Chronic constipation

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Abstract | Chronic constipation is a prevalent condition that severely impacts the quality of life of those affected. Several types of primary chronic constipation, which show substantial overlap, have been described, including normal-transit constipation, rectal evacuation disorders and slow-transit constipation. Diagnosis of primary chronic constipation involves a multistep process initiated by the exclusion of 'alarm' features (for example, unintentional weight loss or rectal bleeding) that might indicate organic diseases (such as polyps or tumours) and a therapeutic trial with first-line treatments such as dietary changes, lifestyle modifications and over-the-counter laxatives. If symptoms do not improve, investigations to diagnose rectal evacuation disorders and slow-transit constipation are performed, such as digital rectal examination, anorectal structure and function testing (including the balloon expulsion test, anorectal manometry or defecography) or colonic transit tests (such as the radiopaque marker test, wireless motility capsule test, scintigraphy or colonic manometry). The mainstays of treatment are diet and lifestyle interventions, pharmacological therapy and, rarely, surgery. This Primer provides an introduction to the epidemiology, pathophysiological mechanisms, diagnosis, management and quality of life associated with the commonly encountered clinical problem of chronic constipation in adults unrelated to opioid abuse.

Constipation is used to describe a variety of symptoms, including hard stools, excessive straining, infrequent bowel movements, bloating and abdominal pain. Constipation can be acute (typically <1 week duration) or chronic, which typically lasts >4 weeks or, in accordance with consensus criteria, >3 months. Most frequently, chronic constipation is the result of a primary disturbance — that is, primary chronic constipation — of bowel function due to dietary factors (such as insufficient fibre intake), lifestyle factors (for example, lack of mobility or sedentary lifestyle) or a disorder of colonic propulsion or rectal emptying (BOX 1). Secondary chronic constipation results from treatment with, for example, opioids or antihypertensive agents, from organic diseases, including systemic diseases (such as hypothyroidism or Parkinson disease) or from a local pathology in the colon (such as colon cancer or diverticular stricture).

In general, three types of primary chronic constipation have been described, which show substantial overlap between each other and with other types of gastrointestinal disorders. These three types are rectal evacuation disorders (also known as outlet delay disorders), slow-transit constipation (also known as colonic inertia or chronic colonic pseudo-obstruction) and normal-transit constipation. Rectal evacuation disorders are the consequence of the inability to coordinate the abdominal and pelvic floor muscles to evacuate stools due to functional or structural defects; dyssynergic defecation is a type of rectal evacuation disorder that is the consequence of functional (and not structural) abnormalities of the pelvic floor and anal sphincter muscles involved in stool evacuation. Slow-transit constipation is the consequence of delayed transit of stool in the colon. The largest group of patients with chronic constipation do not have evidence of slow colonic transit or dyssynergic defecation; this type of constipation is termed normal-transit constipation (also known as functional constipation or constipation without identifiable structural or biochemical cause) and shows overlap with irritable bowel syndrome (IBS) with predominant constipation (IBS-C) (BOX 1).

Chronic constipation is one of the most prevalent gastrointestinal conditions presenting to primary care physicians or subspecialty physicians and surgeons globally[1]. This Primer focuses on primary chronic constipation in adults and addresses the epidemiology and quality of life (QOL) associated with chronic constipation, the mechanisms of colonic fluid fluxes and motor function, the pathophysiology of disorders of colonic propulsion or rectal evacuation and the clinical diagnosis and treatment of chronic constipation. We do not

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focus on chronic constipation associated with opioid treatment or abuse (reviewed elsewhere[2]) or constipation in children (BOX 2).

Epidemiology

The epidemiology of chronic constipation has been studied in numerous population-based cross-sectional surveys. The implicit assumption in these studies is that because organic causes of chronic constipation are rare, the majority of individuals reporting symptoms compatible with constipation have primary constipation. Community surveys conducted in the 1990s used either self-reporting of symptoms or a symptom-based questionnaire to diagnose constipation[3–6]. More-recent studies use one of the iterations of the diagnostic criteria for chronic constipation (that is, the Rome criteria) and are, therefore, more stringent[7].

Suares *et al.*[7] conducted a large meta-analysis to assess the prevalence and risk factors of self-reported chronic constipation in adults in the community; this meta-analysis included 45 cross-sectional surveys conducted in 41 separate adult populations up until 2010. The majority of studies used a validated questionnaire to confirm the presence of chronic constipation. The pooled global prevalence of chronic constipation across all studies was 14%. The prevalence increased only slightly when a longer duration of symptoms was considered, from 13% at 3 months to 15% at 12 months. However, when the somewhat stricter Rome III criteria for chronic constipation were used, the estimated prevalence was ~7%[7]. A similar prevalence was noted using the Rome III criteria in an internet survey[8].

Rectal evacuation disorders account for one-third of cases of chronic constipation in tertiary referral centres[9,10]. In community-based epidemiological studies in the United States, the overall age-adjusted and sex-adjusted prevalences (per 100 individuals) of normal-transit constipation and rectal evacuation disorders were 19.2 (95% CI 16.1–22.3) and 11.0 (95% CI 8.7–13.3), respectively; rectal evacuation disorders were more frequent in women[11]. Although the prevalence of chronic constipation might vary according to ethnicity, lifestyle

factors (such as degree of physical activity), diet, prescribed and illicit drug use and genetic factors, the effect of each of these has not been examined systematically. The next sections address the effect of age, sex, geography and socioeconomic status on the epidemiology of chronic constipation.

Age
The prevalence of chronic constipation is often reported to increase with age[12]. However, the large meta-analysis by Suares *et al.*[7] did not support these data, probably owing to the different age ranges used in individual studies. In three studies that used identical age ranges to report prevalence[13–15], prevalence increased modestly with increasing age, with OR 1.20 (95% CI 1.09–1.33) for ages 30–44 years, OR 1.31 (95% CI 1.09–1.58) for ages 45–59 years and OR 1.41 (95% CI 1.17–1.70) for those aged ≥60 years when compared with those aged <30 years.

Sex
As for most chronic gastrointestinal disorders such as IBS and dyspepsia[16,17], chronic constipation is more common in women than in men. The meta-analysis[7] identified 26 studies that reported the prevalence according to sex. Overall, the pooled prevalence of chronic constipation in women was almost twofold of that in men (17.4% (95% CI 13.4–21.8%) versus 9.2% (95% CI 6.5–12.2%)), with an OR of 2.22 (95% CI 1.87–2.62). This difference in community prevalence is of a relatively modest magnitude compared with the marked female predominance in patients with chronic constipation in a referral setting, in which >75% of patients are women[18]. Importantly, this sex imbalance is not observed in children[19,20] or elderly individuals[21,22] with chronic constipation, suggesting that some of the difference in prevalence is driven by higher rates of symptom reporting in women of reproductive age.

Geography
The majority of studies included in the meta-analysis[7] were conducted in North America and northern Europe; no studies conducted in South Asia, Africa or Central America were identified, and only a few studies were from South America and the Middle East. The prevalence of chronic constipation was remarkably similar — between 14% and 16% — in almost all regions where data were available (FIG. 1).

Socioeconomic status
Low socioeconomic status has traditionally been considered a risk factor for chronic constipation[23–25]. The meta-analysis[7] identified only six studies that examined the association between socioeconomic status and presence of symptoms of constipation. Pooled data showed a modest increase in prevalence of chronic constipation in individuals of lower compared with higher socioeconomic status (OR 1.32; 95% CI 1.11–1.57), but not between those with medium and higher socioeconomic status (OR 1.01; 95% CI 0.92–1.10). Results from more-recent studies conducted in Germany, Brazil and Croatia confirm these findings[22,26,27].

Comorbid conditions

As with most chronic gastrointestinal conditions, symptoms associated with chronic constipation overlap substantially with those attributable to other disorders of the gastrointestinal tract, such as dyspepsia[28,29], gastro-oesophageal reflux disease[30] and IBS[31]. In addition, mood disorders, such as anxiety[4], depression[28] or somatoform-type behaviour[32], are more prevalent in individuals with chronic constipation than in the general population. Whether chronic constipation is associated with an increased risk of developing colorectal cancer is controversial. A meta-analysis by Power et al.[33] argues against such an association, and the American Society of Gastrointestinal Endoscopy recommends that, in the absence of alarm features that point to the presence of organic disease, individuals who are constipated should be subject to the same colorectal cancer screening recommendations as an average-risk population[34].

Mechanisms/pathophysiology

Primary chronic constipation is commonly associated with abnormalities in bowel movements or dysfunction of the coordinated contraction of the pelvic floor muscles during defecation. The motor activity that underlies propulsive motility in most of the gastrointestinal tract is peristalsis, which involves coordinated contraction and relaxation of the intestinal lamina muscularis, resulting in a pressure gradient that propels luminal contents through the intestine. Although peristalsis occurs in the colon, it is not the main mechanism of propulsion. Instead, colonic propulsion that leads to defecation is mainly driven by general contractions — mass movements — that occur a few times per day (FIG. 2). However, other types of colonic propulsions have also been identified.

Box 1 | Chronic constipation

Primary constipation

- Chronic idiopathic constipation: normal-transit constipation and constipation-predominant irritable bowel syndrome
- Rectal evacuation disorders: dyssynergic defecation, rectal intussusception, descending perineum syndrome, rectal prolapse and rectocele (weakness usually affecting the anterior wall of rectum)
- Slow-transit constipation: megacolon associated with Hirschsprung disease, Chagas diseases, chronic idiopathic megacolon and megacolon associated with multiple endocrine neoplasia type 2B

Secondary constipation

Constipation associated with the following:

- Medications: opioids, Ca^{2+} blockers, α2-adrenergic agonists, tricyclic antidepressants, 5-hydroxytryptamine receptor 3 antagonists, dopaminergic drugs, anticholinergic drugs, neuroleptics and chemotherapeutic agents
- Disorders of electrolyte balance: hypercalcaemia and hypokalaemia
- Hormonal changes: hypothyroidism and pregnancy
- Psychiatric disorders: depression and eating disorders
- Neurological disorders: Parkinson disease, multiple sclerosis and spinal cord injury
- Ageing: immobility and comorbid conditions
- Generalized muscle disease: progressive systemic sclerosis and amyloidosis
- Organic disease of the gastrointestinal tract: colorectal cancer or polyps

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Peristalsis

Regulation by the enteric nervous system. In 1899, Bayliss and Starling described 'the law of the intestine', which states that: "Local stimulation of the gut produces excitation above and inhibition below the excited spot. These effects are dependent on the activity of the local nervous mechanism" (REF. 35). In other words, they demonstrated that the neuronal circuitry that is responsible for peristalsis is intrinsic to the gut and consists of an ascending contractile limb and a descending relaxant limb. These findings led to the designation of the enteric nervous system as a third and distinct division of the autonomic nervous system[36] (along with the sympathetic and parasympathetic divisions) and to efforts to identify the cellular elements and intercellular signalling compounds that are responsible for mediating propulsive motility. Activation of a single peristaltic circuit would move the contents of the lumen only a small distance, but this basic circuit is recurrent along the length of the intestine and sequential activation of overlapping peristaltic circuits results in the wavelike propagation of a contractile ring that can drive the intestinal content for long distances.

Peristalsis can be activated by chemical and/or mechanical stimuli that are sensed by enteroendocrine cells, such as the enterochromaffin cells, and/or by mechanosensitive neurons in the enteric ganglia (FIG. 3). Enterochromaffin cells synthesize and release serotonin (5-hydroxytryptamine; 5-HT) in response to nutrients, bile salts, short-chain fatty acids and mechanical stimulation[37–41]. 5-HT can activate serotonergic receptors on primary afferent neurons, which can send signals via interneurons along the myenteric plexus to selectively activate upstream excitatory motor neurons and downstream inhibitory motor neurons. In humans, the projections of interneurons are longer than those of motor neurons, indicating that they are largely responsible for the length of the viscus that is influenced by a given peristaltic reflex circuit[42]. The excitatory motor neurons primarily trigger contraction of the smooth muscle cells via the release of acetylcholine, whereas the inhibitory motor neurons cause relaxation of the smooth muscle cells via purinergic (that is, ATP) and nitrergic (that is, nitric oxide) factors.

Interstitial cells play a part in mediating the excitatory and inhibitory signals between the enteric nervous system and the smooth muscle cells. Two types of interstitial cells — interstitial cells of Cajal (ICCs) and platelet-derived growth factor receptor α-positive (PDGFRα$^+$) cells — contribute to syncytial networks with smooth muscle cells[43]. ICCs, which also serve as pacemaker cells that initiate slow-wave action potentials in the smooth muscle cells of the gastrointestinal tract, receive cholinergic synaptic inputs from excitatory motor neurons and inhibitory nitrergic inputs from inhibitory motor neurons. Excitatory and inhibitory inputs lead to increases in the frequency and decreases in the amplitude of slow-wave potentials, which result in increases or decreases in muscle tone. Activation of purinergic receptors on PDGFRα$^+$ cells leads to hyperpolarization that spreads to smooth muscle cells and inhibits their activity.

Enteric glial cells can also influence the activity of the propulsive motility circuitry, as suppression of glial cells leads to a slowing of colonic motility[44], but the mechanisms by which glial cells influence the function of the motor circuitry in the intestine have not yet been determined.

Regulation by external signals. The enteric nervous system is influenced by extrinsic sympathetic and parasympathetic inputs to the gut[45]. Noradrenaline released from sympathetic postganglionic projections from prevertebral ganglia acts on presynaptic α2-adrenergic receptors on essentially all myenteric nerve terminals and elicits a presynaptic inhibition of neurotransmitter release, thereby decreasing propulsive motility[45,46]. Sympathetic influence on the myenteric plexus can be mediated by local gut–prevertebral ganglion–gut reflexes involving projections from intestinofugal myenteric neurons (that is, projections leaving the intestine) to the prevertebral ganglia and also by conventional central nervous system reflexes involving output from preganglionic neurons to the prevertebral ganglia[47].

The mechanisms whereby parasympathetic efferent projections influence motility are still not clear, given that only subsets of ganglia, let alone neurons, seem to receive extrinsic parasympathetic input[48]. However, parasympathetic input to the colon has a prokinetic effect on colonic motility, and it represents the primary neural pathway by which defecation is driven by the central nervous system[45,49].

Box 2 | Constipation in IBS, opioid abuse and childhood

IBS with predominant constipation
Irritable bowel syndrome (IBS) with predominant constipation is a functional bowel disorder characterized by the combination of recurrent abdominal pain (≥1 day per week in the past 3 months) with ≥2 of the following features: pain associated with defecation; a change in frequency of defecation; or a change in stool consistency (with >25% of bowel movements having Bristol Stool Form (BSF) type 1 (separate hard lumps) or type 2 (lumpy and sausage-like stool) and <25% with BSF type 6 (mushy consistency) or type 7 (liquid consistency)[5].

Opioid-induced constipation
Opioid-induced constipation is characterized by new or worsening symptoms of constipation when initiating, changing or increasing opioid therapy. Symptoms include ≥2 of the following criteria: straining or sensation of incomplete evacuation, anorectal obstruction or blockage during >25% of defecations; BSF types 1 and 2 in >25% of defecations; manual manoeuvres to facilitate >25% of defecations (for example, digital evacuation or support of the pelvic floor); or <3 spontaneous bowel movements per week. In addition, loose stools are rarely present without the use of laxatives[112,224].

Normal-transit constipation in children
In neonates and toddlers (≤4 years of age), diagnosis of normal-transit constipation includes the presence of ≥2 of the following symptoms for ≥1 month: ≤2 defecations per week; history of excessive stool retention, painful or hard bowel movements; large-diameter stools; or the presence of a large faecal mass in the rectum. In toilet-trained children, the following additional criteria may be used: ≥1 episode per week of incontinence after the acquisition of toileting skills and history of large-diameter stools that may obstruct the toilet[225,226].

Normal-transit constipation in children >4 years of age and adolescents is characterized by ≥2 of the following symptoms occurring ≥1 time per week for a ≥1 month with insufficient criteria for a diagnosis of IBS: ≤2 defecations in the toilet per week; ≥1 episode of faecal incontinence per week; history of retentive posturing or excessive volitional stool retention or of painful or hard bowel movements; presence of a large faecal mass in the rectum; or history of large-diameter stools that can obstruct the toilet[225,226].

Colonic propulsion

Mass movements. Colonic propulsion largely depends on mass movements, which are associated with the inhibition of haustral segmentation (that is, the presence of haustra or small pouches that give the colon its segmented appearance) and contractions of the bowel wall[50,51]. Large contractions of the colonic smooth muscle cells result in increases in intraluminal pressure called high-amplitude propagating contractions (HAPCs)[52,53] (FIG. 2c). These are the primary motor pattern associated with mass movements. The neurophysiological mechanisms associated with the generation of the HAPCs are not completely understood. However, they can be observed in response to a high-calorie meal, when waking up[54–56] and in response to chemical stimulation (for example, with the stimulant laxative bisacodyl[57])[58–62]. HAPCs have been associated with the movement of colonic content[63] and defecation[52,59,64]. HAPCs can be propagated from the caecum to rectum[52–56], and imaging studies have shown that >50% of colonic content can be emptied during defecation[65,66].

Retrograde propulsion. Colonic content also moves in a retrograde direction (rather than in the direction of the anus). Over a number of hours, rectally inserted bismuth can move towards the transverse colon or caecum[65]. Distal colonic retrograde propulsion can occur after a meal[67] and when individuals withhold defecation[68]. In fact, real-time monitoring of the movements of an ingested magnet shows that retrograde propulsion occurs in every part of the human colon[69]. The mechanical effect of retrograde movements is the subject of ongoing research, with observations that the majority of contractions in the descending colon are associated with reflux back into the transverse colon[70] and that temporal association between retrograde propagating motor patterns and retrograde flow of colonic content upstream exist[71]. Recent high-resolution colonic manometry recordings (measurement of pressure changes that reflect contractions in the colon) have revealed a retrograde propagating cyclic motor pattern that originates at the rectosigmoid junction[72,73]. This motor pattern increases after a meal[72] and may be initiated by delivery of stool or gas from the upper colon, thereby potentially serving as a brake to prevent rectal filling[74]. In support of this, the greater the frequency of retrograde sigmoid phasic contractile activity is, the fewer the number of defecatory episodes[75]. Conversely, in patients with functional diarrhoea, a reduction in postprandial distal colonic pressure waves was associated with rapid transport of content into the rectosigmoid region[76].

Other mechanisms of colonic propulsion. Although motor patterns have been associated with propulsion of colonic content, studies combining scintigraphy (measurement of colonic transit time using radioisotopes) and colonic manometry also reveal that the majority of propulsive events seem to occur in the absence of propagated contractions[63,71], suggesting that some flow events are associated with motor patterns that do not affect intraluminal pressure. Other factors accounting for these flow events include longitudinal muscle shortening,
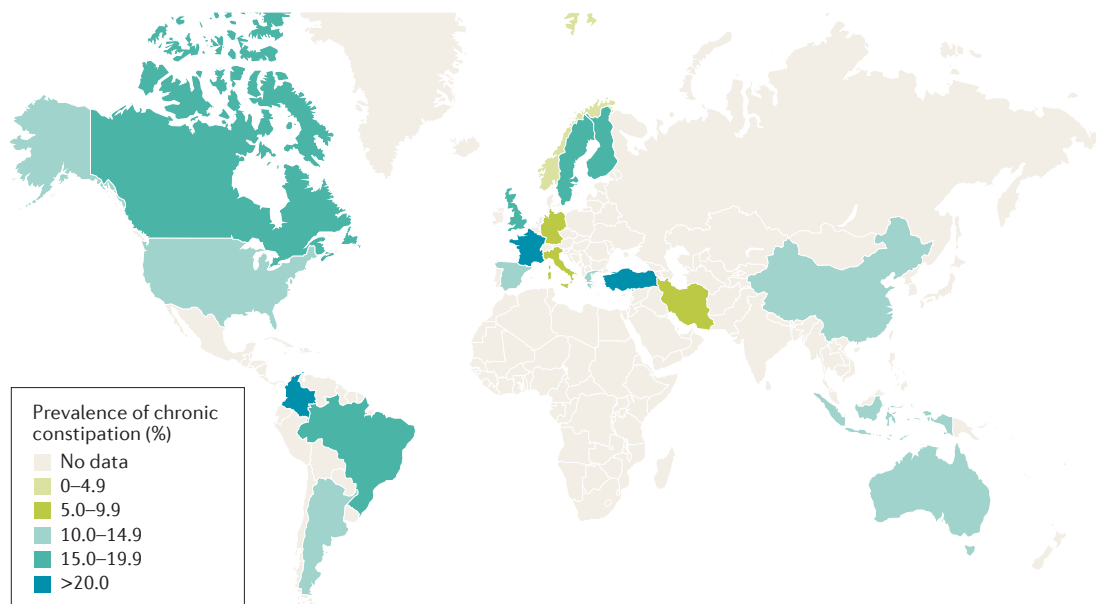
Figure 1 | **Global prevalence of chronic constipation.** Adapted from REF. 7. American College of Gastroenterology.

non-lumen-occluding circular muscle contractions or alterations in regional wall tone[77].

Primary chronic constipation

Normal-transit constipation. The largest group of patients with primary chronic constipation have no evidence of either slow colonic transit or dyssynergic defecation; these patients are classified as normal-transit constipation (BOX 1). The pathophysiology leading to their chronic constipation is unknown. Pain is often substantial, and the condition considerably overlaps with IBS-C.
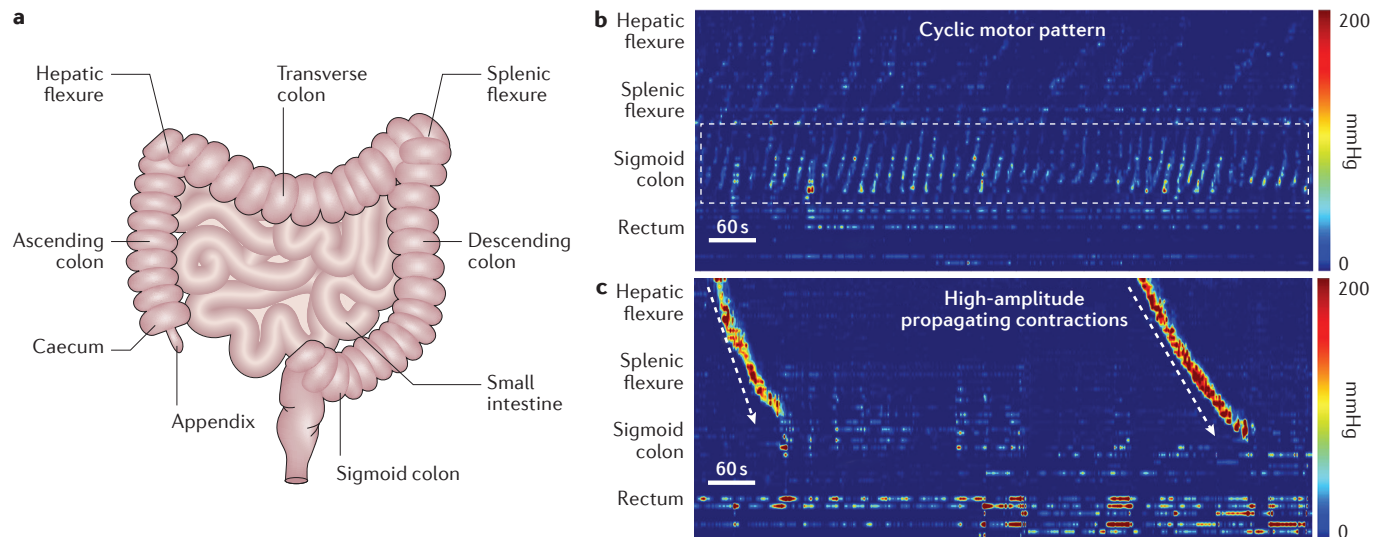
Rectal evacuation disorders. Stool evacuation requires coordination between straining and relaxation of the pelvic floor muscles and anal sphincters. Rectal evacuation disorders include disorders of anorectal function (for example, dyssynergic defecation) or structure (for example, rectocele, descending perineum syndrome, rectal intussusception or rectal prolapse)[10,78]. These disorders constitute the second most common type of chronic constipation.

Dyssynergic defecation is the most common type of the rectal evacuation disorders. Most patients are unable to coordinate abdominal, rectal, anal and pelvic floor muscles during attempted defecation[79] and this incoordination manifests as paradoxical anal contraction, inadequate anal relaxation or impaired rectal or abdominal propulsive force[10,79]. Dyssynergic defecation is an acquired, behavioural disorder of defecation[10,80,81]. In two-thirds of adult patients, it results from faulty toilet habits, painful defecation, obstetric or back injury or dysfunction of the gut–brain axis[10,81]. In the remaining one-third of patients, the process of defecation may not have been learned adequately during childhood, either owing to behavioural problems or parent–child conflicts[81]. Two-thirds of patients with dyssynergic defecation also exhibit rectal hyposensitivity[79,80]; ~60% of patients with dyssynergic defecation have secondary slow-transit constipation[9,10,82].

Paradoxical anal contraction was originally considered an involuntary anal spasm during defecation[83]. However, this conclusion may have been influenced by studies conducted in the supine position. Body position, sensation of stooling and stool characteristics can influence defecation[10]; even healthy individuals may show dyssynergia in the supine position despite having normal function and stool expulsion in a sitting position[84]. On the basis of the hypothesis that dyssynergia results from the spasm of the anal sphincter, sphincter myectomy or botulinum toxin injection in the anal sphincter or pelvic floor has been studied, but these approaches have been generally ineffective[85,86]. Thus, anal sphincter spasm is not considered the mechanism of dyssynergic defecation. However, afferent anorectal-evoked neuronal potentials are impaired in patients with dyssynergia[87] and improve following biofeedback therapy (a behavioural therapy used to treat dyssynergic defecation)[88], suggesting that impaired brain–gut interactions are key mechanisms. Additionally, rectal hyposensitivity (defined as a higher sensory threshold for sensations to defecate) was observed in 60% of patients with dyssynergia[10,80].

Unlike dyssynergic defecation, the pathophysiology of other disorders of evacuation, such as rectocele, descending perineum syndrome and rectal intussusception, is poorly understood. It is generally believed that these disorders are a consequence of prolonged and excessive straining over many years, leading to weakening of pelvic floor muscles, pelvic neuropathy and anterior bulging of the rectal wall[78], but further study is needed.

Slow-transit constipation. A subset of patients with chronic constipation show evidence of delayed emptying of the ascending and transverse colon with prolongation of transit (often in the proximal colon)[2,89,90] and a reduced frequency or even an absence of propulsive HAPCs[54,91–93]. Patients with constipation may also lack a postprandial increase in colonic motor patterns and

a | Anatomy of the colon.

Labels on anatomy diagram: Hepatic flexure, Transverse colon, Splenic flexure, Ascending colon, Descending colon, Caecum, Small intestine, Appendix, Sigmoid colon.

b | Cyclic motor pattern — Hepatic flexure, Splenic flexure, Sigmoid colon, Rectum, 60 s, mmHg 0–200

c | High-amplitude propagating contractions — Hepatic flexure, Splenic flexure, Sigmoid colon, Rectum, 60 s, mmHg 0–200

Figure 2 | **Motor patterns in a healthy adult colon. a** | Anatomy of the colon. **b,c** | Motor pattern recorded by high-resolution, fibre-optic manometry in a healthy adult. The cyclic motor patterns (peristalsis) prominent in the sigmoid colon are shown within the white rectangle (part **b**). Two high-amplitude propagating contractions originating in the proximal colon and travelling to the sigmoid colon are shown (dashed white arrows; part **c**). The cyclic motor pattern is prevalent after a meal and travels predominantly in a retrograde direction.

the normal retrograde propulsion of content from the transverse colon[93]. Slow-transit constipation is associated with abnormalities in the peristaltic circuits due to disturbances of extrinsic parasympathetic or enteric neural control[94,95]. Patients with severe slow-transit constipation have demonstrated evidence of loss or abnormal morphometry of ICCs on pathological examination of resected colon[96,97].

A minority of these patients present with a chronically dilated colon — referred to as chronic megacolon[98] — that is associated with reduced colonic compliance and response to pharmacological stimulation with an acetylcholinesterase inhibitor (neostigmine)[99]. Megacolon may rarely be a manifestation of ganglioneuromatosis of the colon in patients with multiple endocrine neoplasia type 2B[100].

Fluid and ion transport in the intestine

Although colonic fluid control is not a primary factor in the aetiology of constipation (FIG. 4), colonic fluid and electrolyte handling are critical in the treatment of constipation and, therefore, principles of intestinal fluid and electrolyte are briefly discussed. The main mechanisms associated with fluid and ion fluxes are coupled NaCl absorption, electrogenic Na^+ absorption and Cl^- secretion[101]. The ability to dehydrate the stool also depends on epithelial barrier function to prevent the back diffusion of electrolytes and other solutes once they have been absorbed across the epithelium.

On an average day, 9 litres of fluid enter the gastrointestinal tract, 1 litre of residual fluid reaches the colon, and the stool excretion of fluid constitutes about 0.2 litres per day. The colon has a large capacitance and functional reserve and may reabsorb up to four times its usual volume of 0.8 litres per day, provided the flow rate is not too fast for colonic absorption to occur[102]. Thus, the colon can partially compensate for excess fluid delivery that

may result from intestinal absorptive or secretory disorders. On the other hand, prosecretory laxatives may induce sufficient small intestinal fluid secretion to the colon to change stool consistency and accelerate colonic transit[103,104]. Additionally, osmotic laxatives create an osmotic gradient that drives paracellular flow of water into the intestinal lumen.

Coupled NaCl absorption. Coupled NaCl absorption (FIG. 4) is prominent throughout the small and large intestine and involves paired transporters expressed on the apical membrane of surface epithelial cells. These transporters include Na^+/H^+ exchangers (NHE2 or NHE3) and anion exchangers, including the Cl^- anion exchanger SLC26A3 or the anion exchange transporter SLC26A6. Through these transporters, Na^+ and Cl^- enter the cell cytosol and can then be exported across the basolateral membrane via Na^+/K^+-ATPase and a K^+/Cl^- co-transporter (KCC1; also known as SLC12A4)[105]. In general, hormones that increase intracellular levels of cyclic AMP (cAMP), cGMP or Ca^{2+} (such as vasoactive intestinal peptide and 5-HT) reduce transporter activity, whereas transporter activity is increased by agents that induce tyrosine kinase-dependent signalling, such as epidermal growth factor[106].

Electrogenic Na^+ absorption. Uptake of Na^+ occurs at the apical membrane via the heterotrimeric epithelial sodium channel (ENaC) and is compensated for by export of Na^+ through basolateral Na^+/K^+-ATPase. Electrogenic Na^+ absorption (FIG. 4) is defined as ionic current without an equivalent loss of a cation from the cell. This mechanism is prominent in the distal colon and results in Na^+ being additionally absorbed without concomitant uptake of Cl^-. ENaC channel opening and abundance are stimulated by neurohumoral agents that elevate cAMP and are inhibited by increased cytoplasmic Ca^{2+} and/or activated

mitogen-activated protein kinases[107,108]. ENaC activity can also be chronically upregulated by other hormones, specifically aldosterone, which increases in response to a low-salt diet, angiotensin or glucocorticoids[109,110]. Na$^+$ channels other than ENaC also contribute to the absorption of Na$^+$ in the human colon[111].

Cl$^-$ secretion. Cl$^-$ secretion (FIG. 4) is driven by the active secretion of Cl$^-$ ions, predominantly across crypt epithelial cells, through Ca^{2+}-activated Cl$^-$ channels (CaCC) and the cystic fibrosis transmembrane conductance regulator (CFTR). This involves the uptake of Cl$^-$ across the basolateral membrane via a Na$^+$/K$^+$/Cl$^-$ co-transporter, NKCC1 (also known as SLC12A2), with extrusion of Na$^+$ by the basolateral Na$^+$/K$^+$-ATPase and re-cycling of K$^+$ across the basolateral membrane by cAMP-dependent or Ca^{2+}-activated channels. cGMP activates CFTR and guanylate cyclase C receptor agonists (prosecretory agents) can be used to treat constipation.

Diagnosis, screening and prevention

Symptoms associated with chronic constipation are in general nonspecific and include hard or lumpy stools, straining, a sense of incomplete evacuation after a bowel movement, a feeling of anorectal blockage, the need for digital manoeuvres to assist defecation or reduced stool frequency[112]. Health care providers should always exclude 'alarm' features, such as blood with stools, unexplained weight loss, a family history of colorectal cancer or new-onset symptoms after 50 years of age.

Such alarm features should prompt exclusion of organic causes of constipation, such as colorectal cancer.

The Bristol Stool Form (BSF) scale is a validated measure to describe stool consistency using seven different types of stool ranging from separate hard lumps to liquid consistency with no solid pieces; the BSF types correlate with colonic transit time[113,114]. Stool frequency on its own is not a reliable indicator of delayed colon transit[115]. Similarly, the association between sensation of incomplete evacuation or need for digital manipulation and the presence of dyssynergic defecation is weak[116]. Consensus 'diagnostic' criteria for normal-transit constipation based on symptoms are often used, such as the Rome IV criteria (BOX 3), especially for the purpose of ensuring eligibility for clinical trials[116].

The symptoms of the various subtypes of constipation considerably overlap. In clinical practice, the need to determine the exact clinical phenotype often depends on the response to treatment and is often not considered essential if patients are responsive to lifestyle modifications or first-line therapies (FIG. 5). However, the recognition of individual subtypes could pave the way for improved management of constipation, especially if first-line treatment is ineffective. A firm diagnosis of dyssynergic defecation requires fulfilment of all the clinical criteria of normal-transit constipation (BOX 3), in addition to abnormal findings on anorectal structure and function testing; an increase in colonic transit time may result from dyssynergic defecation and, therefore, does not imply a diagnosis of slow-transit constipation.
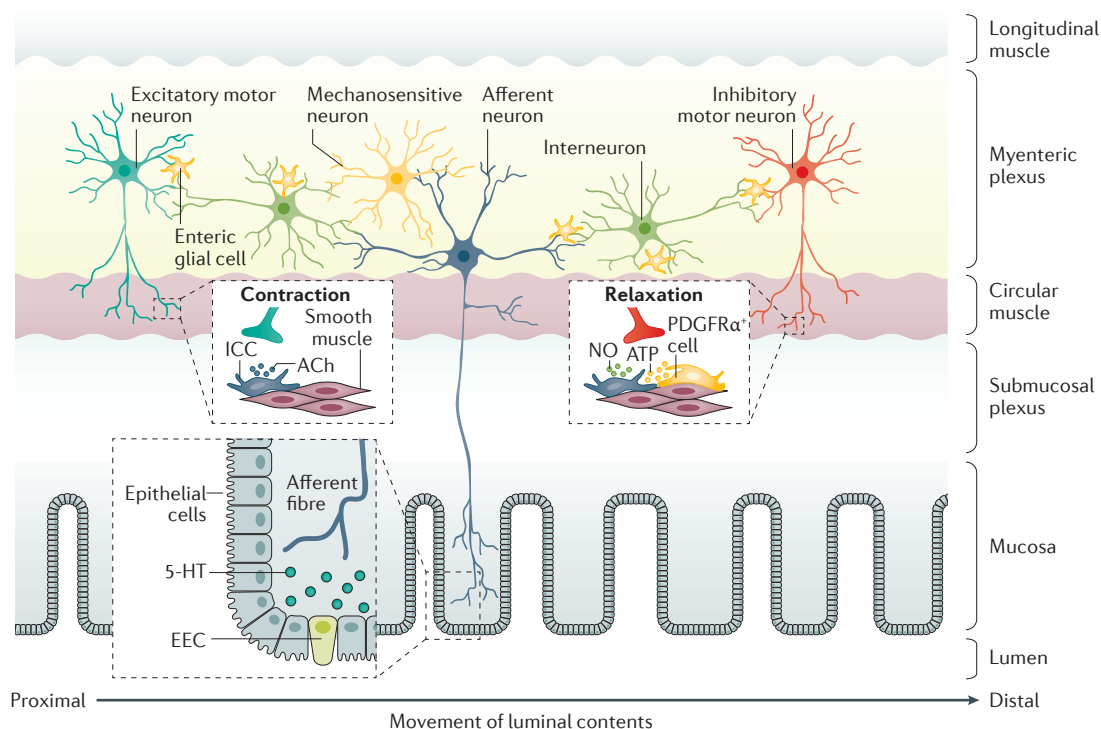
Figure 3 | **Intrinsic reflex circuitry involved in peristalsis.** Peristalsis — the coordinated contractions and relaxation of the intestinal smooth muscle cells — contributes to the movement of luminal content towards the rectum and is controlled by enterochromaffin cells (EECs), the enteric nervous system, interstitial cells (including interstitial cells of Cajal (ICCs)) and platelet-derived growth factor receptor α-positive (PDGFRα$^+$) cells and external signals. 5-HT, 5-hydroxytryptamine (also known as serotonin); ACh, acetylcholine; NO, nitric oxide.

Digital rectal examination

The key elements to seek during a digital rectal examination in patients with chronic constipation are summarized in BOX 4. The test is also important to exclude a rectal mass or other causes of mechanical obstruction (such as anal stenosis, rectal prolapse, rectal intussusception or rectocele). Studies suggest that digital rectal examination offers a sensitivity of 75–93% and specificity of 59–87% to diagnose dyssynergic defecation[117,118]; thus, digital rectal examination is a useful screening test to detect dyssynergia at the bedside[117,118] and for selecting patients for further diagnostic testing. However, digital rectal examination is underused in the evaluation of patients with chronic constipation, even among gastroenterologists[119]. Examination in the squatting position might be necessary to identify a rectal prolapse that may not be seen during examination performed in a left lateral position.

If constipation improves with fibre supplements or over-the-counter laxatives (such as osmotic laxatives or colonic stimulants), no additional diagnostic evaluation is recommended. However, if a patient fails to respond to first-line treatments, prosecretory agents or stimulant laxatives should be considered; if no improvement occurs, a more detailed evaluation to understand the cause should be pursued[120,121]. Various diagnostic tests are available to assess the morphology of the intestine and anus, and the physiology of defecation. Because the presence of rectal evacuation disorder can result in delayed colon transit, testing should begin with an evaluation of the anorectum and pelvic floor[34,114].

Anorectal structure and function testing

Balloon expulsion test. The balloon expulsion test is a simple, reliable test to screen for rectal evacuation disorders[122]. The deflated balloon is placed in the rectum and inflated to 50 ml, and the time taken to expulsion in the seated position is recorded by the patient with a stopwatch; an expulsion time of >1 minute is abnormal[123]. However, the balloon expulsion test does not distinguish between functional and mechanical or anatomical causes of disordered defecation, and abnormal results necessitate additional testing.

Anorectal manometry. Conventional anorectal manometry and high-resolution anorectal manometry are physiological tests that assess sphincter tone in the resting and contracted state, rectoanal reflexes, rectal sensation and pressure changes during attempted defecation. Abnormalities in anorectal function support the diagnosis of dyssynergic defecation[10,124]. At least four reproducible types of dyssynergia[10,80,125] have been recognized by anorectal manometry (FIG. 6). The recognition of these patterns enables the biofeedback therapist to offer patient-specific treatment programmes, such as pushing effort in dyssynergic defecation type II, improved relaxation in dyssynergic defecation type III or both in dyssynergic defecation type IV. In a prospective study, patients with type IV showed poor response to biofeedback therapy[10,124,126].

Anorectal manometry seems to confirm the relevance of two patterns in patients with constipation, which enables discrimination of patients with normal versus
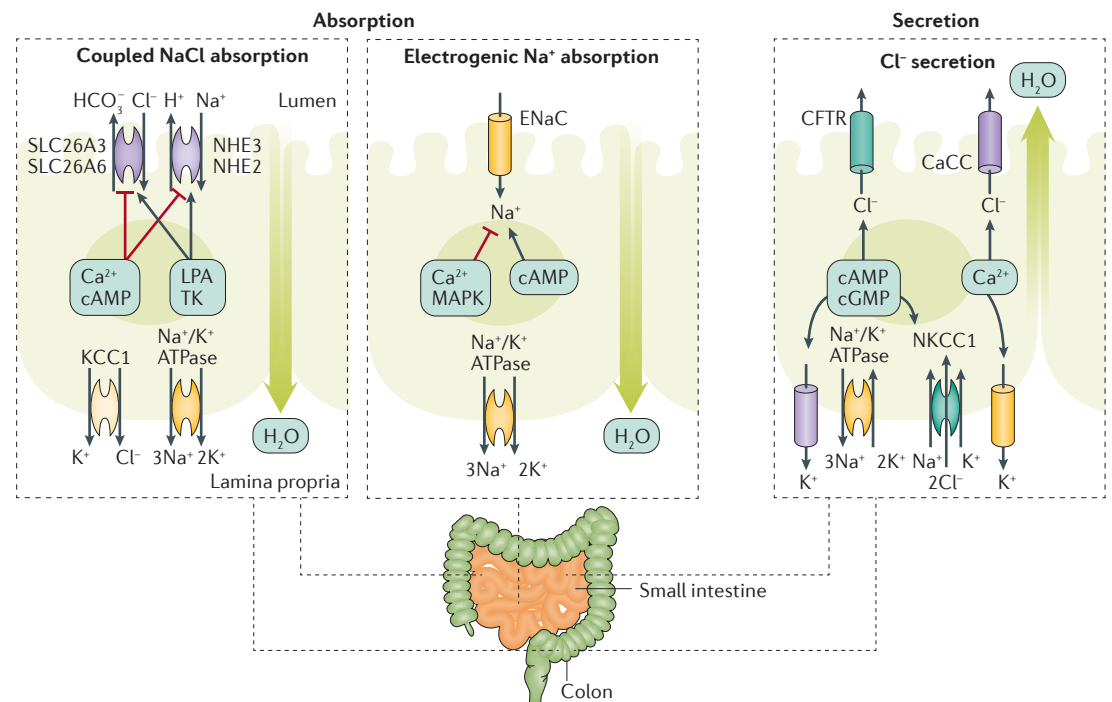
Figure 4 | **Electrolyte and fluid absorption and secretion in the intestine.** Factors that regulate the function or abundance of the transporters are shown in blue boxes. Green arrows indicate paracellular fluid transport. CaCC, Ca²⁺-activated Cl⁻ channel; CFTR, cystic fibrosis transmembrane conductance regulator; cGMP, cyclic GMP; ENaC, epithelial sodium channel; KCC1, K⁺/Cl⁻ co-transporter; LPA, lysophosphatidic acid; MAPK, mitogen-activated protein kinase; NHE, Na⁺/H⁺ exchanger; NKCC1, Na⁺/K⁺/Cl⁻ co-transporter; SLC26A3, Cl⁻ anion exchanger; SLC26A6, anion exchange transporter; TK, tyrosine kinase.

Box 3 | Rome IV diagnostic criteria for normal-transit constipation

Diagnosis of normal-transit constipation requires the presence of the following criteria for the past 3 months with symptom onset >6 months before diagnosis[112].

• Presence of ≥2 of the following criteria:
  - Straining during >25% of defecations
  - Bristol Stool Form (BSF) types 1 and 2 for >25% of defecations
  - Sensation of incomplete evacuation for >25% of defecations
  - Sensation of anorectal obstruction or blockage for >25% of defecations
  - Manual manoeuvres to facilitate >25% of defecations (for example, need for digital manipulation or support of the pelvic floor)
  - Less than three spontaneous bowel movements per week
• Without the use of laxatives, loose stools are rarely present
• Insufficient criteria for irritable bowel syndrome

abnormal balloon expulsion tests: those with high anal pressure at rest and during simulated defecation and those with low rectal pressure and impaired sphincter relaxation during simulated defecation[127]. There is also evidence that rectal hyposensitivity with or without dyssynergic defecation plays an important part in the pathogenesis of constipation and that correction of sensory dysfunction improves bowel function[128].

The rectoanal pressure gradient can be a useful index of dyssynergia, but considerable overlap between patients with constipation and healthy volunteers exists for all of the anorectal manometry parameters. The most robust discrimination seems to be obtained with dyssynergic defecation type IV, that is, no pushing effort with absent or inadequate anal sphincter relaxation[129]. The overall diagnostic use of anorectal manometry by itself is somewhat limited[129] and clinical correlation (including findings in the medical history and digital rectal examination) is essential.

Defecography. Imaging of the anorectum can be accomplished with contrast defecography (using barium) or functional MRI (MR defecography); both are usually available in tertiary care centres. These techniques provide information about the function (dyssynergic defecation) and anatomy (anal stenosis, enterocele, rectal intussusception, rectal prolapse and rectocele) of the anorectum[130]. Some patients find the experience of the test embarrassing, which might lead to erroneous results. For example, the patient might not relax sufficiently to evacuate the contrast. In addition, most MR defecography is performed in the supine position, which is not physiological. MR defecography provides incremental information about the integrity of the anatomical structures of the anorectum and pelvic floor[131,132].

Tests of colonic transit
Radiopaque marker test. The standard means by which to assess colonic transit is through the oral administration of radiopaque markers followed by abdominal radiography at predetermined times to identify the number of retained markers. These tests measure whole-gut transit rather than just colonic transit, although the latter constitutes the largest proportion of whole-gut transit. Among the numerous methods to perform radiopaque marker tests[133–135], the simplest and most widely used in clinical

practice is the Hinton method[135], in which one capsule containing 20–24 radiopaque markers is given on day 1, followed by an abdominal radiograph on day 5. Slow colonic transit is identified if >5 (20%) ingested markers are retained on day 5. Other variations of radiopaque marker tests can provide quantitative total and segmental assessments of colonic transit[134]. The relative simplicity, comparatively low cost and widespread availability are attractive features of radiopaque marker testing, whereas radiation exposure and the need for additional hospital visits are negative aspects of the test.

Wireless motility capsule test. Ingestion of a wireless pH-sensitive capsule enables the detection of segmental and whole-gut transit time by detecting changes in intraluminal pH. Intraluminal pH increases (~3 units) from the stomach to the duodenum and decreases (~1 unit) from the ileum to the caecum. The capsule is also able to detect the amplitude, but not the propagation, of contractions along the gastrointestinal tract. It is useful to detect normal increases in motility following a meal or periods of quiescence during sleep[136]. Colonic transit measured by the wireless motility capsule tests shows a good correlation with radiopaque marker tests in patients with chronic constipation[137,138]. Capsule studies have shown that more than one-third of patients with chronic constipation have abnormalities in transit that extend beyond the colon[139]. The incremental information provided by the capsule can be helpful in patients with overlapping symptoms in the upper and lower gastrointestinal tract and in patients with severe chronic constipation in whom colectomy is being considered.

Scintigraphy. Scintigraphy is used in a few centres to measure colonic transit time. Radioisotopes with a relatively long half-life are used, such as ^{111}In ingested in water along with a standard meal[140] or bound to activated charcoal in methacrylate-coated capsules that undergo pH-sensitive release in the terminal ileum[141]. Scintigraphy at 24 hours and 48 hours enables the calculation of the half-emptying time of the ascending colon (time to 50% emptying) and geometric centre (weighted average of isotope distribution within the colon), which, in turn, enables quantification of overall and regional transit times[9,133,142,143].

Colonic manometry. Conventional and high-resolution colonic manometry measure pressure changes reflective of colonic contraction. With high-resolution colonic manometry, recorded colonic pressures tend to be higher than with conventional water-perfused systems[144], which enables a more-detailed characterization of the phenotypes of chronic constipation.

Experts in the field have reported that colonic manometry can identify patients with underlying colonic myopathy (low amplitude contractions in the absence of megacolon) or neuropathy (absence of colonic response to high-calorie meal ingestion or to intravenous neostigmine or intraluminal bisacodyl); these features have been documented predominantly in children and adults with constipation[145]. Although the clinical importance
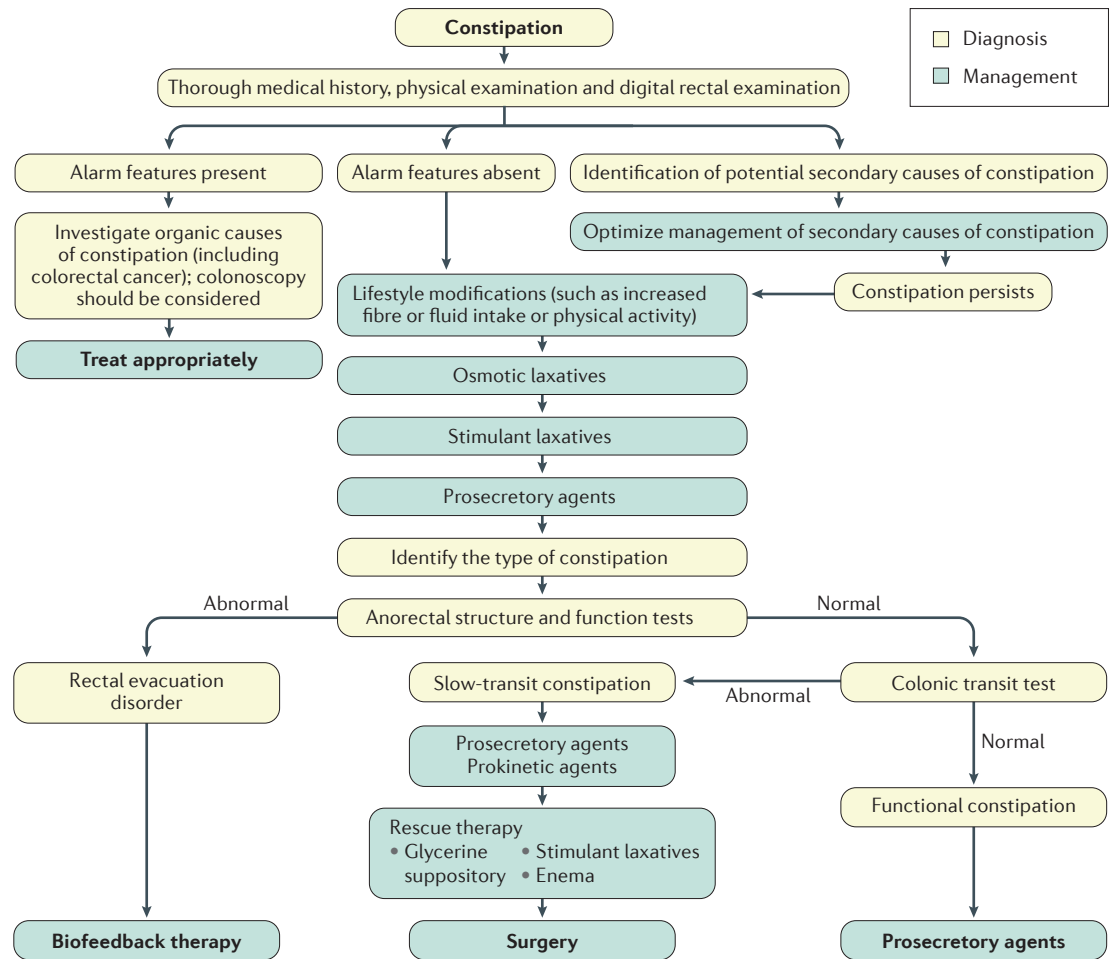
Figure 5 | Diagnosis and management algorithm for chronic constipation. Schematic overview of the sequence of medications and when to perform diagnostic tests, which often depends on the response to treatment. Algorithm adapted based on data in REFS 121,227.

of the diagnosis of myopathy or neuropathy based upon manometric findings has not been established, studies have shown that patients with colonic neuropathy who failed medical therapy but showed a response to biofeedback therapy, can benefit from a colectomy[146]. Colonic manometry is not widely available, although there is a current procedural terminology (reimbursement) code for this procedure in the United States. Widespread use of this test could conceivably prevent unnecessary colectomies and provide a rational approach to the clinical management of slow-transit constipation in patients who do not have evidence of colonic myopathy or neuropathy.

Management
Lifestyle modifications
Dietary and lifestyle modifications are often used as first-line management strategies for patients with chronic constipation. The validity of this approach is based on epidemiological studies linking constipation to various dietary and lifestyle factors, such as low intake of dietary fibres, low liquid consumption and physical inactivity, although the findings of these studies are somewhat inconsistent[23,147–149].

Fluid intake. Although increased fluid intake is often recommended to improve symptoms in patients with constipation, no high-quality evidence or randomized controlled trials suggesting that constipation can be treated successfully by increasing fluid intake exist, unless there is evidence of dehydration[150]. In addition, the commonly used recommendation to ingest dietary fibre supplements with extra water has little support in the literature and is challenged by a study in healthy individuals in whom adding extra fluid to wheat bran had no effect on gastrointestinal function[151].

High-fibre diet. Most available guidelines recommend a diet rich in fibre for patients with constipation, and the recommended intake of fibre is at least 25–30 g per day[152–154]. A randomized controlled trial showed that intake of 12.5 g fibre per day (wheat bran) did not improve symptoms associated with constipation[155]. Systematic reviews support the recommendation to increase dietary fibre intake and, particularly, intake of soluble fibres, for example, pectins, gums, mucilages and storage polysaccharides present in oat bran, barley, nuts, seeds, beans, lentils, peas, some fruits and vegetables

and psyllium fibre supplements[154,156–158]. Data regarding insoluble fibres (for example, cellulose, hemicelluloses and lignin present in wheat bran, vegetables and whole grains) for constipation are conflicting, with potential negative effects particularly in patients with IBS-C in whom insoluble fibres may worsen symptoms[156,159–161].

The mechanisms that drive a laxative effect with fibre vary. Large and/or coarse insoluble fibre particles (for example, bran) mechanically irritate the gut mucosa, which stimulates water and mucus secretion. The high water-holding capacity of gel-forming soluble fibre (for example, psyllium) resists dehydration and carries water to the colon to loosen stool consistency[162]. Failure to respond to dietary fibre supplementation may suggest an additional factor contributing to constipation, such as dyssynergia or slow colonic transit[120].

Physical activity. Increasing the level of physical activity in young patients with severe constipation is rarely helpful. However, some studies suggest a positive effect on overall gastrointestinal symptoms and well-being in patients with IBS, irrespective of the predominant bowel habit[163]. Increased physical activity as part of an overall rehabilitation programme in elderly patients with pronounced physical inactivity might be beneficial for constipation[164].

FODMAPs. Some patients with IBS-C may respond favourably to a diet restricting the intake of poorly absorbed fermentable carbohydrates (fermentable, oligosaccharides, disaccharides, monosaccharides and polyols; FODMAPs), although the evidence was graded as poor and further trials were deemed necessary[157]. No clinical trials assessing the effect of this diet specifically in individuals with constipation have been performed.

Pharmacological therapy

The main classes of approved pharmacotherapies for constipation are osmotic laxatives, stimulant laxatives, prosecretory agents and serotonergic 5-HT$_4$ receptor agonists (TABLE 1).

Osmotic laxatives. In patients with chronic constipation who do not respond to diet and lifestyle modifications, osmotic laxatives are the next recommended treatment[34,154] (TABLE 1). Osmotic laxatives create an intraluminal osmotic gradient resulting in water and electrolyte secretion into the intestinal lumen, thereby reducing stool consistency and increasing faecal volume.

The osmotic laxative polyethylene glycol was tested in several high-quality, randomized controlled trials of up to 6 months' duration, with improvements in the symptoms of chronic constipation compared with placebo[165]. In head-to-head trials, polyethylene glycol was superior to lactulose (another osmotic laxative)[166] and non-inferior to prucalopride (5-HT4 receptor agonist)[167]. Lactulose, a non-absorbed sugar, is fermented by colonic bacteria to short-chain fatty acids and can improve symptoms of mild-to-moderate constipation but often causes bloating[168]. Poorly absorbed salts,

such as magnesium and phosphate, are commonly used for the treatment of constipation, although there is little evidence of their effectiveness from randomized controlled trials[169].

Stimulant laxatives. Stimulant laxatives are frequently recommended in patients who do not respond to osmotic laxatives. Stimulant laxatives induce water and electrolyte secretion, stimulate intestinal motility and prostaglandin release[170] and accelerate colonic transit[171] (FIG. 3). Although widely used, no large, randomized controlled trials with anthraquinones at the currently recommended doses in patients with chronic constipation have been performed. Two randomized placebo-controlled trials with bisacodyl[172] and sodium picosulfate[173] demonstrated improvement in constipation-associated symptoms. A systematic review and network meta-analysis[174] found that the relative risk of having >3 complete spontaneous bowel movements (CSBMs) per week was 2.46 (95% CI 1.14–5.31) for bisacodyl and 2.83 (95% CI 1.27–6.31) for sodium picosulfate compared with placebo. Bisacodyl seems to be superior to the other drugs assessed in this study, including sodium picosulfate, prucalopride, lubiprostone and linaclotide. Chronic use of stimulant laxatives does not seem to lead to tolerance or rebound constipation on termination of treatment[150] or to damage to the colon[175].

Prosecretory agents. Currently available prosecretory agents (that is, lubiprostone, linaclotide and plecanatide) treat constipation by increasing fluid secretion into the intestinal lumen through direct action on intestinal epithelial cells (FIG. 4). Lubiprostone increases Cl$^-$ secretion into the lumen of the small intestine and colon, followed by Na$^+$ and water to maintain electrical neutrality. In a randomized controlled trial, 4-week treatment with lubiprostone increased stool frequency, improved stool consistency, reduced straining and bloating and improved overall constipation symptoms compared with placebo[176]. At week 4, 57.8% of patients receiving lubiprostone compared with 27.9%

Box 4 | Digital rectal examination in constipation

Visual inspection

- Anal fissure (a tear in the skin of the anal canal)
- Failure of pelvic floor to relax and descend or paradoxical anal sphincter contraction during stimulated defecation
- Rectal prolapse

Digital examination

- Inability to contract abdominal wall musculature, lack of propulsive force to push examining finger out of rectum or insufficient anal sphincter relaxation during stimulated defecation
- Contraction of the puborectalis during stimulated defecation
- Examination in the squatting position to identify rectal mucosal prolapse

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of patients receiving placebo reported >3 CSBMs per week. The most common adverse event reported was nausea (31.7% for lubiprostone versus 3.3% for placebo), although most cases were mild and only 5% of patients withdrew from the study owing to nausea[176]. A lower (8 μg) dose of lubiprostone has also been shown to be effective for the treatment of IBS-C and is associated with less nausea than the higher (24 μg) dose[177].

Linaclotide and plecanatide are guanylate cyclase-C receptor agonists, which increase cGMP in the intestinal epithelial cells, ultimately leading to the opening of the CFTR (FIG. 4). In two randomized controlled phase III trials[178], 12 weeks of linaclotide was more effective than placebo in increasing stool frequency and improving stool consistency, straining and overall constipation symptoms in patients with chronic constipation. In addition, more patients receiving linaclotide had >3 CSBMs per week and an increase of >1 CSBM over baseline for >9 out of the 12 weeks compared with patients receiving placebo. The most common adverse effect was diarrhoea (16% for linaclotide versus 5% for placebo), which led to discontinuation in 4.2% of patients. Linaclotide also improved bowel and abdominal symptoms in patients with chronic constipation with moderate-to-severe bloating[179].

In a phase III clinical trial, once-daily treatment with plecanatide for 12 weeks improved constipation-related symptoms (for example, stool frequency, stool consistency and straining)[180]. Plecanatide significantly increased the proportion of overall responders (that is, >3 CSBMs per week and >1 CSBM over baseline for 9 out of 12 weeks and 3 of the last 4 weeks of the trial), which was 21.0% and 19.5% in the plecanatide 3 mg and 6 mg groups, respectively, compared with 10.2% in the placebo group. Diarrhoea affected 1.3% of the placebo group, 5.9% of the 3 mg plecanatide group and 5.7% of the 6 mg plecanatide group. Diarrhoea in individuals taking plecanatide rarely led to discontinuation of therapy. Importantly, the efficacy of plecanatide and linaclotide is similar based on the efficacy relative to placebo[178,180].

Serotonergic agonist. Prucalopride is a highly selective 5-HT$_4$ receptor agonist that activates signalling of the afferent neurons and increases intestinal motility (FIG. 3). Although not currently available in the United States, prucalopride has been available in Europe since 2010 as a treatment for chronic constipation. Several large, high-quality clinical trials have shown that prucalopride improves stool frequency, stool consistency and straining compared with placebo[181]. In a phase III trial, 2 mg or 4 mg of prucalopride once daily resulted in significantly more patients having >3 CSBMs per week over the 12-week trial (30.9% for 2 mg prucalopride, 28.4% for 4 mg prucalopride and 12% for placebo)[182]. Prucalopride is generally well tolerated with no substantial cardiovascular effects or drug interactions. The most common adverse effects include gastrointestinal disorders (such as diarrhoea, nausea and abdominal pain) and headache.

Anorectal biofeedback therapy

For patients with constipation associated with dyssynergic defecation, anorectal biofeedback therapy has been demonstrated to be more effective with good long-term results than sham therapy, laxatives or the anti-anxiety drug diazepam[183–186]. Anorectal biofeedback therapy is a behavioural training technique in which the anorectal
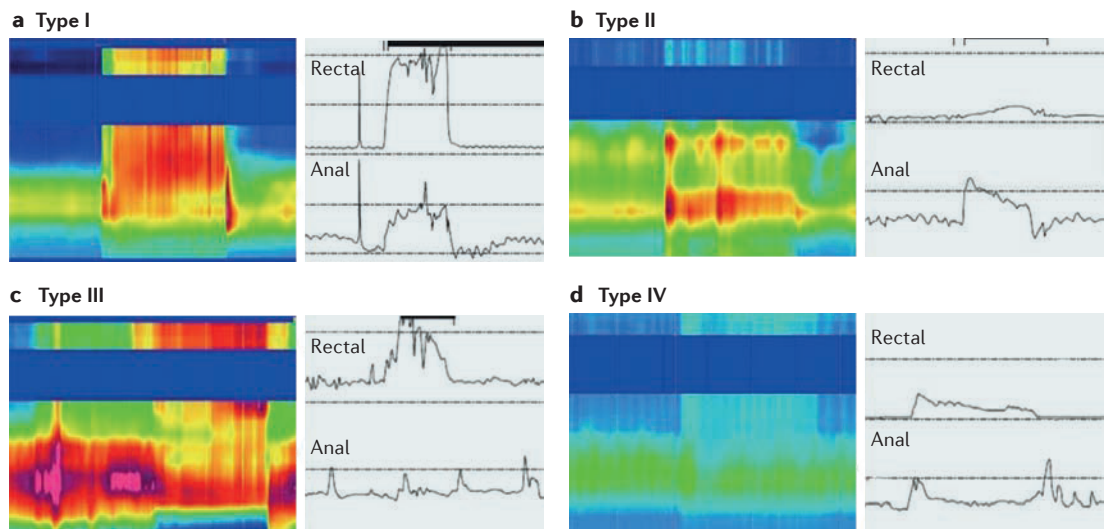
Figure 6 | **Anorectal manometry patterns during attempted defecation.** High-resolution anorectal manometry (coloured panels) and conventional manometry (line graphs) in the rectum (top panels) and anus (lower panels) are shown. A normal response consists of an increase in intrarectal pressure combined with a relaxation of the anal sphincter. **a** | In dyssynergic defecation type I, intrarectal pressure increases appropriately, but the anal sphincter paradoxically contracts. **b** | In dyssynergic defecation type II, intrarectal pressure does not increase and a paradoxical anal sphincter contraction is observed. **c** | In dyssynergic defecation type III, intrarectal pressure increases but no or inadequate relaxation of the anal sphincter is observed. **d** | In dyssynergic defecation type IV, intrarectal pressure and anal sphincter relaxation are absent or inadequate. Adapted from REF. 121, Macmillan Publishers Limited.

Table 1 | **Pharmacological management of chronic constipation**

Drug	Mechanism of action	Effectiveness	Adverse events
Osmotic laxatives			
Polyethylene glycol	Creation of an osmotic gradient draws water into the small intestine	Improvement in stool frequency, stool consistency and straining	Diarrhoea and abdominal distention
Lactulose		Improvement of symptoms of mild-to-moderate constipation; safe in pregnancy	Abdominal gas, bloating and cramping can occur and are dose-dependent
Poorly absorbed salts		Evidence of efficacy is poor	Excessive use, particularly in patients with renal insufficiency or elderly patients, may lead to electrolyte disturbances
Stimulant laxatives			
Anthraquinones (for example, cascara sagrada and senna)	Stimulation of water and electrolyte secretion, intestinal motility and prostaglandin release by acting on the enteric nervous system	Effective and generally well tolerated, but no large, randomized controlled trials have been performed	Diarrhoea and abdominal pain are common
Bisacodyl		Improvement of symptoms	
Sodium picosulfate			
Prosecretory agents			
Lubiprostone	Cl⁻ channel protein 2 agonist	Improvement of stool frequency, consistency and overall constipation symptoms and reduced straining and bloating	Nausea
Linaclotide	Guanylate cyclase-C receptor agonists, which increase intracellular cyclic GMP levels and promote Cl⁻ secretion through cystic fibrosis transmembrane conductance regulator	Increases stool frequency and consistency and reduces straining and overall symptoms	Diarrhoea
Plecanatide		Improvement of symptoms	
Serotonergic agents			
Prucalopride	5-Hydroxytryptamine (4) receptor agonist	Improvement of stool frequency, stool consistency and straining	Headache, nausea, abdominal pain and diarrhoea

physiology is monitored and shown to the patient so that he or she can be trained to correct the dyssynergic anorectal function. The number of biofeedback sessions varies, but most centres include the following steps in their protocol: patient education on appropriate defecation effort; training on how to strain to improve abdominal pushing effort; training to relax pelvic floor muscles while straining by visual feedback of anal canal pressure or averaged anal electromyography activity; and practice of simulated defecation by use of the balloon expulsion test[121,152]. In some centres, sensory retraining is also used as part of the biofeedback protocol for patients with impaired rectal sensation to lower the threshold for the sensation of urgency to defecate. Overall, 70% of patients will respond to biofeedback therapy, and this treatment has been afforded a grade A recommendation by the American and European Neurogastroenterology and Motility Societies[187].

Surgery
Patient selection. Surgical intervention for constipation is rarely indicated and requires strict criteria. Only patients with intractable constipation in whom correctable issues (for example, endocrine abnormalities, medications or opiate abuse) are ruled out and pharmacological treatment has been shown to be ineffective should be considered. In addition, surgery is only recommended for patients with slow-transit constipation,

but not for those with pelvic floor dysfunction leading to dyssynergic defecation or IBS-C. For combined dyssynergic defecation and slow-transit constipation, pelvic floor dysfunction must be corrected before surgical intervention becomes an option[34]. If dyssynergia resolves with biofeedback therapy but symptoms of constipation persist, a colonic transit study should be performed to identify patients with slow-transit constipation. If no evidence for slow-transit constipation is found, patients should be counselled and motivated to pursue biofeedback therapy; stoma creation is the only surgical option if biofeedback therapy fails.

Delayed transit in both the small intestine and colon (demonstrated by scintigraphy or wireless motility capsule) might be due to diffuse gastrointestinal dysmotility or, most likely, the transit in the small intestine is delayed due to slow transit in the colon. These patients may require small intestinal manometry to exclude chronic intestinal dysmotility; if this test is inconclusive or unavailable (which is the case at most centres), a temporary loop ileostomy may be required to isolate the colon from the gastrointestinal tract and to re-evaluate symptoms to appraise the role of slow small bowel transit. Patients with diffuse gastrointestinal dysmotility or small intestine dysmotility are not optimal surgical candidates, as the outcomes from colectomy are poorer than in patients without such extra-colonic dysmotilities[188].

Surgical procedures. The surgical options for treatment of slow-transit constipation are: ileostomy (surgery in which the ileum is brought through an opening in the abdominal wall to form a stoma); total colectomy with ileorectal anastomosis (surgery in which the colon is removed and the ileum is joined to the rectum); cecostomy with antegrade enemas; repair of rectoceles, rectal intussusception and rectal mucosal prolapse; or sacral nerve stimulation. The evidence and indications for these different surgical procedures are reviewed elsewhere on the basis of the American Society of Colon and Rectal Surgeons' Clinical Practice Guideline[189]. The use of colectomy with ileorectal anastomosis rather than simple ileostomy for constipation due to disordered defecation is highly controversial. As documented in the guideline, most of the recommendations for the other surgeries are weak and based on low-quality evidence, with the exception of total colectomy with ileorectal anastomosis, which is given a strong recommendation based on low-quality evidence[189].

Patients with slow-transit constipation may benefit from total colectomy. Those with combined slow-transit constipation and dyssynergic defecation may benefit from a total colectomy if pelvic floor dysfunction is corrected first. In the presence of severe, uncorrectable pelvic floor dysfunction, the only surgical intervention that relieves symptoms is an ileostomy. Cecostomy with antegrade enemas tend to be reserved for children with chronic intractable constipation. Sacral nerve stimulation is still considered an experimental treatment for chronic constipation in adults and recent publications, including a Cochrane meta-analysis, suggest it is not an effective option[190–195].

Multiple approaches for colectomy have been reported, ranging from right and left segmental colectomy to total colectomy. It is important to understand that slow-transit constipation is associated with ICC loss throughout the colon and rectum[196,197]. Hence, although segmental colectomy may result in temporary improvement in constipation, this improvement is not sustained. The best results are achieved with total colectomy with ileorectal anastomosis. Although loss of ICCs extends into the rectum, the rectum within the confines of the pelvis acts as a reservoir that can be emptied by increased intra-abdominal pressure rather than relying on coordinated colorectal contractions. Hence, any deficiency in coordinated contractions in the residual rectum is compensated by compression and emptying by the increased intra-abdominal pressure induced by straining.

The total colectomy with ileorectal anastomosis surgery can almost always be performed laparoscopically[198]. The anastomosis should be created in the pelvis, below the sacral promontory, usually 14–15 cm from the anal verge to avoid recurrence of symptoms from the residual distal sigmoid. As the majority of patients are young women, a laparoscopic approach minimizes adhesions and the risk of infertility[199].

A psychiatry consult should be strongly considered preoperatively. Patients with slow-transit constipation and dyssynergic defecation frequently have a history of physical or sexual abuse and psychiatric disorders. In one study of patients who had undergone total colectomy with ileorectal anastomosis for slow-transit constipation, 85% reported a current psychiatric condition and 62% reported a history of sexual abuse[200].

Outcomes of surgery. Strict selection criteria result in good outcomes. In one study of 74 patients who underwent colectomy with ileorectal anastomosis, 97% of patients were satisfied with the surgery and 90% reported a good or improved QOL[201]. Similar results have been reported in other studies[202,203]. A review of 13 studies of 362 patients who underwent colectomy between 1988 and 1993 reported a high degree of patient satisfaction (88%)[204]. On the other hand, earlier studies that did not completely exclude dyssynergic defecation or pan-gastrointestinal motility disorder were associated with optimal outcomes in ~50% of patients[188]. In one study, >90% of patients reported that they would undergo total abdominal colectomy with ileorectal anastomosis for their constipation because of the effect of the symptoms on QOL[205].

Quality of life
QOL instruments serve to measure the physical and emotional disease burden associated with a range of physical, psychological and social stressors. Using validated measures of generic QOL and disease-related QOL, studies have demonstrated impaired QOL in individuals with chronic constipation. In addition, chronic constipation poses a considerable economical and health care burden and affects work productivity and school attendance.

Generic QOL
Population-based studies using the Medical Outcomes Short-Form Health Survey (SF-36 and SF-12) instruments in the general population and in individuals who seek treatment (clinical setting) demonstrated lower physical and mental component scores (PCS and MCS, respectively), implying poorer QOL in individuals with chronic constipation than in individuals without constipation[206]. The Psychological General Well-Being Index (PGWBI) was lower in individuals with constipation in the clinical setting than in individuals from the community[206]. In individuals with or without constipation, women reported lower PCS and MCS values than men[207]. In all age groups, lower QOL scores were recorded for those with constipation than in those without constipation, even when adjusted for sex. The presence of anxiety and symptoms of depression were independent risk factors for worse QOL scores[208]. Individuals who showed symptoms of constipation and were unemployed or retired reported worse QOL than individuals who were constipated and employed[207].

When comparing different types of constipation, patients with slow-transit constipation or <3 stools per week had better PGWBI scores than those with normal-transit constipation or >3 stools per week, possibly because normal-transit constipation may overlap with IBS[209]. Individuals with constipation in the community had similar QOL scores as individuals with

stable inflammatory bowel disease, chronic allergies and dermatitis. Patients with constipation in the clinical setting had QOL scores that were comparable to those of patients with functional dyspepsia or active inflammatory bowel disease; PGWBI scores were at least as severe as those associated with untreated peptic ulcer disease, gastro-oesophageal reflux disease and mild asthma[206].

Disease-related QOL

The Patient Assessment of Constipation QOL (PAC-QOL) questionnaire is a 28-item questionnaire with four subscales of worries or concerns, physical discomfort, psychosocial discomfort and satisfaction[210]. Satisfaction with bowel movements and treatment was affected in individuals with chronic constipation, as was physical discomfort, as individuals often reported a feeling of bloating, heaviness, discomfort or the inability to have a bowel movement. Disease-related QOL scores tended to be worse in patients in the United States than in patients in Europe, Canada and Australia[210].

PAC-QOL scores were worse in constipated patients with more-severe symptoms of constipation[208,210,211] than in those with mild-to-moderate constipation[210] and in those with IBS-C compared with individuals with normal-transit constipation or those with no constipation on the basis of the Rome criteria[211]. Disease-related QOL was also worse in individuals with constipation with abdominal symptoms (for example, discomfort, pain, bloating and stomach cramps) than in those with constipation without abdominal symptoms[210,211]. Total PAC-QOL scores were not associated with age, sex or duration of constipation[211].

Economic burden

A US population study examined the burden of disease in IBS-C and chronic constipation with abdominal symptoms (≥1 time per week)[8]. Among working or school-going respondents, those with IBS-C or chronic constipation with abdominal symptoms reported a mean of 0.8 missed days per month due to gastrointestinal symptoms, compared with a mean of 0.4 days in those with chronic constipation without abdominal symptoms. The mean number of days with disrupted productivity was 4.9, 3.2 and 1.2 days per month in patients with IBS-C, chronic constipation with abdominal symptoms and chronic constipation without abdominal symptoms, respectively[8].

The related health care costs are considerable; for example, the mean annual all-cause and gastrointestinal-related costs in the United States for patients with chronic constipation were US$11,991 and $4,049, respectively[212]. Health-care costs of patients with chronic constipation exceed those of age-matched and sex-matched controls[212–215]. Of the costs associated with chronic constipation, 45% are associated with outpatient services, including outpatient visits or tests for comorbidities (such as fatigue, headache, insomnia or other chronic pain disorders) and 34% of costs are associated with gastrointestinal-related issues[212]. Costs were higher in those with abdominal pain and/or bloating than in patients without pain and/or bloating[212].

Outlook

Chronic constipation is a highly prevalent symptom. Considerable advances in diagnosis and management have ensured that the majority of individuals with chronic constipation are able to achieve satisfactory symptom relief and improved QOL. One of the recent advances is a greater appreciation of the prevalence of dyssynergic defecation by gastroenterologists, which leads to more-accurate diagnosis and treatment of dyssynergic defecation[9,216]. A second advance is the recognition of frequent overlap or association of bloating and pain that would be consistent with IBS-C, and treatment of patients with IBS-C for chronic constipation often results in improvement; in fact, medications are approved for both indications, that is, lubiprostone and linaclotide[8,31,217]. In addition, chronic constipation may present with upper gastrointestinal symptoms, such as nausea, in patients with disorders of colonic transit or rectal evacuation[218]. Furthermore, chronic constipation is associated with Ehlers–Danlos hypermobility syndrome, which also manifests with other gastrointestinal symptoms, although most frequently with chronic constipation[219–221]. Finally, several effective pharmacological agents for the treatment of chronic constipation have been developed, as illustrated in a recent meta-analysis[174].

However, many issues still need to be addressed. Future advances are required to improve diagnostic accuracy, as well as the identification and widespread delivery of care for rectal evacuation disorders. Ideally, assessment of defecation should be performed in the sitting position and with a sensation of stool. The development of wireless solid-state catheters may facilitate evaluations of defecatory functions in the physiological seated position in contrast to the current methods, which assess anorectal functions in the left lateral position[222]. Other important avenues for future research are: understanding the potential aetiological role of the microbiota in chronic constipation; identifying the causes and reversibility of dyssynergic defecation without the need for the intense and laborious biofeedback-assisted retraining of pelvic floor and anal sphincter function; and understanding the neuropathology that results in severe colonic motility disorders, such as slow-transit constipation and the less-severe normal-transit constipation. In addition, in terms of management, more-effective nonsurgical approaches should be developed through pharmacological approaches that are safe in the long term or use alternative or integrative medicine approaches, such as transabdominal electrical stimulation. Indeed, the use of an interferential current applied via four self-adhesive conducting electrodes with two placed in the paraspinal (T9-L2) region and the paired electrodes positioned diagonally opposite on the anterior abdominal wall below the costal margin increased colonic propagated contractions and defecation frequency in children with chronic constipation and reduced colonic transit time in children with slow-transit constipation[223]. Finally, an immediate goal is to disseminate the advances summarized in this Primer to benefit patients with chronic constipation seen in the primary care setting.

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M.C. serves on an advisory board for Ironwood Pharmaceuticals and Shire Pharmaceuticals, with compensation to his employer and not to him personally, and has received grant and research support from NGM Pharmaceuticals. A.C.F. has received grant and research support from Almirall and has acted as a consultant and speaker for Almirall, Norgine and Shire Pharmaceuticals. S.S.R. serves on the advisory board for Forest Labs, Salix Pharmaceuticals, Takeda Pharmaceuticals and Synergy Pharmaceuticals and has received research grants from Forest Labs and Medtronic Corporation. M.S. has received grant and research support from Danone Nutricia Research and Ferring Pharmaceuticals and has acted as a consultant and speaker for Allergan, Almirall, Danone Nutricia Research, Menarini, Nestlé, Shire Pharmaceuticals, Takeda Pharmaceuticals and Tillotts. L.C. has served on advisory boards for BioAmerica, Cairn Diagnostics, IM Healthcare Science LLC, Napo Pharmaceuticals, Salix Pharmaceuticals, and Synergy Pharmaceuticals. All other authors have no relevant conflicts of interest related to the content of this Primer to declare.

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