life at 12 and 52 weeks [58].

Overall, despite the abundance of literature suggesting the possible negative impact of HP infection on levodopa absorption and motor symptoms, the only single centre randomised controlled trial so far showed no short-term or long-term clinical improvements after HP eradication. Further high-quality multicentre studies of enriched PD populations with motor fluctuations are required to evaluate whether HP screening is justified in PwP.

Diet

Levodopa bioavailability can be affected by various dietary factors, including meal timing and the type and quantity of food consumed (see Table 2). Levodopa transit time through the small intestine is around 3 h, and levodopa's half-life is short, ranging from 0.7 to 1.5 h [67,68]. Levodopa absorption is rapid, with time to peak plasma levodopa concentration ranging from 15 to 60 min [69,70]. Therefore, levodopa intake with respect to meal times is the easiest to influence in early to mid-stage PD, when patients typically take levodopa three to four times daily.

Meal timing

Several studies have demonstrated that the timing between levodopa and meal consumption can affect levodopa absorption and clinical effect (see Table 2) [70,71,76].

In general, the time to peak is shorter, peak plasma concentrations are higher, and the onset of clinical benefit is sooner when levodopa is taken in the fasting state. Thus, in patients taking oral levodopa, these studies suggest that taking medication on an empty stomach, adhering to a scheduled levodopa regimen and avoiding interactions with meals can improve the levodopa dose–response relationship to promote optimal absorption conditions in the GI tract and transportation conditions in the blood, leading to a shorter time to medication effect onset and longer duration of the clinical response.

TABLE 1 Original research studies investigating the impact of *Helicobacter pylori* infection on levodopa absorption, motor symptoms and complications in Parkinson's disease.

Study design	Study population	HP diagnosis	Main outcomes	Reference
Randomized, double-blind, placebo-controlled, parallel-group	34 patients with PD with HP infection and motor fluctuations on levodopa monotherapy	Gastric biopsy	HP eradication led to -↑ levodopa absorption (AUC) -↓ clinical disability (UPDRS-III) -↑ 'on-time' duration (UPDRS-III) -↓ gastritis/duodenitis scores at 2 weeks and 3 months after eradication	56
Double-blind, placebo-controlled, crossover group	7 patients with advanced PD and HP infection	Serum antibodies	HP eradication led to -↑ levodopa absorption (AUC) at 1 week after eradication	55
Open label, longitudinal, case–control	36 patients with PD, H&Y stage 2–4, disease duration ≥3 years	Serum antibodies	18 (50%) patients HP+ Eradication of HP led to -↓ motor dysfunction severity in on state (UPDRS-III) -↓ time to on -↑ on duration (diary) -↑ daily on time (diary) at 1 week after eradication	59
Case–control, cross-sectional	75 patients with PD, disease duration ≥4 years	^{13}C-labelled urea breath test	20 (27%) patients HP+ HP+ compared to HP− had -↓ severity of motor complications (UPDRS-IV) -↓ occurrence of WOF symptoms (WOF-9)	60
Retrospective survey	66 patients with PD	Gastric biopsy when positive screening test	HP eradication in 12 HP+ patients led to -↓ hypokinesia (gait test) over a median of 1.9 years	61
Open label, longitudinal	82 patients with PD	^{13}C-labelled urea breath test	27 (33%) patients HP+ Eradication of HP led to -↓ time to on (diary) -↑ on duration (diary) -↓ motor dysfunction severity (UPDRS-III) -↓ motor complications severity (UPDRS-IV) -↑ quality of life (PDQ-39) at 12 weeks post eradication	62
Case–control, cross-sectional	102 patients with PD	^{13}C-labelled urea breath test	33 (32%) patients HP+ HP+ compared to HP− had -↑ age -↑ motor dysfunction severity (UPDRS-III, pegboard and timed gait)	63

TABLE 1 (Continued)

Study design	Study population	HP diagnosis	Main outcomes	Reference
Open label, longitudinal, case–control	65 patients with PD and motor fluctuations	^{13}C-labelled urea breath test	35 (54%) patients HP+ HP+ compared to HP− had -↑ time to on (diary) -↓ on duration (diary) Eradication of HP led to -↓ time to on (diary) -↑ on duration (diary) at 12 weeks post eradication	64
Open label, longitudinal, case–control	94 patients with PD	^{13}C-labelled urea breath test	22 (23%) patients HP+ Eradication of HP led to -↓ motor dysfunction severity (UPDRS-III) at 1 year post eradication	65
Open label, longitudinal, case–control	40 patients with PD with motor fluctuations	^{13}C-labelled urea breath test	22 (55%) patients HP+ Eradication of HP led to -↓ daily off time (diary) -↑ daily on time (diary) -↓ WOF severity (WOF-9) -↓ GI symptoms (seven-item GI complaint score) at 6 weeks post eradication	66
Case–control, cross-sectional	73 patients with PD and motor fluctuations, H&Y stage 2–4	Stool antigen test	25 (34%) patients HP+ No differences in levodopa absorption between HP+ and HP− (AUC)	57
Randomised, double-blind, placebo-controlled, parallel-group	67 patients with PD and HP infection	^{13}C-labelled urea breath test and serum antibodies	Eradication of HP led to - no changes in motor severity (MDS-UPDRS-III) - no changes in motor complications severity (MDS-UPDRS-IV) - no changes in non-motor severity (MDS-UPDRS-I) - no changes in quality of life (PDQ-39) at 12 and 52 weeks after eradication	58

Abbreviations: AUC, area under the curve; H&Y, Hoehn and Yahr scale; HP, *Helicobacter pylori*; MDS, Movement Disorder Society; PD, Parkinson's disease; PDQ, Parkinson's Disease Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; WOF, Wearing off.

TABLE 2 Original research studies investigating the impact of diet on levodopa absorption, motor symptoms and complications in Parkinson's disease.

Study design	Study population	Main outcomes	Reference
Meal timing			
Intra-subject randomized crossover	17 PD patients fasting after taking second daily oral dose of carbidopa/levodopa 1:10 ratio or benserazide/levodopa either 2 h before food or 30 min after food	When levodopa was taken after food: • ↑ triple the time to peak levodopa absorption, from 45 ± 23 min (fasting) to 134 ± 76 min • ↓ peak plasma concentrations (30% less)	70
Intra-subject randomized crossover	8 PD patients taking controlled release carbidopa/levodopa 50/200 mg in two separate sessions after fasting: 2 h before consuming a standard meal and 30 min after the standard meal	When levodopa was taken after food: -↑ time to detectable plasma levodopa levels (mean 30 min to 75 min peak plasma levodopa concentrations were similar) - ↑ time to onset of clinical motor response (mean time to 67 min after fasting vs. 157 min after eating) ↓ response duration (mean 124 min after eating vs. 203 min before eating)	71
Protein interaction			
Intra-subject crossover	5 PD patients with motor fluctuations in three situations: (1) 1.6 g/kg protein day (high-protein diet) (2) 0.8 g/kg protein/day distributed throughout the day's 3 meals (3) 0.8 g/kg protein/day, with protein intake restricted to only the evening meal [66]	All conditions demonstrated similar plasma levodopa levels (measured hourly) After high-protein diet, patients had -↓ daily 'on' times -↑ mean plasma LNAA levels	72
Double-blind crossover	10 PD patients with unpredictable symptom fluctuations consumed milkshakes containing either (1) high protein (80 g/day for men and 70 g/day for women) or (2) low protein (50 g/day for men and 40 g/day for women), protein distributed throughout the day	- Plasma levodopa levels were similar (measured in only 8 participants) regardless of diet - No difference in dyskinesias During high-protein diet participants had: -↓ 'on' time (64% vs. 71%)	73
Crossover; longitudinal observational	8 PD patients with motor fluctuations after consuming either 2 g/kg/day of protein vs. total 10 g protein/day; also 7 PD patients maintaining a low-protein diet (0.5 g/kg/day, divided) from 2 to 12 months	Higher protein consumption associated with -↑ motor fluctuations Participants that maintained a low-protein diet had -↓ levodopa dose requirements -↓ motor fluctuations	74
Crossover	9 PD patients with severe motor fluctuations after receiving oral levodopa and during continuous intravenous infusion; during fasting state and 15 min after eating	After eating, levodopa had -↑ time to clinical effect -↑ time peak plasma levels -↓ peak plasma concentrations	69
Retrospective observational	1047 PD patients; 877 taking levodopa; 52 with motor fluctuations	- 59% of participants reported protein interaction - 12% of those with motor fluctuations reported protein interaction Average time to develop protein interaction ~13 years after start of motor symptoms, 8 years after starting levodopa	75

Abbreviations: LNAA, large neutral amino acids; PD, Parkinson's disease.

Protein

Dietary protein can interfere with levodopa bioavailability and reduce the clinical response in PD for several reasons [77]. Protein can delay gastric emptying [78]. Furthermore, LNAA in dietary proteins can hinder levodopa absorption in the small intestine and compete with levodopa transport across the blood–brain barrier [20]. A number of studies have investigated the effect of dietary protein on

levodopa response in PD, which are summarised in Table 2. These studies show that meals containing higher proteins, and specifically LNAAs, reduce levodopa clinical effect, whilst meals with less protein, especially when the protein is concentrated in the latter part of the day, can optimise levodopa effect. A study by Tsui et al. found that, in PwP with motor fluctuations, consuming a low-protein diet was associated with a trend toward better motor performance compared to a high-protein diet, although no difference in dyskinesias was observed between high- and low-protein diets [73]. The amount of dietary protein ingestion may affect the short-term and long-term therapeutic efficacy of levodopa, and PwP who are maintained on a low-protein diet for months may have improvement in motor fluctuations and require less levodopa to maintain optimal symptoms control [74].

Collectively, these findings support that dietary protein can affect levodopa's absorption and that LNAA competition with levodopa for active transport is more problematic at the blood–brain barrier than in the intestine. Although these results suggest that following the World Health Organization's recommended dietary allowance of 0.75 g protein/kg body weight daily should not affect the levodopa dose–response [79], it is possible that lower daily protein consumption can improve clinical levodopa response and motor fluctuations in PD; however, a low-protein diet should not be attempted without the involvement of both a clinician and dietitian due to the risk of protein malnutrition.

Based on the available evidence, oral levodopa intake on an empty stomach (45–60 min before a meal) is recommended if tolerated (no nausea). In addition, avoiding dietary protein (dairy, nuts, meat, beans, seeds, whole grain) 30 min before or after levodopa intake is advisable.

Gut microbiota and small intestinal bacterial overgrowth

Over the last decade, the role of the gut microbiota, a network of resident bacteria, protozoa, fungi and viruses that live symbiotically within the GI tract, has been studied with increasing attention in PD [80]. Two recent metanalyses have shown enrichment of specific bacteria (including *Akkermansia* and *Lactobacillus* genera) and depletion of short-chain fatty acid producing bacteria in PwP compared to healthy controls, resulting in a pro-inflammatory gut dysbiosis [9,81]. The latter has been suggested to play a potential role in the pathogenesis of PD.

The myriad of microorganisms duelling in the GI tract and their metabolic products can affect levodopa's absorption. According to preclinical evidence, bacterial strains expressing tyrosine decarboxylase (TDC) can prematurely decarboxylate levodopa to dopamine in the small intestine before it is absorbed, reducing the levels of bioavailable levodopa [19,82]. In stool samples of PwP, van Kessel et al. showed a positive association between the relative abundance of bacterial TDC gene and dopaminergic medication use and disease duration [83]. Another study showed that in the small intestine of rats receiving oral levodopa/carbidopa, levodopa plasma levels were negatively associated with the abundance of bacterial TDC gene [19]. Thus, PwP who have high levels of these resident gut bacteria in the small intestine may require increased levodopa doses to achieve symptomatic benefit. However, a recent study on PwP on levodopa-carbidopa intestinal gel infusion found no association between the presence of TDC producing bacteria and levodopa plasma concentration [84].

Levodopa's absorption can also be influenced by the presence of small intestinal bacterial overgrowth (SIBO) which is defined as an increased concentration of bacteria above 10^5 colony-forming units/ml or the presence of unusual colonic-type bacteria in the small intestine. Like other disorders associated with abnormalities of GI motility (i.e., diabetes mellitus), an increased prevalence of SIBO has been reported in PwP (up to 55%) [85] compared to healthy subjects [86]. Common predisposing conditions for SIBO in PD include GI dysmotility, longer disease duration and proton pump inhibitor therapy. Moreover, a concomitant HP infection, frequently requiring prolonged proton pump inhibitor treatment and eventually favouring GI impaired motility, is an additional risk factor [85].

Small intestinal bacterial overgrowth has been associated with increased frequency of motor fluctuations, longer 'off' phases and suboptimal response to levodopa, resulting in worse motor function overall [86,87]. SIBO may be able to create and maintain an inflammatory environment in the intestinal mucosa that contributes to levodopa malabsorption. Moreover, SIBO eradication with antibiotic treatment such as rifaximin might improve motor performance in PD [88]. However, several studies have shown no changes in levodopa pharmacokinetic measurements after eradicating SIBO, suggesting that the underlying mechanism is probably multifactorial and highlighting the need for further research on the topic [82,88,89].

CONSTIPATION

Constipation has a prevalence of 20%–89% [3,34,90] and is up to six-fold more common amongst PwP than amongst age- and sex-matched controls [90,91]. In PD, constipation is mainly associated with impaired colonic motility leading to prolonged colonic transit times and clinically reflecting in slow transit constipation [16,17]. 'Outlet' constipation, caused by anorectal dysfunction with defaecatory problems, occurs in up to twothirds of PwP but does not directly affect levodopa absorption and pharmacokinetics, respectively, although it can exacerbate slow transit constipation [3,18]. Slow intestinal transit contributes to a delay, reduction or even blockage of oral levodopa uptake, with potential delay or loss of effect (see Figure S3) [40,92]. Slow transit constipation can, indeed, exacerbate delayed gastric emptying via a cologastric brake/reflex (rectal distension may inhibit gastric emptying via neural and humoral components) [93,94], prolong oral levodopa transportation time and increase the chances for levodopa to be prematurely metabolised by AADC and COMT in the GI tract [47].

TABLE 3 Diagnostic and therapeutic management of gastrointestinal dysfunction in Parkinson's disease.

GI barrier	Objective diagnostic tests	Therapeutic strategies
Dysphagia	• Flexible endoscopic evaluation of swallowing (FEES) • Video fluoroscopic swallowing study (VFSS)	• Maximize 'on' time with dopaminergic treatment • Swallow therapy from speech and language therapists including FEES assisted biofeedback • Expiratory muscle strength training • Gastrostomy for severe cases
Delayed gastric emptying	• ^{13}C-octanoate breath test • Gastric scintigraphy • Ultrasonography • Electrogastrography • Magnetic resonance imaging • Wireless motility capsule	• Dietary modifications (e.g., low-fat diet with small, frequent meals) • Peripheral dopamine blockers (domperidone) • Motilin receptor agonists (erythromycin or azithromycin • Serotonin agonists (mosapride or prucalopride) • Cholinergic enhancers (bethanechol or pyridostigmine)
Helicobacter pylori infection	• Urea breath test • Stool antigen test • Serological tests • Endoscopic biopsy samples with histological analysis or rapid urease testing	• 'Triple therapy', which includes a proton pump inhibitor and clarithromycin and amoxicillin or metronidazole
Small intestinal bacterial overgrowth	• Glucose or lactulose hydrogen breath tests • Jejunal aspirate	• Eradication with rifaximin
Constipation	• CTT studies with radiopaque markers	• Adequate fluid intake, increase dietary insoluble fibre • Regular physical activity • Probiotics and prebiotics • Osmotic laxatives (e.g., Macrogol, Movicol® or Miralax®) • Bulk laxatives (e.g., psyllium or linseed) • Stimulant laxatives (e.g., Bisacodyl) • Prokinetic agents (e.g., cisapride, mosapride, tegaserod) • Chloride channel activator (lubiprostone)

Abbreviations: CTT, colonic transit time; GI, gastrointestinal.

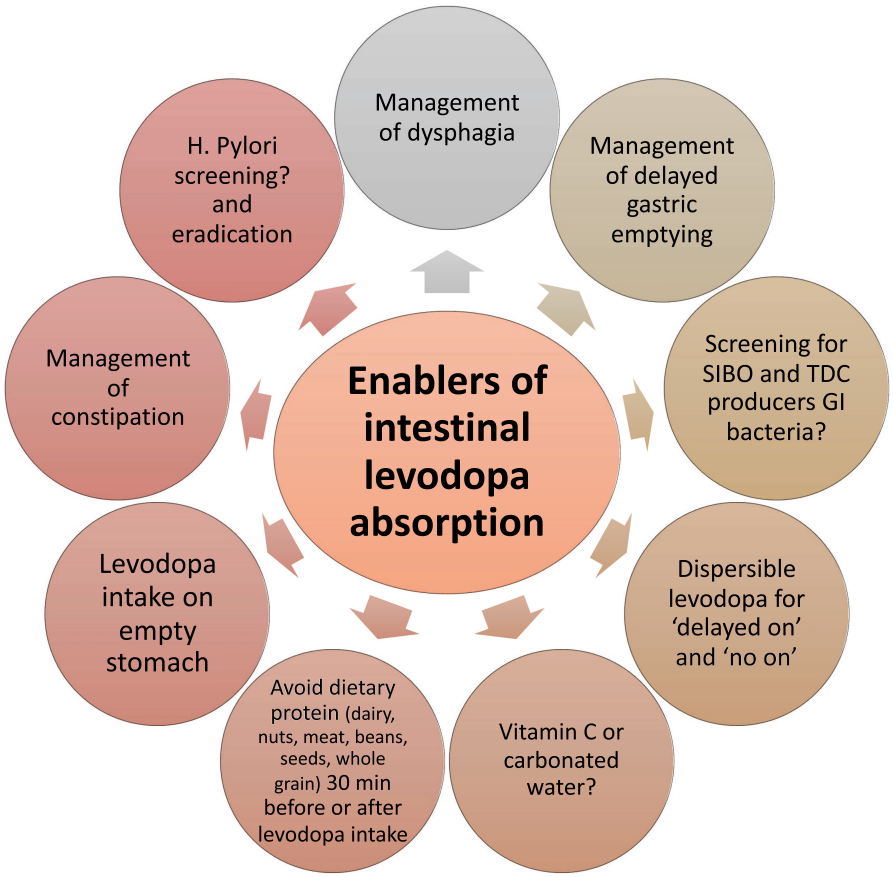

FIGURE 4 Enablers of intestinal levodopa absorption in Parkinson's disease. H. Pylori, *Helicobacter pylori*; SIBO, small intestinal bacterial overgrowth; TDC, tyrosine decarboxylase.

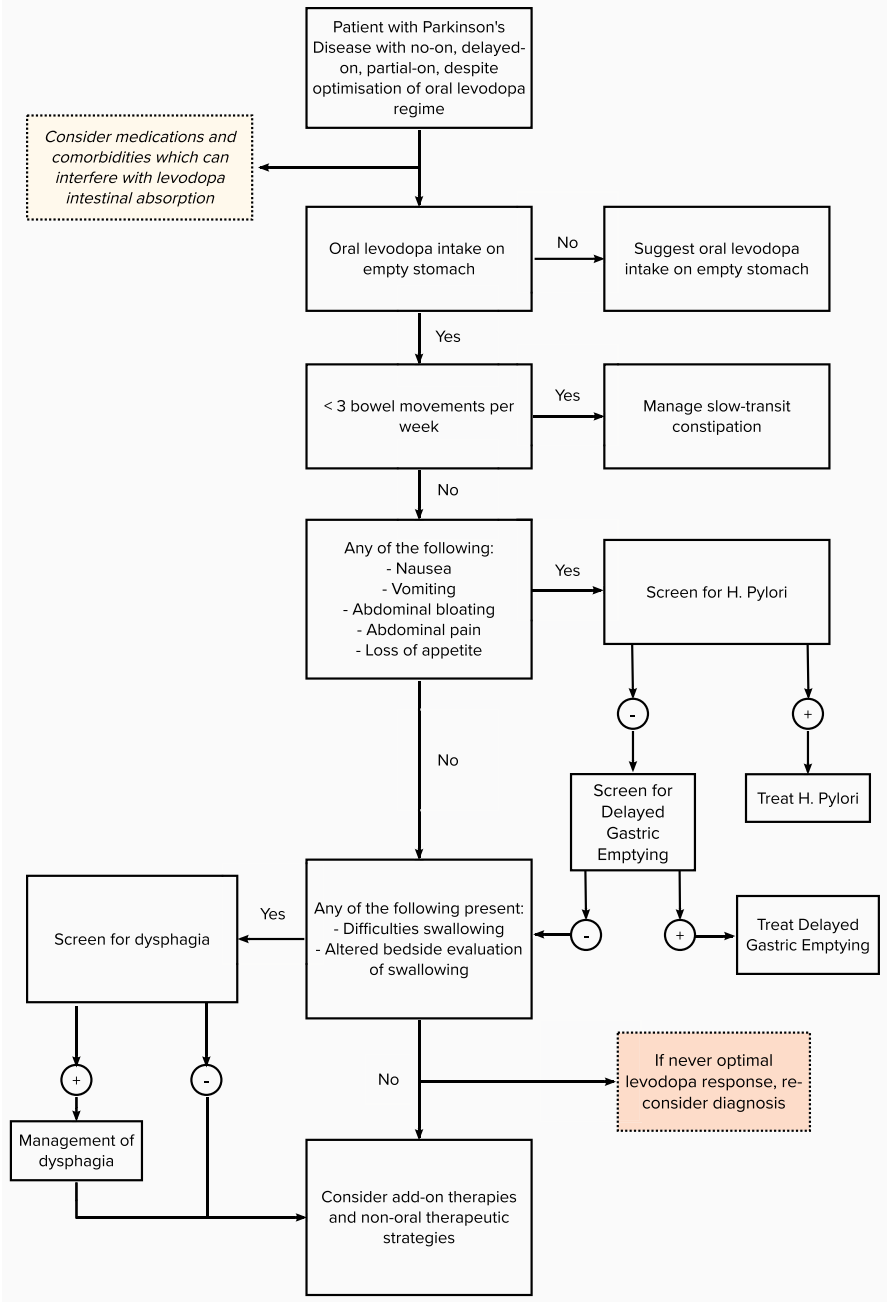

FIGURE 5 Pragmatic algorithm on how to tackle gastrointestinal barriers to levodopa transport and absorption in patients with Parkinson's disease and non-optimal oral levodopa response in clinical practice. It is envisaged that gut microbiota screening will shortly be included in clinical practice to identify the abundance of bacterial species able to metabolise levodopa in patients with PD with non-optimal levodopa response.

Although, to the best of our knowledge, there are no studies investigating the impact of constipation on levodopa pharmacokinetics in PD, it can be argued that slow transit constipation can impair levodopa transport and absorption and contribute to the development of motor complications such as severe 'off' periods.

Iatrogenic factors

Since levodopa's absorption occurs in a small portion of the intestine, any surgical procedure affecting the GI tract might influence levodopa pharmacokinetics. However, to the best of our knowledge, the possible role of GI surgery in affecting oral levodopa's absorption has not been systematically investigated. To date, only a few case reports and small case series exist, with controversial results [95–98].

Regarding medication, previous studies on both rats and humans showed that the concomitant administration of anticholinergic drugs whilst receiving levodopa may interfere with its GI absorption by delaying gastric emptying and inducing constipation [99]. Other substances affecting gastric motility may have a role in the pharmacokinetics of levodopa. For example, antacids initially favour levodopa transport and absorption by promoting gastric emptying [100]. However, their prolonged use leads to excessive neutralisation of gastric acidity, eventually reducing levodopa absorption. Additionally, antacids containing aluminium may also contribute to delayed gastric emptying as well as other drugs shown in Figure S1. Ferrous sulfate, a compound used to treat and prevent iron deficiency, may also interfere with levodopa pharmacokinetics by decreasing its absorption in the proximal small intestine [101].

Medical comorbidities

General medical conditions that primarily affect the absorption process—particularly those involving the bowel absorptive surface—should be considered as potential barriers to levodopa's absorption [102]. Despite being relatively common, their impact on levodopa pharmacokinetics has not been investigated, with only anecdotal evidence being available [103]. Short bowel syndrome secondary to intestinal resections, Crohn's disease, coeliac disease as well as radiation enteritis might represent obstacles to levodopa's absorption in PwP with non-optimal levodopa response.

Management strategies

Given the important influence of GI tract morphology and functionality on levodopa pharmacokinetics, it is crucial to evaluate the presence of GI barriers to levodopa transport and absorption in PwP presenting with poor levodopa response and motor complications, such as 'delayed on' and 'no on' phenomena. The concomitant presence of upper or lower GI symptoms may further indicate a possible underlying GI dysfunction and prime management strategies aimed at identifying and treating GI obstacles to levodopa transport and absorption (see Table 3); however, GI dysfunction in PD can often be asymptomatic, and the absence of GI-related symptoms should not automatically rule out its presence.

It is a common clinical practice to use the dispersible formulation of levodopa in PwP with GI symptoms and 'delayed on' episodes given the shorter time to peak of levodopa with the dispersible formulation compared with the standard form [104,105]. In addition, ascorbic acid intake combined with levodopa might improve the absorption of the latter [106,107]. These and other practical management strategies enabling intestinal levodopa absorption are summarised in Figure 4.

Once GI barriers have been identified, and if management strategies to address them have failed, clinicians should consider the use of non-oral therapeutic strategies for dopaminergic delivery to bypass the dysfunctional GI tract. Use of rotigotine transdermal patch and device-aided therapies such as apomorphine subcutaneous injection and infusion, levodopa-carbidopa intestina gel (LCIG) infusion and deep brain stimulation (DBS) represent useful therapeutic options (see Figure 5). Other non-oral approved formulations and delivery systems include levodopa-carbidopa-entacapone intestinal infusion, sublingual apomorphine and inhaled levodopa. Of note, preliminary data suggest that use of rotigotine transdermal patch, LCIG infusion and DBS can also improve symptoms related to GI dysfunction in PwP [108–111].

CONCLUSION

Throughout its journey from the mouth to the brain, oral levodopa faces a multitude of obstacles in the GI tract, leading to alteration of its pharmacokinetics, non-optimal levodopa response, and ultimately motor and non-motor fluctuations. Identification and management of GI barriers to levodopa transport and absorption should be integral to routine clinical practice in the management of PwP.

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