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Diabetes Mellitus and the Colon

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Opinion statement

Diabetes mellitus (DM) can affect the structure and function of the colon promoting commonly encountered lower gastrointestinal symptoms such as constipation, diarrhea, abdominal distention, bloating, and abdominal pain. Specific colonic disorders for which adults with DM are at greater risk include chronic constipation, enteropathic diarrhea, colorectal cancer (CRC), inflammatory bowel disease, microscopic colitis, and *Clostridium difficile* colitis. Smooth muscle structure and function, density of the interstitial cells of Cajal, and the health and function of the autonomic and enteric nerves of the colon are all potential affected by DM. These effects can in turn lead to alterations in colon motility, visceral sensation, immune function, endothelial function, and the colonic microbiome. The evaluation and treatment for slow transit constipation as well as pelvic floor dysfunction should be considered when constipation symptoms are refractory to initial treatment measures. DM-related medications and small bowel conditions such as celiac disease and small intestinal bowel overgrowth should be considered and excluded before a diagnosis of enteropathic diarrhea is made. Given the higher risk of CRC, adults with DM should be appropriately screened and may require a longer bowel preparation to ensure an adequate evaluation.

Keywords

Diabetes; Colon; Slow transit constipation; Diarrhea

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that is characterized by hyperglycemia and variable degrees of insulin deficiency and/or resistance. DM is further classified based on the underlying pathology to either that of type 1 DM or that of type 2 DM, with type 1 DM resulting from the destruction of the beta cells of the pancreas and

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resultant absolute insulin deficiency versus that of type 2 DM representing a combination of insulin resistance and relative insulin deficiency. Type 2 DM is considerably more common in adults representing more than 90% of the cases of DM [1].

In the USA, roughly 9.3% of the population (29.1 million people) have DM, which is a marked increase since 1994 when 4.4% of the population had DM. It currently affects over 25% of those ≥ 65 years of age, and it is believed that roughly 8 million people are still left undiagnosed [1, 2]. DM carries a large burden to society. In 2012, the estimated cost of DM in the USA was $245 billion dollars ($176 billion in direct medical costs and $69 billion in indirect costs). In addition, patients with DM have higher rates of morbidity, mortality, and overall worse quality of life with nearly 40% of adults with DM perceiving their health as either fair or poor [1]. It is estimated that there will be nearly 590 million people worldwide with DM by 2035 [2].

Those with DM are at increased risk for a variety of gastrointestinal (GI) complications that span the entire GI tract including gastroesophageal reflux; esophageal dysmotility; impaired gastric relaxation and accommodation; impaired gastric contraction and emptying; dysmotility of the small bowel, colon, and rectum; and non-alcoholic fatty liver disease and celiac disease (in association with type 1 DM) [3–5]. It has been suggested that roughly 75% of patients with DM have associated GI symptoms which can include heartburn, acid regurgitation, non-cardiac chest pain, dysphagia, postprandial fullness with nausea, bloating, abdominal pain, diarrhea, constipation, and fecal incontinence [6– 8].

This review will focus on clinical disorders of the colon that pose a higher risk in DM as compared to the general population, including chronic constipation, enteropathic diarrhea, colorectal cancer, inflammatory bowel disease, microscopic colitis, and *Clostridium difficile* colitis. We will discuss how DM may modify risk of these particular colonic disorders and provide the most current treatment approach to these conditions.

Pathophysiology

The underlying mechanisms of GI dysfunction associated with DM appear to be multifactorial and complex and remain incompletely defined. Known and emerging mechanisms include neuropathic injury and alteration to the autonomic nervous system, enteric nervous system, and interstial cells of Cajal (ICCs), as well as direct myopathic changes to the smooth muscle [9]. The neuropathic effects of diabetes can involve the entire GI tract including the colon. The well-described changes of the vagus nerve including segmental demylelination, axonal degeneration, and a reduction in motor as well as sensory ganglions are also presumed to involve the autonomic nerves of the colon as well [9]. Indeed, DM-related changes to the myenteric plexus of the colon have been repeatedly demonstrated in rat models to include neuronal degeneration and neuronal reduction [10–12]. A case series of seven patients with diabetes has also revealed a reduction in density of interstial cells of Cajal (ICCs) in the colon [13]. Recent in vivo and ex vivo studies of a rat model have also demonstrated a blunted afferent nerve response of the colon to luminal distention [14]. Emerging evidence has demonstrated remodeling of the muscle layer of the colon resulting in colonic wall thickening, decreased compliance, and a reduction in the relaxation as well as muscle contraction [15]. These myopathic changes in the colon are

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believed to be the result of increased glycation end-products (AGEs) which in turn leads to increases in the production of collagen [15]. These DM-induced neuropathic and myopathic effects on the colon can lead to altered colonic motility, modification of the colonic microbiota, and altered sensory as well as motor responses of the colon. These can range from mild effects with unperceived GI symptoms to that of severe effects with disabling GI symptoms [16].

Constipation

Constipation is one of the most commonly reported GI symptoms by diabetics. In one study of 136 diabetic adults, nearly 60% reported symptoms of constipation [6]. Other epidemiologic studies have reported a prevalence ranging from 11 to 56% [7, 17-19]. What is clear is that the prevalence of constipation is greater in adults with diabetes compared to the general population.

Although the underlying cause of constipation in diabetes is likely to be multifactorial, given the increased risk of autonomic and enteric neuropathy, there is higher likelihood of altered colonic motility underlying the constipation than in the general population. Indeed, one pilot study found prolonged colonic transit time in a group of 10 diabetics with constipation (compared to controls) [20]. In another study, diabetics with autonomic dysfunction (assessed by the sinus arrhythmia resulting from a single forced respiratory cycle) were more likely to have constipation than diabetics without autonomic dysfunction (22 vs 9%, $p < 0.04$) [21, 22•].

Evaluation

When evaluating constipation in a diabetic, careful attention should be taken to review the medications as these may be contributors to the constipation [16, 22•, 23]. It should also be noted that anorectal disorders are prevalent in diabetics and can also contribute to constipation; as such, a careful rectal examination to screen for coexistent pelvic floor muscle dysfunction should be performed [23, 24]. Despite the evidence for altered colonic motility and potentially increased prevalence of slow transit constipation in diabetics, from a practical standpoint colonic transit testing should be reserved for those patients failing to respond to initial laxative therapies. There are several validated methods for the assessment of colon transit including the use of radiopaque markers, colonic transit scintigraphy, and the wireless motility capsule [25].

Treatment considerations in constipation (Table 1)

Despite being one of the most commonly reported GI symptoms in diabetics, there is very limited evidence-based treatment for DM-related constipation. As such, general treatment measures for diabetics with constipation are extrapolated from the general population. The first step in the treatment of mild constipation symptoms should include lifestyle modification such as increasing physical exercise and increased dietary fiber. Such lifestyle modification is generally recommended by the American Diabetes Association (ADA) to improve blood sugar management [22•]. The next therapeutic step should include the use of bulk, osmotic, or stimulatory laxatives. Most of these agents are available over the counter,

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and have proven long-term efficacy and safety in management of chronic constipation. Although there are no clinical trials demonstrating a superiority of one of these agents over another in diabetics with constipation, there are a few caveats to consider. It has been suggested that lactulose may have an added effect at lowering blood glucose [26]. With that being said, bloating caused by lactulose can often be rate limiting [22•]. If colonic transit is either presumed or proven to be delayed, the osmotic and stimulatory laxatives would be preferred to increased dietary fiber and bulk laxatives. When there is failure to these agents either individually or as combination therapy, a variety of pro-secretory agents can be considered. All of these agents require a prescription. This includes the peripheral acting guanylate cyclase-C agonists, linaclotide, and plecanatide [27, 28]. Both agents have been shown to stimulate intestinal fluid secretion and transit. Lubiprostone, a peripheral-acting derivative from prostaglandin E1 that activates CIC-2 chloride channels stimulating intraluminal fluid secretion, has been studied in a diabetic population [29••].

A recent randomized, double-blind controlled trial examined the effectiveness of lubiprostone on constipation symptoms and colonic transit time specifically in diabetics [29••]. In this trial, 76 diabetic patients were randomized with baseline measurements of spontaneous bowel movements (SBM), quality of life, and colon transit time (utilizing a wireless motility capsule). Participants received either lubiprostone (24 mcg twice a day) or placebo. The study found that at 8 weeks, diabetic patients on lubiprostone had approximately 1.83 ± 0.8 ($p = 0.02$) more SBMs than those on placebo. In addition, after 4 weeks of treatment, those on lubiprostone had a 20.3 ± 7.3 h difference in CTT than placebo ($p = 0.006$). Prucalopride is a selective, high-affinity, 5-hydroxytryptamine 4 receptor agonist (5-HT4) that stimulates colonic motility which is available in Europe and Canada, although not yet available in the USA [30]. It has also been suggested that increasing the availability of acetylcholine in the myenteric plexus may help improve colonic motility. A randomized controlled study assessed the effect of cholinesterase inhibitor, pyridostigmine, on colonic function in patients with diabetes and constipation [31••]. In this study, 30 patients with diabetes and chronic constipation, under the age of 70 years, and without defecatory disorders, were randomized to pyridostigmine (starting at 60 mg three times a day, increasing by 60 mg every third day up to a maximum tolerated dose or 120 mg three times a day) or placebo. Gastrointestinal and colonic transit (assessed by scintigraphy) and bowel function were evaluated. Compared to placebo, pyridostigmine accelerated colonic transit time but not gastric emptying or small bowel transit. Stool frequency, consistency, and ease of passage were also significantly improved with pyridostigmine.

Diarrhea

Chronic diarrhea is a common intestinal manifestation of diabetes and can occur to up to 22% of patients with autonomic neuropathy [6, 17, 32]. Patients often report painless symptoms that are worse at night and can be associated with fecal incontinence [11].

Evaluation

Secondary causes of diarrhea should be sought out, especially conditions that are associated with diabetes such as small intestinal bacterial overgrowth (SIBO), hyperthyroidism, celiac

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disease, microscopic colitis, bile acid malabsorption, pancreatic insufficiency, infections (i.e., C. difficile colitis), medications, and diet (i.e., sorbitol, mannitol, xylitol, and lactose) [33, 34]. Diabetic medications represent a particularly common cause of diarrhea including metformin, acarbose, and miglitol [35]. Metformin is the most common medication used in diabetes to cause diarrhea. This has been reported to occur in over 50% of users, promoting a malabsorptive diarrhea possibly due to reduced disaccharidase activity at the brush border [35]. This diarrhea can occur immediately or following chronic stable dosing of metformin. Acarbose and miglitol can lead to an osmotic diarrhea due to inhibition of alpha glucosidase. Other medications used in the treatment of diabetes that can cause diarrhea include exenatide and orlistat. If a secondary cause of diarrhea is identified, this should be treated. Once these secondary causes have been addressed, the most likely explanation for ongoing diarrhea may be due to diabetic neuropathy of the small bowel, colon, or both organs.

Treatment considerations in diabetes-related enteropathic diarrhea (Table 2)

The first step in the treatment of diabetic diarrhea is improved glycemic control. Another dietary intervention to consider is the pursuit of a low FODMAP diet under the guidance of a qualified dietician. Although no studies have been performed on diabetic diarrhea, this dietary approach has proven efficacy in functional diarrheal syndromes [36]. When choosing medications for the treatment of persistent diarrhea, safety and side effects of therapy should be primary considerations. There have been a small number of case reports of bile acid-binding resins, such as cholestyramine, improving diabetic diarrhea. Bile acid-binding resins also have an added benefit for diabetics with studies showing a reduction of HbgA1c and LDL [37]. Cholestyramine can be challenging due to its form of administration as a powder for oral suspension. Other bile acid resins such as colestipol and colesevelam are available in pill form and as such may be better tolerated. Resin therapy can also prove challenging to the diabetic with polypharmacy due to the potential for these agents to impair the absorption of other drugs. Two of the most commonly used anti-diarrheals in the USA include loperamide and diphenoxylate. Although neither of these agents have been directly evaluated in the treatment of diabetic diarrhea, loperamide has proven efficacy in the treatment of chronic functional diarrhea [38]. Unlike diphenoxylate, which is a central acting mu opioid receptor agonist and prone to CNS side effects and tolerance, loperamide is peripheral acting making this a preferred therapy. Both agents can lead to constipation, and should be titrated slowly.

There are additional evidence-based medical therapies to consider in diabetic diarrhea; however, tolerance, side effects, and cost of therapy can be limiting and for this reason, these should be reserved for failure to the first-line treatments of diarrhea. Clonidine is an alpha$_2$-adrenergic agonist which was first shown to help patients with diabetic diarrhea in the early 1980s [39]. Clonidine remains one of the best studied medications for diabetic diarrhea. A recent systematic review and meta-analysis found 24 studies that assessed clonidine as a treatment for diarrhea [40]. Clonidine was given for a variety of etiologies including irritable bowel syndrome, diabetes, withdrawal-associated diarrhea, neuroendocrine tumors, intestinal failure, and cholera. Collectively, these studies demonstrated a strong effect of

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clonidine on diarrhea with a decrease in stool volume by 0.97 l per day, a decrease in stool frequency by 0.4 times/day, and an increase in transit time by 31 min [40]. Of the 24 studies, 6 assessed patients specifically with diabetes. Of those six studies, three were uncontrolled observational studies and three were case reports. Of the three uncontrolled studies, there were 25 patients [39–42]. The doses ranged from 225 mcg per day to 700 mcg per day. However, one study focused on gallbladder contraction and small bowel transit time and did not specifically look at the colon [42]. Side effects noted were reduction in systolic blood pressure, orthostatic hypotension, bradycardia, fatigue, dry mouth, and headache which are known to limit use of this drug.

Somatostatin and its analog, octreotide, are used to reduce diarrhea in patients with short bowel syndrome, ileostomy, and tumor-induced secretory diarrhea. Since the mid 1980s, there have been multiple case reports of somatostatin analogs improving refractory diabetic diarrhea [3, 43–45]. However, side effects such as hypoglycemia and steatorrhea require close monitoring and may be limiting [3].

Selective serotonin 5-hyroxytryptamine type 3 (5-HT_3) inhibitors, such as ramosetron and ondansetron, which have been developed as antiemetic agents, have been reported to help in diabetic diarrhea [46–48]. It has been suggested that by inhibiting the excitatory neurons of the enteric system, there is a prolongation in colonic transit time and decrease in colonic compliance, and has been shown to improve diarrhea in a randomized trial of patients with irritable bowel syndrome with diarrhea [49].

Colorectal cancer (CRC)

Prospective studies and subsequent meta-analysis have suggested a strong link between DM and CRC (OR 1.27; 95% CI 1.21–1.34) [50–53]. It is widely believed that shared risk factors such as increasing age, obesity, high fat diet, sedentary lifestyle, and alcohol and tobacco use all play a role between diabetes and CRC [54–56]. While not fully understood, the proposed biological mechanisms are from the unique interactions between hyperglycemia, insulin and insulin-like growth factor (IGF) axis, inflammation, and the microbiota [55, 57].

Diabetics not only are at an increased risk for CRC but also appear to have worse outcomes when diagnosed. Using data from a large adjuvant chemotherapy trial of patients with colon cancer, patients with diabetes had a worse 5-year disease-free survival, higher recurrence rate, and more treatment-related diarrhea [58, 59]. Multiple studies have also shown that diabetics have worse outcomes in colorectal surgery [60, 61].

In addition to standard chemotherapy regimens, there is growing literature on therapeutics that target both cancer and diabetes. A recent comprehensive review by González et al. focused on potential therapeutics for specific molecular mechanisms that address both cancer and DM such as 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoa) reductase inhibitors, renin-angiotensin-aldosterone system (RAAS) targeting (i.e., angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)), vitamin D receptor (VDR) activators, endothelin receptor antagonists such as atrasentan, anti-fibrotic agents such as anti-CTFG mAb FG3019 and anti-TGF-B1 mAb, anti-inflammatory agents

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such as chemokinetargeting agents and JAK/STAT inhibitors), epidermal growth factor inhibitors, and mTOR inhibitors [53].

Interestingly, there has also been data to suggest that metformin may have chemopreventative properties against CRC. A systematic review of observational studies suggested that diabetic patients on metformin have a reduction in the rate of CRC compared to their diabetic counterpart not on metformin [53, 62–64]. Furthermore, a multicenter double-blind, randomized controlled phase III trial found that non-diabetic patients who received metformin 250 mg daily were less likely to have metachronous adenomas 1 year after polypectomy compared to those who received placebo (RR 0.67; 95% CI 0.47–0.97) [65]. Despite this association between DM and CRC, the screening guidelines remain the same as that for the general population.

Diabetes mellitus and bowel preparation for colonoscopy

Despite the advancement ofpotential therapeutics, the best way tocombat CRC in diabetics is with prevention. Diabetics are 22% more likely to be up to date with their CRC screening; however, having DM is an independent risk factor for inadequate bowel preparation [53, 66–69]. This is most likely due to diabetics having slower gastric emptying and colonic transit [70]. A recent prospective, investigator-blinded study compared the efficacy of split-dose polyethylene glycol (PEG) for diabetic and non-diabetic patients. They found a significant difference in bowel preparation quality, where only 40% of diabetic patients had adequate preparation compared to 70% from the non-diabetic group ($p = 0.003$) [71]. While current guidelines do not recommend a disease-specific preparation for diabetic patients undergoing screening endoscopy, there have been a few studies that assessed bowel prep and diabetes. One such study randomized diabetic patients to either receive conventional bowel preparation (split dose of 4 L PEG solution) or a diabetes-specific preparation which included a high-intensity educational intervention, which consisted of an en-docrinologist and a dietician, with conventional bowel preparation [72]. Their findings showed that inadequate bowel cleansing was more frequent in the conventional group compared to the diabetes-specific educational group (20 vs 7%, $p = 0.014$). An editorial to the study also suggested pyridostigmine as an aide [73]. A separate study assessed magnesium citrate as an adjunct to standard bowel preparation. In this single-blinded study, nearly 200 diabetic patients were randomly assigned to a preparation which consisted of magnesium citrate 2 days prior to colonoscopy and 10 oz of magnesium citrate with 4 L PEG the day prior to colonoscopy vs the control which received 10 oz of magnesium citrate with 4 L PEG the day prior to colonoscopy. They found that the patients who received the additional magnesium citrate 2 days prior had improved bowel preparation compared to standard dosing (70 vs 54%, $p = 0.02$) [70].

Microscopic colitis

Microscopic colitis (MC) is an uncommon yet well-known cause of chronic diarrhea. The prevalence ranges from 48 to 219 per 100,000 people [74, 75]. MC is generally considered to be a disease of the elderly, with risk factors such as non-steroidal anti-inflammatory drug (NSAID) use, smoking, and proton pump inhibitor (PPI) use. MC has been associated with

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autoimmune diseases, celiac disease, and notably type 1 DM [76]. In one retrospective study of 116 Norwegian patients with MC, 1.7% had type 1 DM compared to 0.3% of the general population [76]. The association with type 2 DM seems to be mixed. Interestingly, a case-control study consisting of 190 patients with MC and 128 controls found that oral anti-diabetic medications may be associated with a decrease in incidence of MC (OR 0.14; 95% CI 0.03– 0.76) [77]. There are no specific guidelines that recommend treating diabetic patients with MC differently. A meta-analysis of six randomized controlled trials show benefit of budesonide in the treatment of MC and is considered first-line therapy [78]. For patients in which budesonide is not feasible or optimal, the American Gastroenterological Association has recommended treatment with mesalamine, cholestyramine with mesalamine, or bismuth salicylate. For refractory cases, azathioprine, 6-mercaptopurine, and anti-TNF agents have been used [78, 79].

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an immune-mediated disorder that appears in genetically susceptible patients. A case-control study, in which roughly 660 patients with type 1 DM were compared to 600 controls (matched for age and sex), found that patients with type 1 DM were more likely to have IBD than controls (OR 5.5; 95% CI 1.2–24.9) [80]. DM is one of the most common diseases associated with ulcerative colitis (UC) [81]. DM and UC share similar complications of neuropathy, cholelithiasis, arthritis, venous thrombosis, and post-operative complications. Longstanding corticosteroids can lead to the development of DM and acute DM-related complications including ketoacidosis and hyperosmolar hyperglycemic states. It is therefore extremely important that diabetic patients with acute, severe UC have their glucose monitored closely and that changing corticosteroids to alternate agents such as cyclosporine or anti-TNF agents be considered when blood glucose levels are unstable. The use of tacrolimus should be limited as an alternate steroid-sparing agent in diabetics as it can induce long-term hyperglycemia [81].

Patients with IBD and DM appear to have overall worse outcomes. Similar to colorectal surgery for CRC, patients with DM undergoing colorectal surgery for IBD often do worse than those without DM [81–84].

Clostridium difficile—*Clostridium difficile* infection (CDI) is a gram-positive, spore-forming anaerobic bacillus that is the most common cause of infectious nosocomial diarrhea in the USA. It usually occurs after antibiotics have disrupted the gut microbiota [85]. CDI accounts for about 15–25% of antibiotic-associated diarrhea. Well-known risk factors for CDI are antibiotics, age, acid suppression, and recent hospitalizations. DM has been shown to be a significant independent risk factor for CDI (RR 2.63; 95% CI 1.12–6.15) and recurrent CDI [86, 87].

However, in a case-control study, patients on metformin were less likely to have CDI than those who were not on metformin (33 vs 53%, $p < 0.001$) [85]. The cause for metformin's protective mechanism is thought to be from its interaction with the gut microbiota.

Treatment for CDI is based on severity. There are no specific guidelines to treat diabetic patients differently than the general population. For mild cases, metronidazole is the first-

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line therapy. For recurrent or more severe cases of CDI, vancomycin or fidaxomicin is used as a sole therapy or in combination with metronidazole depending on the clinical situation. For recurrent cases failing repeated courses of therapy, fecal microbiota transplant is utilized [88].

Summary

In summary, DM is associated with a greater risk for a variety of colonic disorders including chronic constipation with a greater likelihood of being associated with delayed colon transit, enteropathic diarrhea, colorectal cancer, inflammatory bowel disease, microscopic colitis, and *Clostridium difficile* colitis. Despite this increased risk for these oftentimes chronic colonic conditions, there are few clinical trials in diabetics. In most cases, treatment is extrapolated from studies in the general population or those with functional bowel disorders. It is important for the clinician to be aware of these associated conditions with DM as prevention, early detection, and treatment will improve outcomes. This also underscores the need for more clinical trials, especially treatment trials in the setting of constipation and diarrhea in diabetics.

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Table 1

Pharmacologic therapy for constipation in diabetes

Agent	Mechanism of action	Dosage	Clinical considerations
Available over the counter			
Water-soluble fiber supplements (psyllium, methylcellulose, calcium polycarbophil, wheat dextrin)	• Increases water retention • ability of stool • Bulk stool • May increase movement of stool through colon	Initial dose 5 g/day Maximum total fiber include dietary fiber is 25 g/day	Must consume adequate water with fiber Side effects limiting (gas, bloating, abdominal pain)
Polyethylene glycol	• Poorly absorbed • Creates osmotic gradient moving water into intestinal lumen	Initial dose 17 g/day Maximum dose 34 g/day (single or split dosing	Must consume adequate water (8–12 oz with laxative) Bloating can be limiting Preferred over fiber if colon transit is slow
Senna	• Irritates the colon wall increasing contractions • Stimulates sensory nerves lining the colon • May inhibit water absorption in the colon	Initial dose 8.6 mg once daily in evening Maximum dose 34.4 g split dosed	Short acting (8–12 h) Side effects include cramping and abdominal pain Preferred therapy if colon transit is slow Can be used a sole therapy or in combination with osmotic
Bisacodyl	• Irritates the colon wall increasing contractions • Stimulates sensory nerves lining the colon • May inhibit water absorption in the colon	Initial dose 5 mg once daily in the evening Maximum dose 15 mg at one time	Similar considerations as senna More potent stimulant than senna More likely to cause abdominal cramping or abdominal pain than senna
Available by prescription only			
Lactulose	• Poorly absorbed • Creates osmotic gradient moving water into intestinal lumen	Initial dose 10 g/day Maximum dose 40 g/day	May lower blood sugar Bloating can be limiting
Lubiprostone	• Direct activation of CIC-2 chloride channels on enterocytes • Causes passive movement of sodium and water into intestine	24 mcg twice daily Lower dosage available (8 mcg) which is indicated for IBS-C	Demonstrates superiority to placebo at increasing spontaneous bowel movements as well as accelerating colon transit in an RCT of diabetics

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Agent	Mechanism of action	Dosage	Clinical considerations
Linaclotide	• Direct activation of guanylate cyclase C receptors on enterocytes • Results in activation of CFTR chloride channel • Causes passive movement of sodium and water into intestine	145 mcg once daily 290 mcg dose available and indicated for IBS-C 72 mcg dose available for those unable to tolerate 145 mcg due to diarrhea	Proven safety and efficacy large RCTs involving chronic constipation at 12 and 26 weeks as wellas IBS-C at 12 weeks Diarrhea can be limiting
Plecanatide	• Direct activation of guanylate cyclase C receptors on enterocytes in a pH-dependent manner • Results in activation of CFTR chloride channel • Causes passive movement of sodium and water into intestine	3 mg once daily	Proven safety and efficacy in large 12 weeks RCT involving chronic constipation Diarrhea can be limiting
Prucalopride	• Highly selective 5-HT4 receptor agonist • Stimulates colonic motility	2 mg once daily 1 mg day with severe renal impairment (GFR < 30 mL/min)	Available in Europe and Canada Not available in USA
Pyridostigmine	• Cholinesterase inhibitor • Accelerates colon transit	Initial dose 60 mg three time daily Maximum/therapeutic dose 120 mg three times daily	Demonstrates acceleration in colon transit time in diabetics with slow transit constipation Side effects include abdominal pain/cramping, excessive sweating, hypersalivation

RCT = randomized controlled trial

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Table 2
Pharmacologic therapy for diabetes-related enteropathic diarrhea

Agents	Mechanism of action	Dosage	Clinical considerations
Available over the counter			
Loperamide	• μ opioid receptors agonist • Increases non-propulsive contractions • Decreases longitudinal propulsive peristalsis • Provides increased tine for absorption	Initial dose 2 mg once daily Maximum daily dose 16 mg in divided dosing	For doses, less than 2- or 2-mg increments needed, loperamide available as suspension 1 mg/5 mL
Available by prescription only			
Bile acid sequestrants (cholestyramine, colestipol, and colesevelam)	• Binds bile acids in the small bowel • Results in reduction in colonic bile acid (bile acids known for intestinal secretion, increased mucosal permeability, and acceleration of colonic transit)	Cholestyramine 4 g once to twice daily Colestipol 1 g once to twice daily Colesevelam 625 mg three times daily to a maximum daily dose of 3750 mg	This is an off-label use Has benefit of lowering LDL cholesterol and hemoglobin A1c in diabetes Should be taken an hour after or 4–6 h before other medications to as not affect absorption Palatability of cholestyramine can be limiting
Clonidine	• Alpha 2-adrenergic agonist • Results in inhibition of acetylcholine release from nerves in the myenteric plexus and neuromuscular junction reducing intestinal motility	225 mcg to 700 mcg daily	Decreased stool volume and stool frequency and increased colon transit in several small observational studies and case reports Hypotension, bradycardia, fatigue, dry mouth, and headache can be limiting
Diphenoxylate (marketed as diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg per tablet)	• μ opioid receptors agonist • Increases non-propulsive contractions • Decreases longitudinal propulsive peristalsis • Provides increased time for absorption	5 mg (2 tabs) once to maximum of four times daily	Crosses the blood–brain barrier with risk of causing sedation, euphoria, and potentially leading to dependence with chronic use
Octreotide	• Reduces release of gut peptides and splanchnic blood flow • Results in decreased motility and secretion	Initial dose 100 mcg SQ QD or 50 mcg SQ BID Max dose 100 mcg SQ BID	Evidence in diabetic diarrhea limited to case reports
Ondansetron	• Inhibition of the excitatory neurons of the enteric nervous system • Results in prolongation of colon transit time	4–8 mg TID	One case report of use in type 1 DM, resolving diarrhea and associated fecal incontinence after 2 days of therapy Improved stool form, frequency, and urgency in RCT of 120 IBS-D patients