MANAGEMENT OF SLOW COLONIC TRANSIT CONSTIPATION IN PARKINSON'S DISEASE: CURRENT EVIDENCE AND A COMMUNITY PHARMACY PERSPECTIVE

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ABSTRACT

The non-motor symptoms of Parkinson's disease are often under-recognised and undertreated. Constipation is exceedingly common in Parkinson's disease, reportedly affecting up to 70% of patients. Pharmacists are ideally positioned to screen patients with Parkinson's disease for constipation and to optimise constipation management. This review will describe the evidence base for the use of different treatments in the management of constipation in patients with Parkinson's disease. PubMed, Embase and Web of Science were searched using the following search terms: "constipation" OR "gastrointestinal dysfunction" OR "slow colonic transit" OR "defecatory dysfunction" OR "slow motility" AND "treatment" OR "management" OR "therapy" AND "Parkinson* disease". The literature indicates macrogol is a safe and effective treatment for constipation in Parkinson's disease; it should be considered a first line treatment and can be recommended by the pharmacist over-the-counter. Pharmacists can provide information regarding fibre supplementation with psyllium, which may be effective and can be initiated early. Lubiprostone appears to be a promising option, but larger and longer trials are warranted. Although many commonly employed treatments for constipation have not been evaluated for efficacy in Parkinson's disease, pharmacists can utilise available data to make evidence-based recommendations to optimise management of constipation and improve patient quality of life.

Keywords: Constipation, Parkinson's disease, Treatment, Non-motor, Pharmacy practice

INTRODUCTION

While the typical motor symptoms of Parkinson's disease (PD) are well known, the wide array of non-motor symptoms associated with this condition are often under-recognised and therefore undertreated. Patients report non-motor symptoms such as sleep disorders, loss of sense of smell, depression and gastrointestinal symptoms to have a greater burden on their day-to-day life than their motor-symptoms do [1]. Parkinson's patients suffer various gastrointestinal disturbances, which can present across different stages of the disease and in all parts of the gastrointestinal tract leading to symptoms ranging from drooling to reflux and constipation [2]. Constipation is the most common gastrointestinal disturbance in PD, with a reported prevalence ranging from approximately 15 to 70% [3-5]. The two main causes of constipation in patients with PD are slow colonic transit and defaecatory dysfunction [6].

In PD, slowing of colonic transit is likely due to impaired peristalsis [7], which in turn may be attributed to the presence of Lewy bodies (proteinaceous cytoplasmic inclusions) in the enteric nervous system (ENS) [8-12] and dorsal motor nucleus of the vagus (DMV) of the spinal cord as well as severe degeneration in the DMV [13]. Loss of dopaminergic enteric neurons has also been reported in patients with PD [14], although the clinical significance of this is unclear as these dopamine cells only represent 1-2% of the total ENS population and are thought to play an inhibitory role on gut motility. It is possible that by losing these inhibitory signals the gastrointestinal tract is not able to optimally perform the coordinated action of contraction and relaxation required for peristalsis. Not all studies have reported a loss of neurons in the myenteric plexus; prior reports found no change in the amount of nitric oxide, vasoactive intestinal polypeptide or catecholamine expressing neurons in PD patients compared to healthy controls [11, 13]. In addition to the pathological changes that occur in PD, dopaminergic and anticholinergic treatments can contribute to constipation. While constipation may worsen following the initiation of dopaminergic treatment [15, 16], such drugs cannot be the sole cause of this symptom as constipation is present in many patients prior to pharmacological intervention [17].

Defaecatory dysfunction, the other cause of constipation in Parkinson's patients, is due to disruption of the coordinated activity required for faecal expulsion. The physiological defaecation process involves relaxation of the puborectalis muscles to open the anorectal angle, reflex opening of the internal anal sphincter and voluntary relaxation of the external anal sphincter [9, 18]. This action is mediated by reciprocal interactions between neurons in the sacral parasympathetic nucleus of the spinal cord and Onuf's nucleus in the sacral cord, which innervates the external sphincter and pelvic floor [19]. The sacral defaecation reflex is also regulated by supraspinal mechanisms such as the descending inputs of the medullary raphe nuclei to Onuf's nucleus [20]. The medullary raphe nuclei is reported to be affected in early PD, therefore the activation, instead of inhibition, of Onuf's motoneurons seen in PD could be due to impaired modulation from supraspinal mechanisms, ultimately resulting in the passing of fewer stools or incomplete defaecation. Parkinson's patients are reported to have α-synuclein pathology in the lateral collateral pathway, a region of the sacral spinal dorsal horn important for the relay of pelvic visceral afferents, this is also likely to contribute to defaecatory dysfunction constipation [21]. Defaecatory dysfunction constipation is very difficult to treat as routine laxatives fail to improve the impaired anorectal muscular coordination. Specific treatments include botulinum-toxin injections into the puborectalis muscle and sacral nerve stimulation, both of which require specialist medical care. As the pathology of constipation in the Parkinson's patient population may differ from other presentations of chronic constipation, management should include treatments that have been evaluated specifically in this patient group.

Braak and colleagues staging of PD states the gastrointestinal tract as one of the earliest regions to develop Lewy body pathology, suggesting unidentified toxins may cross the mucosal barrier of the intestine inducing pathology in the axon terminal of the vagus nerve, which subsequently progresses in a retrograde manner to the brain [22]. Once in the brain damage can occur to the dopamine-producing cells in the substantia nigra, resulting in development of the typical motor symptoms [8]. In line with Braaks hypothesis, several studies have reported constipation develops up to 20 y earlier than the motor symptoms [23, 24]. Due to this early presentation patients

may not associate the gastrointestinal disturbance and their PD and therefore fail to discuss the problem with their doctor or neurologist. Pharmacists are therefore in an ideal position to screen patients with PD for constipation when they present to have their motor-symptom medication dispensed. The pharmacist can use this opportunity to question appropriately and provide advice regarding the management of constipation in this patient group, to allow early intervention and substantially boost patient outcomes. Early identification is important to prevent progression to serious complications such as intestinal pseudo-obstruction, bowel perforation, sigmoid volvulus and megacolon, which may require surgical treatment [2, 25, 26].

This review will focus on the evidence base for effective treatment of slow colonic transit constipation in PD and provide commentary regarding the important role the pharmacist can play in screening for and in providing treatment advice to improve quality of life for patients with PD.

Screening for constipation in patients with Parkinson's disease in community pharmacy practice

Screening for constipation can be challenging as frequency of bowel movements can vary considerably between individuals, therefore it is usually the change in bowel movements that is diagnostic [27]. In patients with PD, constipation may have developed slowly over many years, making a distinct change in bowel habits difficult to discern. Thus, a detailed assessment is required to establish if constipation is present; for suggested screening questions the pharmacist can use in conversation with patients with PD see table 1. Constipation should be screened for when the patient first presents to the pharmacy with a diagnosis of Parkinson's disease, for example when they first present to fill a prescription for motor-symptom medication. The pharmacist then has the opportunity to monitor symptoms by asking about changes in bowel habits as the patient presents regularly to have their motor-symptom medication dispensed. The pharmacist can also play a key role in educating the patient regarding the link between constipation and PD so they can self-monitor for indicative symptoms. Once constipation has been confirmed the pharmacist should screen for reversible causes (see table 2 for suggested questions to establish contributing factors) and for 'red flag' symptoms, which indicate referral to a medical practitioner is warranted (see table 3).

In patients with PD, if defaecatory dysfunction is suspected (characterised by excessive straining, accompanied by pain and a sense of incomplete evacuation), the patient should be referred to their medical practitioner, as over-the-counter treatments are typically ineffective.

Table 1: Suggested screening questions to determine if the patient is likely to be experiencing constipation [28-30]

Screening questions	Response criteria
On average, could you estimate how many bowel movements you have had per w over the last 3 w?	Less than three per w is usually indicative of constipation.
Do you have pain, discomfort or a sensation of incomplete evacuation when having a bowel movement?	Positive response can indicate constipation.
Would you say the consistency of the stool was hard, soft or normal?	Hard consistency would be considered a sign of slow colonic transit constipation.
How often have you had to strain during bowel movements over the last 12 w?	Straining for greater than 25% of bowel movements suggests constipation.
Have you had to take laxatives or perform any manual manoeuvrers to pass a bowel motion over the last 12 w? If so, how often?	A positive response indicates faecal impaction. If intervention was necessary for greater than 25% of bowel movements in the last 12 w it suggests constipation.
How often do you have difficulty relaxing or letting go to allow the stool to come out during a bowel movement?	This is indicative of defaecatory dysfunction.

Table 2: Screening questions to assess contributing factors and/or underlying cause/s of constipation [31, 32]

Screening questions	Response criteria
When did your symptoms begin? Did your symptoms come on suddenly or gradually worse over time?	Determining time and manner of onset can help identify the underlying cause by establishing time-course relationships.
On average how much water and other fluids do you drink per d? Has your fluid intake changed recently?	Inadequate fluid intake can lead to constipation. Suggested adequate intake of fluids is at least 2 l per d.
Does your diet include foods high in fibre? Have you recently changed your diet? Has you intake of foods high in fibre increased or decreased?	A low fibre diet may predispose to constipation. Insoluble fibre (e. g. legumes, skins of fruit and vegetables, wholegrain foods) and soluble fibre (e. g. oats, psyllium husk, fruits and vegetables) can be effective in preventing or alleviating constipation in those with inadequate baseline intake.
Do you engage in regular physical activity? Has your activity level changed recently?	Insufficient physical activity may predispose to constipation. Constipation may develop during periods of inactivity, e. g. while recovering from an injury.
Do you ever suppress the urge to pass a bowel movement?	Responding immediately to the urge to defaecate may provide a benefit in those with constipation.
Are you currently taking any medications?	Medications that can cause constipation include: • antacids containing aluminium and calcium • some anticonvulsants (e. g. carbamazepine, phenytoin, pregabalin) • antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) • sedating antihistamines • antimuscarinic drugs • many antipsychotics (e. g. olanzapine, risperidone, quetiapine) • calcium supplements • clonidine • diuretics • dopaminergic drugs

	• iron
	• opioid analgesics
	• sucralfate
	• verapamil
	• vinca alkaloids
	• 5-hydroxytryptamine ($5HT_3$) receptor antagonists
Do you have any other medical conditions? (in addition to Parkinson's disease)	Relevant medical conditions which may be predispose to constipation include:
	• coeliac disease
	• psychiatric conditions (e. g. depression, anxiety)
	• diabetes mellitus
	• hypothyroidism
	• irritable bowel syndrome
	• multiple sclerosis

Table 3: A list of 'red flag' symptoms, which indicate referral to a medical practitioner is warranted [31, 33]

Red flag symptoms
Persistent or severe abdominal pain
Nausea and vomiting
Constipation alternating with diarrhoea
Unintentional weight loss
Blood and/or mucus in the stool (including black 'tarry' stool)
Tenesmus (continuous feeling of the need to defaecate)
Fever
Sudden change in bowel habit>2 w in duration, not attributable to changes in diet or lifestyle, a medical condition or medication
Rectal pain causing the patient to suppress the defaecatory reflex

MATERIALS AND METHODS

Papers for review were identified through an electronic search of PubMed, Embase and Web of Science databases (Feb 2016) using the following search terms: "constipation" OR "gastrointestinal dysfunction" OR "slow colonic transit" OR "defecatory dysfunction" OR "slow motility" AND "treatment" OR "management" OR "therapy" AND "Parkinson* disease". Reference lists of articles identified through initial search were reviewed to identify additional articles of relevance. Only papers published in English were included.

DISCUSSION

Management of slow colonic transit constipation in Parkinson's disease

Differences in the underlying cause of constipation in patients with PD mean different treatments strategies are appropriate for slow colonic transit constipation compared with defaecatory dysfunction. As slow colonic transit is exceedingly common in patients with PD [34], this review will focus on the evidence for treatments used for this form of constipation.

Dietary and lifestyle interventions

Before recommending a pharmacological intervention for constipation in PD, as with other patient groups experiencing constipation, the pharmacist should provide advice regarding lifestyle modifications that can be trialled. Such interventions include increasing and/or supplementing dietary fibre and increasing fluid intake as well as increasing exercise levels. However, the pharmacist will need to weigh up the efficacy and appropriateness of these measures in light of the stage of PD the patient is experiencing, as discussed below.

Increased fluid intake

Patients suffering from constipation are often advised to increase their fluid intake, yet data to support this recommendation are surprisingly scarce. Clinical studies investigating constipation in multiple populations have demonstrated only minimal benefit in terms of changes in stool frequency, stool consistency and difficulty during defaecation, with benefits deemed unlikely to be clinically relevant [35-37]. Increasing fluid intake alone may only attenuate constipation in those with insufficient fluid intake [38].

Patients with PD, particularly advanced disease, present with a higher risk of dehydration than the general population as gastrointestinal symptoms, such as drooling and difficulty swallowing, could lead to reduced fluid intake [23]. Hence, it is possible this patient group may respond better to increased fluid intake than others who suffer from chronic constipation. Ueki and Otsuka [23] investigated the potential association between decreased water intake and constipation in 94 patients with PD. Total water intake was significantly lower in PD patients, than in controls and 70% of the patients were defined as having constipation. The amount of water consumed in patients with PD was inversely correlated with severity of constipation. Intriguingly, PD patients also tended to not feel thirsty and therefore had little desire to drink water throughout their life, suggesting water depletion may have preceded the development of constipation [23].

Increased dietary fibre intake

Astarloa and Mena [39] have demonstrated that when Parkinson's patients increase their daily intake of insoluble dietary fibre from approximately 10 g to 28 g they have a significant improvement in their severity of constipation. This dietary intervention also produced improvements in the patients' motor scoring likely due to better absorption of L-dopa, which was evident by substantially higher total plasma L-dopa levels [39]. In Astarloa's study the increase in fibre was achieved through supplementation with a mixture of tablets containing wheat bran, pectin and dimethyl-polyoxylhexane-900. This approach may be particularly suitable for patients with advanced PD that may have low fibre intake as a result of difficulties in chewing, which often accompanies high fibre foods. Another viable option to introduce higher amounts of fibre in a PD patients' diet is consumption of fibre supplements such as psyllium (botanical name: *plantago ovate*, also known as ispaghula husk), which functions as a bulk-forming laxative. Ashraf and Pfeiffer [40] assessed the effect of psyllium on constipation in PD, in a small randomised placebo-controlled trial, finding that although psyllium increases stool weight and frequency, it does not change colonic transit or anorectal function.

Increased physical activity

To date no studies have directly assessed whether increasing exercise attenuates constipation in patients with PD. However, exercise may produce the same improvement in defaecation pattern and colonic transit time for this sub-group as it does for others suffering chronic idiopathic constipation [41]. Leading a sedentary lifestyle is associated with an increased risk of developing

constipation [42], and may therefore be playing a role in constipation in PD patients whose debilitating motor symptoms and increased risk of falls and fall-related injuries, such as fractures, leads to a more inactive lifestyle [43, 44]. Importantly, health care professionals need to weigh the benefit: risk ratio of different forms of physical activity on an individual basis in patients with PD as their higher risks of falls may render some exercise interventions too unsafe for the potential benefit [45, 46].

Dietary probiotic supplements

Currently only one study has assessed the effect of probiotics on constipation in PD. In this study, the authors reported the combination of dietary intervention (following nutritional recommendations for fluid and fibre intake) with 65 ml of fermented milk containing *Lactobacillus casei* Shirota daily, had superior effects than dietary intervention alone [47]. Specifically, the probiotics were able to improve stool consistency, bloating, abdominal pain and the sensation of incomplete evacuation in patients that showed no improvement from the just dietary intervention. The use of probiotics may have the additional benefit of repopulating the bowel with normal flora as PD patients have been shown to have an increased prevalence of small intestinal bacterial overgrowth [48, 49]. Treating PD patients who have small intestinal bacterial overgrowth can potentially also improve the patients' motor symptoms as these patients tend to have longer off-time in response to their medication and worse motor fluctuations [50].

Pharmacological interventions

If non-pharmacological interventions, including bulking agents, are unsuccessful or inappropriate, the pharmacist can provide advice regarding pharmacological laxatives, which can be added for the management of constipation. A variety of over-the-counter and prescription treatments are available, ranging from osmotic laxatives and stool softeners to stimulant laxatives and secretagogues. In general, evidence to substantiate the relative efficacy and tolerability of the different types of laxatives is scarce, thus pharmacist-led drug selection should be based upon factors such as the required onset of action, hardness of stool, patient preference, adverse effects, effectiveness of previous treatments and cost [51]. Differences in the underlying constipation pathology may also influence the efficacy of specific treatments. The following section outlines the direct evidence for the use of different types of laxatives for constipation in patients with PD, in the context of efficacy data for constipation in other populations.

Osmotic laxatives

There is more evidence for the efficacy for macrogols (also known as polyethylene glycols), in constipation in PD patients than for any other laxatives available over the counter. Macrogol 3350, commonly administered in a formulation containing electrolytes to minimise electrolyte and water loss, works by increasing the water content and volume of the stool. It achieves this by increasing the osmolality of the gastrointestinal lumen, thereby stimulating water to enter the lumen to balance the osmolality. The osmotic action of macrogol results from its high water binding capacity [52].

Two studies, one open-labelled and the other a randomised, double-blind parallel group study, have assessed the benefit of macrogol for constipation in PD patients, both reporting positive outcomes in terms of more frequent bowel movements, softened stool consistency, increased ease of defaecation and a reduced need of rectal laxatives [52, 53]. Zangaglia and Martignoni [53] administered either placebo (flavoured maltodextrine in 250 ml water) or macrogol electrolyte solution (7.3 g in 250 ml water) twice a d for 8-w. Their intervention was well tolerated and considered safe with minimal risk in patients with PD [53, 54].

Other osmotic laxatives such as lactulose, lactitol, sorbitol and mannitol are yet to be directly assessed in PD patients. In other types of constipation such as opiate-induced constipation, polyethylene glycol 3350+electrolytes is reported to be more effective with fewer adverse effects than lactulose [55]. Similarly, in hospitalised patients macrogol with electrolytes is more effective than treatment with psyllium [56].

Rectal osmotic laxative formulations contain poorly absorbed ions such as magnesium, sulfate, phosphate and citrate, which retain fluid in the colon by osmotic effect and stimulate peristalsis [51]. While no studies have compared oral laxatives with rectal formulations in PD patients, rescue treatment with rectal laxatives (enemas) can be trialled if oral medications have failed [57].

Stool softeners

Stool softeners used in the management of constipation include docusate, poloxamer, liquid paraffin (also known as mineral oil), seed oils and arachis oil. No studies have investigated the efficacy of stool softeners in constipation associated with PD.

In other groups suffering constipation, docusate is the most widely used stool softener. Docusate sodium (dioctyl sodium sulpho-succinate) is a synthetic anionic detergent; it assists in the treatment of constipation by reducing surface tension, thereby allowing penetration of water and fats into the faeces. Although initiation of a stool softening agent is often regarded as the first step in treating constipation, at least one study suggests psyllium is superior to docusate, furthermore, in other states of refractory constipation, such as opioid-induced constipation, stool softeners alone are generally insufficient. Thus, the role for stool softeners as a sole therapy for constipation in patients with PD is likely to be limited.

Liquid paraffin, seed oils and arachis oil work as lubricants to assist faecal movement, despite being used clinically for decades, evidence of efficacy has not been demonstrated in randomised, controlled trials [56]. Furthermore, these treatments carry the risk of lipoid pneumonia if aspirated, and are therefore contraindicated in patients at risk of aspiration [58]. Given 'silent' aspiration without any recognisable swallowing difficulty is common in patients with PD [59], liquid paraffin and oral seed/arachis oils should be avoided in this patient group.

Stimulants

Stimulant laxatives, such as senna and bisocodyl aid in constipation by promoting intestinal motility, thereby reducing the time for absorption of salt and water. Such drugs also increase release of histamine, serotonin and prostaglandins in the colon, of these mediators, prostaglandins are thought to be the most important in increasing bowel movements. As is the case for stool softeners, no stimulant laxatives have been evaluated specifically in PD.

Prokinetics

Prokinetic drugs are usually reserved for refractory cases of constipation. Cisapride, tegaserod, mosapride and prucalopride are 5-HT$_4$ receptor agonists that have been evaluated for treatment in constipation. Activation of serotonergic receptors in the gastrointestinal tract assists in treating constipation by stimulating peristalsis, increasing intestinal secretions and reducing visceral hypersensitivity.

Cisapride also stimulates gastrointestinal motility by promoting the physiological release of acetylcholine from the postganglionic nerve endings of the myenteric plexus. In contrast to many constipation treatments, cisapride has been investigated specifically for constipation in PD in 3 clinical trials. In a pilot study all 20 PD patients benefited from cisapride 5 mg twice a d, demonstrating reduce colonic transit time radiographically [34]. In a further study cisapride 10 mg twice a d was found to accelerate colonic transit time by approximately 40% in this patient group [60]. Unfortunately, a long-term follow up study, in which patients were treated with cisapride 10 mg twice a d, observed reduced efficacy at 6 mo, and virtually no benefit over baseline following one year of sustained use [61].

Cisapride however, was withdrawn from the market world-wide following reports of serious cardiac events [62], thought to results from its effects on human ether-a-go-go-related gene (hERG) potassium channels. In many countries cisapride remains available only via special or compassionate access schemes for use in gastroparesis under specialist care. Tegaserod, a partial 5-HT$_4$ agonist found to be beneficial in the management of constipation in PD in an open label study [63] but not in a small randomised

controlled trial [64], has similarly been withdrawn due to cardiovascular toxicity concerns.

Unlike cisapride, the 5-HT$_4$ agonist mosapride is devoid of D2 dopaminergic and hERG potassium channel blocking effects. It has also been tested in a small number of patients with PD in an open label Japanese trial [65]. In this trial a dose of 15 mg per d was effective in shortening colon transit time, improving subjective bowel movement frequency and reducing difficult defaecation [65]. Mosapride was well tolerated by 6 of 7 PD patients, with one patient ceasing treatment due to epigastric pain [65]. Accessibility limits clinical use in many countries, while it is available in parts of Asia and South America, it is not on the market in the US, Europe, the UK or Australia. Further larger, randomised studies should be performed before mosapride can be recommended in PD.

Prucalopride, another 5-HT$_4$ agonist that does not inhibit hERG potassium channels, is more widely available than mosapride (on the market in Australia, Canada, Europe, the UK and some parts of Asia), although it has not yet been approved by the US Food and Drugs Administration (FDA). To date prucalopride has not been studied in the PD population and results in patients with severe chronic constipation have been inconsistent. Prucalopride, dosed at either 2 mg or 4 mg once daily, did significantly improve bowel habit assessments relative to placebo in three large, randomized, double-blind, 12-w trials in patients with severe chronic constipation [66]. However, a trial published earlier this year failed to find an increase in the frequency of spontaneous, complete bowel movement vs. placebo using 2 mg daily dose over 24 w. In light of these inconsistent results and lack of population-specific data, prucalopride is not yet recommended in PD. New generations of highly selective 5-HT$_4$ agonists under development (velusetrag, noranopride) are hoped to progress to provide prokinetic options with greater efficacy and safety [67].

Other traditional prokinetics include dopamine antagonists domperidone and metocolpramide. However of the two dopamine-2 receptor antagonists used clinically, only domperidone is suitable for use in patients with PD as it does not reach the central nervous system. Metoclopramide must be avoided as it crosses the blood-brain barrier leading to blockade of central dopamine receptors, which can quickly exacerbate parkinsonian symptoms. Domperidone improves nausea and reflux symptoms in PD, however the beneficial effects seen it the upper gastrointestinal tract were not observed in patients with constipation [68]. It should also be noted that domperidone increases levodopa absorption and subsequently produces motor benefits. In patients with PD domperidone has been trialed for various indications in doses from 10 mg to 120 mg daily; despite this doses above 30 mg/d, should be used with particular caution due to the risk of arrhythmia, sudden death and cardiac arrest, especially in patients with additional risk factors for QTc interval prolongation [69]. Although domperidone is not FDA approved it is widely available elsewhere, and is even accessible over the counter in some regions. The pharmacist has a critical role in screening for drug interactions between domperidone and cytochrome P450 3A4 inhibitors, p-glycoprotein inhibitors or other drugs that can prolong the QTc interval in PD patients, particularly in areas where domperidone is available without a prescription.

Secretagogues

Lubiprostone is a well-tolerated, FDA approved bicyclic fatty acid metabolite analogue of prostaglandin E1 that works by activating type-2-chloride channels on the mucosal epithelia [70]. Studies have shown that lubiprostone dose-dependently increases fluid secretion in the intestinal lumen, which is thought to contribute in the improvement of constipation [71]. Ondo and Kenney [72] performed a double blind, randomized, controlled trial assessing the effectiveness of lubiprostone for short-term relief of constipation in 54 patients with PD. In this study, lubiprostone titrated up to a dose of 24 microg twice daily, improved patient reported constipation scale scores and increased stool frequency at the 4-w follow-up. Additionally, this treatment was well-tolerated; the main adverse effect reported was loose stools, which were mild and self-limiting [72].

Other pharmacological interventions

Linaclotide, is a newer agent approved for the treatment of chronic constipation in the US, UK and some other parts of Europe. It is a guanylate cyclase C receptor agonist and thereby promotes formation of guanosine monophosphate to increase secretion of chloride and bicarbonate into the intestinal lumen [73]. In turn this action increases luminal fluid secretion and accelerates intestinal transit. Although not studied in patients with PD, two double blind, randomised controlled linaclotide trials found doses of 145 mg to 290 mg improved the frequency of complete spontaneous bowel movements vs. placebo [73], thus it may be a useful option if other treatments are unsuccessful. As an additional benefit linaclotide inhibits pain via the C-fibers and can therefore attenuate abdominal pain [74], which is an issue for some PD patients [75].

Other new agents in development for chronic constipation include elobixibat, an ileal sodium/bile acid cotransporter modulator (partial inhibitor), which increases fluid secretion and motility by increasing delivery of bile acid to the colon; itopride, an inhibitor of acetylcholinesterase and dopamine-2 antagonist; and the ghrelin analogues such as relamorelin, which is a ligand for growth hormone secretagogue-1a [67]. Although results in chronic constipation in general are promising, studies to confirm efficacy in constipation in patients with PD are required.

Finally, a number of older medications licensed for alternative indications have been trialled for constipation in PD and may be of use when established treatments fail. One case report from the 1980's reported colchicine, a drug traditionally used to treat gout, given at low doses (0.3-0.6 mg) to be successful in controlling constipation in patients that were unresponsive to standard measures like other laxatives and enemas [76]. Similarly, Sadjadpour [77] provides commentary indicating pyridostigmine bromide, typically used to treat myasthenia gravis, is effective at relieving constipation for PD patients who fail to respond to ordinary measures like bulk-forming laxatives. Pyridostigmine bromide works by enhancing intestinal motility but at large doses has been reported to cause diarrhoea and abdominal cramps [77]. Nizatidine is a selective histamine-2 receptor antagonist, which, unlike other histamine antagonists, is thought to promote gastric motility via inhibition of acetylcholinesterase, in addition to reducing gastric acid secretion [78]. In a recent open-label study nizatidine 150 mg twice daily was able to decrease gastric emptying time in patients with PD who had delayed gastric emptying at baseline. Interestingly, the improvement in colonic transit time was not significant in the cohort without stratifying for baseline transit time. In this study nizatidine was safe and well-tolerated, and it is available over the counter in a number of countries [78].

Interestingly, a recent retrospective review of medical records found use of beta-blockers to be associated with a 70% lower relative risk of constipation, while dopaminergic treatments appeared to increase the risk of constipation by 50%. As discussed previously, intestinal motility is regulated by the autonomic system, thus beta-blockers may positively augment gastrointestinal transit by modulating sympathetic input [79]. Additional research is required to determine if/how beta-blockers may be utilised in the management of constipation in PD.

Herbal medicines

If lifestyle interventions are unsuccessful or inappropriate, and the patient requests a herbal option the pharmacist could discuss the following herbal medicines that have specifically been assessed for treating constipation in PD.

Dai-Kenchu-tou®

Dai-Kenchu-tou® is a dietary herb extract containing 50% ginger, 30% "Nin-jin" (*ginseng*) and 20% "Sansho" (Japanese pepper, *Zanthoxylum piperitum*), which is used in Eastern countries to ease abdominal distension [80]. The pharmacological action of Dai-Kenchu-tou® to increase gastric motility is likely due to the serotonergic 5-HT$_3$ receptor agonist properties of the active component, hydroxy-(r)-sanshool hasi [81]. Activation of serotonergic neurons in the gastrointestinal system in turn induces

acetylcholine release from the myenteric plexus, stimulating the gastrointestinal tract to contract [82]. Two case studies have documented beneficial effects of Dai-Kenchu-tou® for constipation in Parkinson's patients, including increased frequency of bowel movements, shortened colonic transit time and a reduction in difficult defaecations [80, 83]. The herb extract was well tolerated; the only adverse effect reported was 'bitter taste'. However, large, randomised, blinded and controlled studies need to be performed to verify the case report results.

Rikkunshi-to®

Rikkunsh-to® is a dietary herb extract containing 17% *Atractylodis lanceae*, 17% *Poria cocos*, 17% *ginseng*, 17% *Pinellia ternata*, 9% ginger, 9% orange peel, 9% *Ziziphus jujuba* and 4% *Glycyrrhiza*, which is given in Eastern countries to alleviate vomiting, abdominal distention and pain [84, 85]. The small, open-labelled study showed Rikkunsh-to® to be well tolerated with the only adverse effect reported being its bitter taste. However, while Rikkunshi-to® improved gastrointestinal symptoms such as appetite loss, bloating and gastric emptying it failed to change the patients' complaints of constipation [85].

CONCLUSION

Macrogol (polyethylene glycol) is a safe and effective treatment for constipation in patients with PD; pharmacists should consider it a first line treatment option. Fibre supplementation with psyllium may also be effective and can be initiated early. Lubiprostone appears to be a promising option for managing constipation in PD, but larger trials with a longer duration of treatment are warranted. Based upon the literature discussed above, fig. 1 provides a flow-chart summary to guide the management of constipation in patients with PD in community pharmacy practice.

It remains to be determined if newer drugs, such as the 5-HT$_4$ agonist prucalopride or the guanylate cyclase C receptor agonist linaclotide, will prove beneficial in treating constipation in patients with Parkinson's disease. Pharmacists are ideally positioned to play a key role in both screening for constipation in patients with PD and in recommending evidence-based treatments for managing constipation in this often difficult to treat patient population.
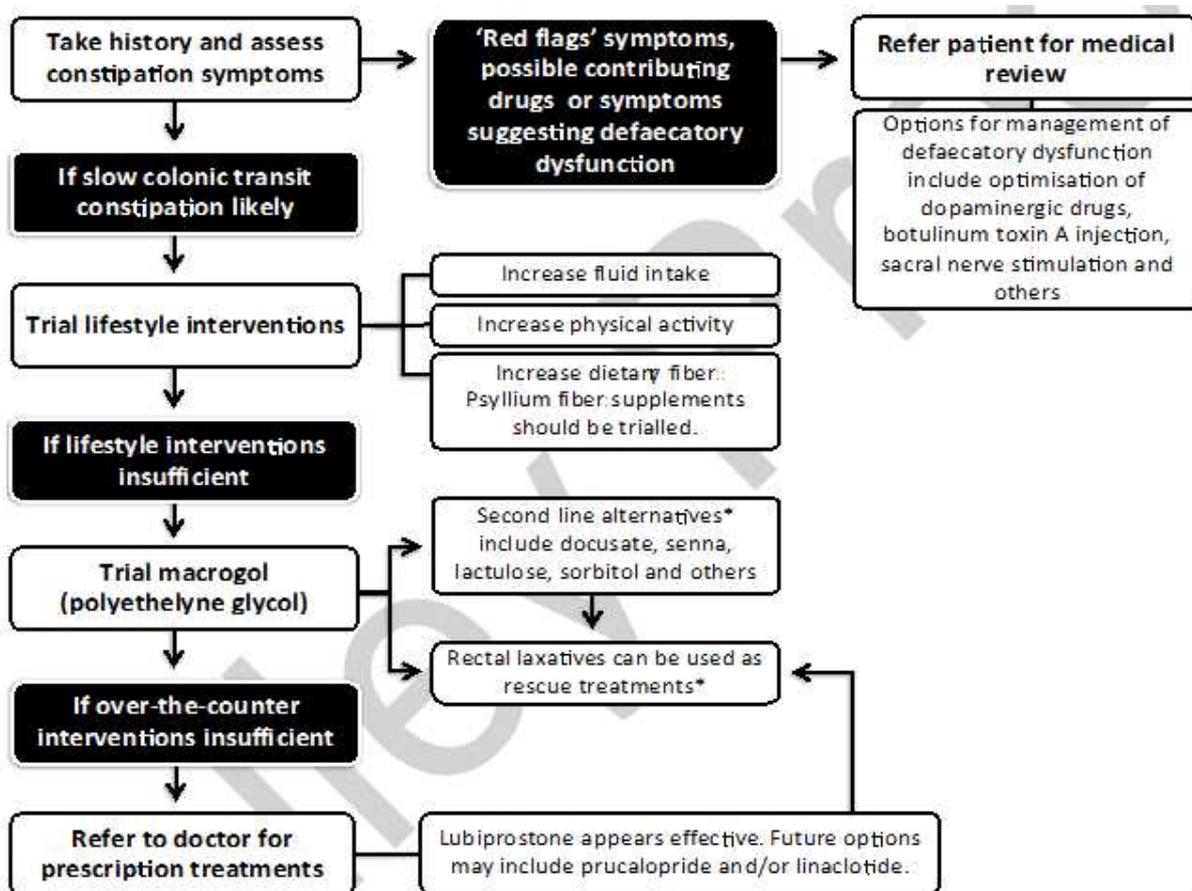

Fig. 1: Flow diagram of the management of constipation in patients with Parkinson's disease in community pharmacy [23, 39-41, 52, 53, 72]

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest

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