# Gastrointestinal pain

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Abstract | Gastrointestinal (GI) pain — a form of visceral pain — is common in some disorders, such as irritable bowel syndrome, Crohn's disease and pancreatitis. However, identifying the cause of GI pain frequently represents a diagnostic challenge as the clinical presentation is often blurred by concomitant autonomic and somatic symptoms. In addition, GI pain can be nociceptive, neuropathic and associated with cancer, but in many cases multiple aetiologies coexist in an individual patient. Mechanisms of GI pain are complex and include both peripheral and central sensitization and the involvement of the autonomic nervous system, which has a role in generating the symptoms that frequently accompany pain. Treatment of GI pain depends on the precise type of pain and the primary disorder in the patient but can include, for example, pharmacological therapy, cognitive behavioural therapies, invasive surgical procedures, endoscopic procedures and lifestyle alterations. Owing to the major differences between organ involvement, disease mechanisms and individual factors, treatment always needs to be personalized and some data suggest that phenotyping and subsequent individual management of GI pain might be options in the future.

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Gastrointestinal (GI) pain shares most of the basic characteristics of other conditions involving visceral pain, which refers to pain that originates from the internal organs. This type of pain is common, although linking specific symptoms with an underlying aetiology remains a clinical challenge. Compared with acute somatic pain (that is, pain of the muscle, skin, bone or tendon), which is often associated with protective nociceptive reflexes that prevent harm, the biological significance of visceral pain is less clear[1]. One possible explanation is that visceral pain might be a signal for the organism to rest, which could protect the body during inflammatory insults (such as in appendicitis). The underlying causes of visceral pain can be organic and related to a specific disease process (known as secondary visceral pain according to the International Classification of Diseases, 11th Revision (ICD-11)), or be functional such as in irritable bowel syndrome (IBS; known as primary visceral pain in the ICD-11), whereby no specific pathophysiology can be identified[2,3]. The term nociplastic pain (that is, pain that arises from altered peripheral or central nociception despite no clear evidence of actual or threatened tissue damage) is another term for functional pain[4]. Visceral pain can classified as acute or chronic based on the duration of pain (whereby chronic pain lasts or recurs for >3 months[3], based on ICD-11 criteria). Chronic visceral pain in particular may lead to changes in the central nervous system (CNS), which can also result in behavioural symptoms such as anxiety, fear and depression[5,6].

Typical visceral pain conditions include classic and vasospasmic angina pectoris and other cardiac pain conditions[7,8]; achalasia and oesophageal spasms[9]; peptic ulcer[10]; chronic pancreatitis[11]; biliary disorders[12]; kidney stones[13]; endometriosis[14,15]; and functional (or primary) visceral pain conditions, such as IBS[16], bladder pain syndrome or interstitial cystitis[17,18], prostatitis; and testicular and vulvar pain syndromes[19,20]. This Primer focuses on GI pain, as a common type of visceral pain associated with diagnostic challenges, disability and substantial health-care costs. GI pain can be associated with neurogenic inflammation (whereby sensory neurons release inflammatory mediators), changes in GI motility and permeability with symptoms such as diarrhoea and emesis, in addition to ischaemia, organ distension and changes in the microbiota[21,22], although frequently no objective abnormalities are demonstrable.

Diagnosis of GI pain is challenging as the pain is often poorly localized and may be referred to somatic and other visceral structures[23], and owing to the association of this pain with other sensations such as early satiety and organ fullness (BOX 1). Management of GI pain is more difficult than treatment of somatic pain as the associated unpleasantness, intense activation of the autonomic nervous system and presence of organ spasms are less responsive to conventional pain treatments. In addition, the treatment of GI pain is complicated by the fact that many analgesics are associated with adverse effects, many of which affect the gut, and many causes of GI pain can affect drug absorption and metabolism.

Box 1 | **Clinical characteristics of GI pain**

- True gastrointestinal (GI) pain is poorly localized and often associated with autonomic symptoms, such as the initial phase of acute appendicitis.
- Referred pain to somatic structures is observed in typical dermatomes according to the affected organ, but may be abnormal in localization and extent, especially in functional diseases.
- Cross-organ sensitization can lead to symptoms in otherwise healthy organs and may complicate diagnosis.
- Involvement of the enteric nervous system is frequent and can result in GI dysmotility that may be symptomatic.
- When a GI disease affects the peritoneum or other visceral membranes, the clinical presentation may shift from typical visceral (diffuse) to somatic (sharp, well-localized) pain.
- GI pain may increase sympathetic and parasympathetic activity and vagal reflexes can, for example, change fluid transport, pancreatic function and cardiac and respiratory rhythm; accordingly, diarrhoea, sweating and palpitations can dominate the clinical picture.
- Sensitization and neuroplastic changes are frequently observed in GI diseases and may explain the chronicity of pain despite normalization of organ function and afferent barrage.

This Primer discusses mechanisms of GI pain associated with organ damage, and the underlying pathophysiology of the most common diseases, together with recommendations for management, whereas functional disorders are only briefly mentioned as they have been thoroughly reviewed previously[16].

## Epidemiology

Pain arising from the viscera is common. Community-based cross-sectional studies have estimated that the prevalence of intermittent abdominal pain in adults is up to 25%[24,25]. However, reported prevalence estimates are highly variable, and some studies have suggested that abdominal pain is more common in females than in males, and, in particular, in functional disorders in adults between 20 and 40 years of age[24,26,27]. Disorders associated with chronic abdominal pain are the most common GI diagnoses in the USA, accounting for >12 million outpatient consultations per year[25]. These disorders include GI cancers, chronic pancreatitis and inflammatory bowel diseases. In general, functional disorders are more frequently diagnosed than organic diseases, but the incidence and prevalence vary greatly between conditions.

Abdominal pain is one of the presenting symptoms in 50–70% of patients experiencing the initial onset or exacerbations of inflammatory bowel disease[28]. However, the clinical presentation of these disorders, in particular Crohn's disease is heterogeneous and insidious, as it depends on disease location, severity of inflammation and disease behaviour (for example, luminal versus fistulating Crohn's disease)[29]. Upper abdominal pain is the primary symptom of chronic pancreatitis and is present in most patients during the course of the disease[30]. Risk factors for chronic pancreatitis-associated pain are multifactorial and include smoking and alcohol misuse, as well as disease-related factors including morphological changes of the pancreas and recurrent attacks of pancreatitis with ensuing damage to pancreatic nerves[31]. Several GI malignancies are associated with the presence of visceral pain, including pancreatic cancer, in which upper abdominal pain was the primary symptom in 44% of patients in a large case–control study[32]. However, up to 80% of patients with pancreatic cancer develop pain during the course of disease[33]. The prevalence of pain in other GI malignancies is less certain and prevalence estimates have been incompletely documented.

The most prevalent functional GI disorders associated with chronic abdominal pain are IBS and functional dyspepsia[16]. Abdominal pain and discomfort are central to the diagnostic criteria of these disorders. For example, using the most recent definition of IBS (that is, the Rome IV criteria)[34], the prevalence of IBS is ~5% in the western European population[35]. However, higher estimates have been found in earlier studies that used different definitions of IBS, with a pooled global prevalence of ~11%[36]. The incidence of IBS is difficult to determine owing to the very dynamic nature of symptoms and substantial overlap with other functional disorders[16].

## Mechanisms/pathophysiology

### *GI pain pathways*

The GI tract is innervated by both intrinsic and extrinsic afferent (mainly sensory) neurons (also known as visceral primary afferents). Intrinsic afferents are considered part of the enteric nervous system, project locally within the wall of the GI tract, and are mainly involved in regulation of physiological functions such as secretion, motility, mucosal transport and blood flow[37]. In addition, intrinsic afferents might also have a role in chronic pain states when they become sensitized.

Acute pain is predominantly mediated by the extrinsic afferents that project from the GI tract to the CNS[38]. Extrinsic afferents project to the spinal cord within splanchnic nerves, which contain both extrinsic afferents and sympathetic fibres. Parasympathetic fibres do not normally have a major role in visceral pain transmission, but may be indirectly involved[1,39] (see below). Most of the nociceptive output from the GI tract is conveyed to the dorsal horn of the spinal cord via extrinsic afferent fibres (in this case, also known as nociceptors or nociceptive afferents as they are involved in the transmission of pain signals)[40] (FIG. 1). This nociceptive output is conducted by unmyelinated C-fibres and thinly myelinated A$\partial$ fibres[41]. Although different sensory endings have been described in the gut, most visceral primary afferents are polymodal (that is, they respond to several types of sensory information) but peripheral sensitization and activation of 'silent afferents' (that is, nociceptors that are normally unresponsive to noxious stimuli, but become responsive following injury or inflammation) may change the afferent input to the CNS (details are provided in REF.[1]).

Indeed, during acute GI diseases, afferent neuron terminals typically respond to chemical agents — including $H^+$, $K^+$, bradykinin, ATP, inflammatory molecules and trypsin[42] — that are released following cellular damage caused by ischaemia, inflammation and tissue necrosis (FIG. 2). These mediators activate local nociceptors, and induce a cascade-like release of other pain-promoting factors, such as activation of voltage-sensitive calcium, sodium and potassium channels, modulation of different sensory transducer channels and increased gene

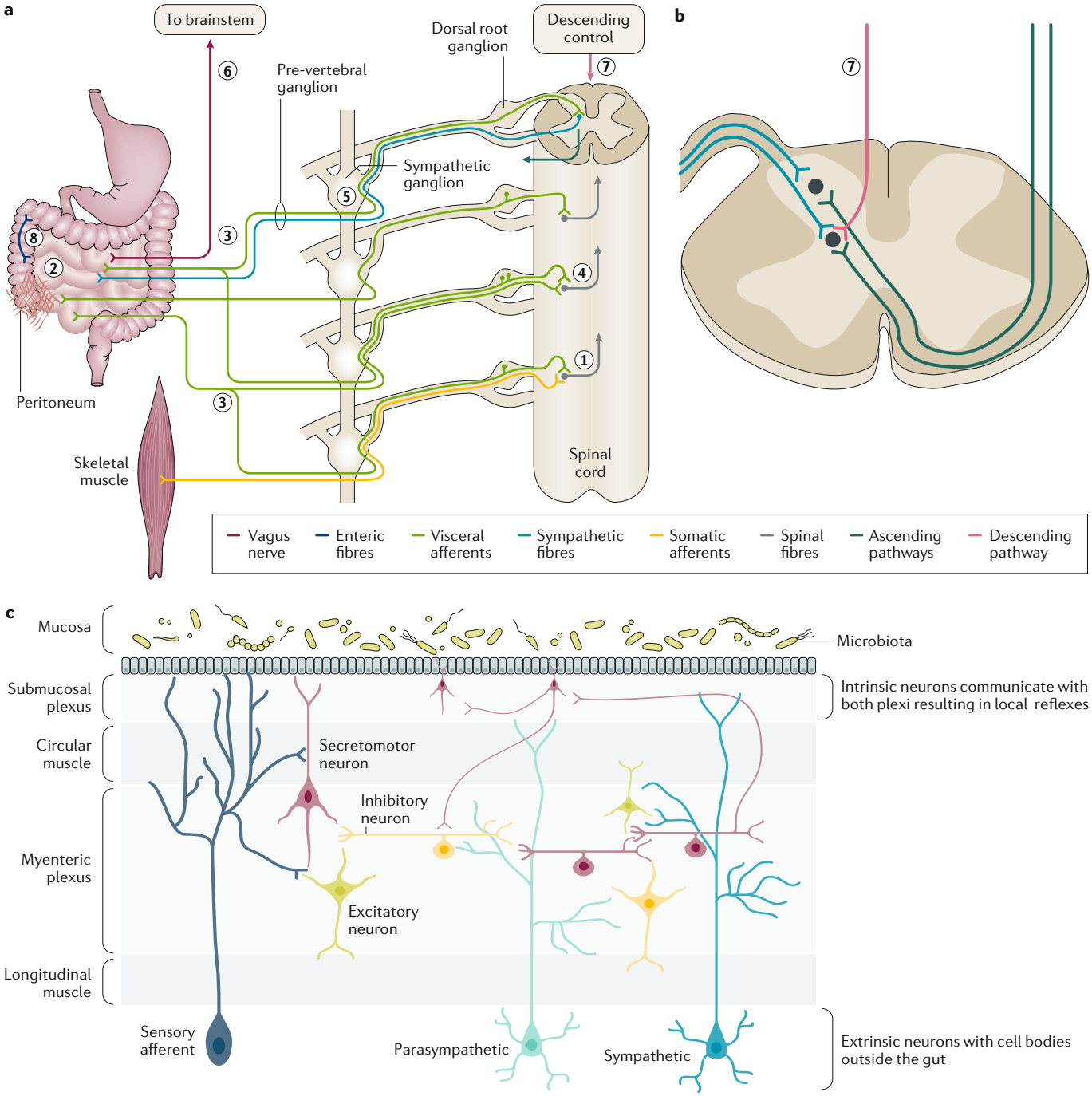


Fig. 1 | **Pathways and mechanisms that contribute to GI pain.** Somatic nerve fibres (such as skin and muscle afferents) have a somatotopic organization throughout the central nervous system, meaning that pain is distinct and well-localized. By contrast, visceral nerve fibres terminate at several segmental levels of the dorsal horn in the spinal cord (part **a**), leading to a diffuse localization of visceral pain (such as gastrointestinal (GI) pain). Although simplified, visceral nerve fibres converge with somatic nerve fibres in the spinal cord (step 1), which could explain how GI pain is referred to somatic structures (for example, to the epigastrium and back in pancreatitis). The nerve supply to the peritoneum is similar to the innervation of somatic tissues (step 2), and, therefore, when affected, the pain characteristics are typically similar to those of somatic pain. Visceral primary afferents can also dichotomize and terminate at several levels of the spinal cord (step 3) which, together with viscero–visceral spinal convergence (whereby different visceral primary afferents terminate onto the same spinal cord neuron (step 4)), explains why GI diseases can give symptoms from remote organs. In addition, visceral primary afferents project to the spinal cord with the same nerves as sympathetic nerves, which can lead to crosstalk at the local and central level (step 5) and result in autonomic reflexes, muscle tension and the long-term trophic changes in somatic tissue. The vagus nerve and other parasympathetic afferents (step 6) normally mediate non-painful sensations but can activate brainstem centres responsible for descending inhibition of the peripheral input and therefore dampen pain (step 7) (part **b**). The enteric nervous system (step 8) can also be affected by autonomic reflexes, which explains some manifestations of GI pain such as paralysis of the gut and associated symptoms (part **c**). Finally, some visceral afferents can become active during pathological states, such as inflammation, and contribute to the afferent barrage and resulting symptoms.

transcription and attraction of immune cells, that ultimately results in sensitization of the neurons (in a process known as peripheral sensitization; increased sensitivity of the nerve fibres). Afferent nerve fibres can also be activated by pressure and stretch, especially in the circumferential direction such as during distension of the gut[43]. The increased afferent barrage to the CNS can lead to central sensitization with neuroplastic changes including neuronal excitation and opening of latent pathways that do not normally mediate pain. Under such circumstances, pain can persist despite normalization of the original organ dysfunction. A detailed review of the peripheral and central mediators involved in GI pain is outside the scope of this Primer, but readers are referred to REFS[31,44–47].

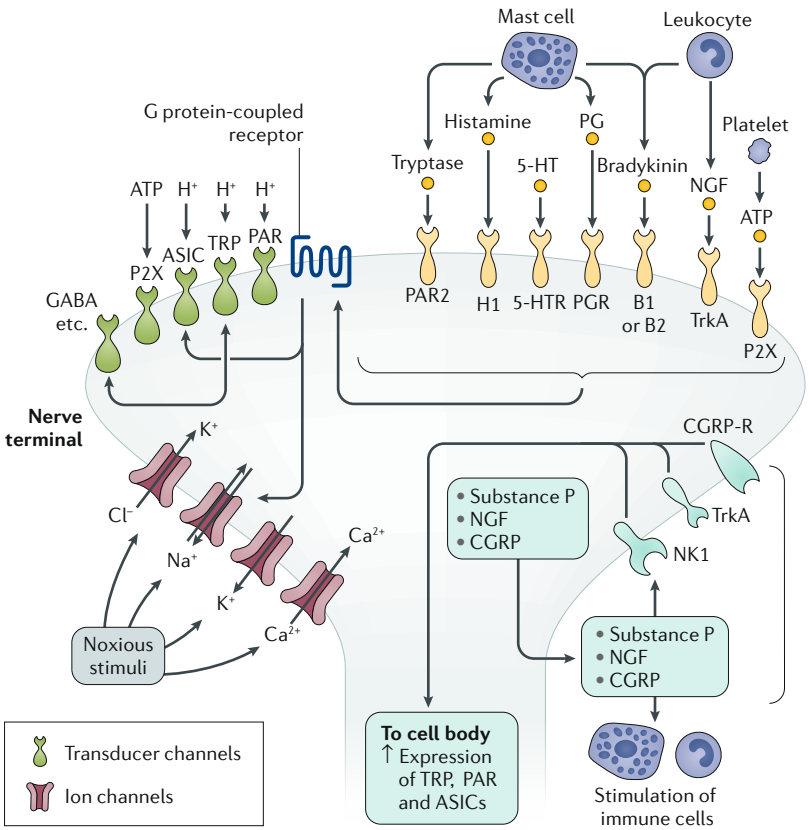


Fig. 2 | **Peripheral nerve activation.** Ischaemia and tissue damage caused by gastrointestinal (GI) diseases can lead to release of mediators from the mucosa, epithelial lining, blood and sympathetic varicosities, such as bradykinin, histamine, 5-hydroxytryptamine (5-HT), tryptase, prostaglandin (PG) E and ATP. These molecules can bind to specific receptors at neuronal termini and reduce the threshold for neuronal activation either directly, such as PGs, ATP and protons, or indirectly through the activation of G protein-coupled receptors, for most other molecules. Activation of G protein-coupled receptors (GPCRs) leads to the phosphorylation of ion and transducer channels, rendering them more sensitive to external activation. Histamine also acts indirectly by generation of PGs (not shown). During inflammation, mast cells, leukocytes and platelets interact with the visceral afferents via chemical mediators, described above, and via chemokines, cytokines and neuropeptides, such as substance P, calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF). These neuropeptides have specific receptors that activate cellular pathways and can sensitize other receptors. In addition, receptor activation leads to increased gene transcription and upregulation of other receptors such as transient receptor potential (TRP), protease-activated receptors (PAR) and acid-sensing ion channels (ASICs), as well as neuronal production and release of more neuropeptides, which can stimulate the immune cells in a positive feedback loop. This cycle renders the cells more responsive to external stimuli and maintains the neurogenic inflammation where glia cells also become activated. 5-HTR, 5-HT receptor; B1 and B2, bradykinin receptors; GABA, γ-aminobutyric acid; H1, histamine receptor 1; NK1, neurokinin 1; P2X, purinoceptor; PGR, prostaglandin receptor; TK1, tachykinin receptor 1; TrkA, tropomyosin receptor kinase A.

After entering the spinal cord, nociceptive signals transmit to the brain through several pathways. Most nociceptive signals are conveyed to the brain via the spinothalamic tract to the thalamus, but the dorsal column–medial lemniscal pathway also conveys nociceptive afferent information in the spinal cord[1]. In addition, nociceptive signals are conveyed to the brain via the spinoparabrachial pathways, which project via the periaqueductal grey, rostroventral medulla and the dorsolateral pontine tegmentum, then to the insula, hypothalamus, amygdala and higher cortical regions such as the cingulate and prefrontal cortices. The insula has an important function for integrating visceral sensory and motor information and is important in pain perception from the gut[21,48]. By contrast, the anterior cingulate and prefrontal cortices are part of the medial pain system, which (although simplified) mediate the affective, emotional and cognitive components of the pain experience[49]. In addition, some nociceptive signals ascend in the spinoreticular tract, which mediates arousal and autonomic responses through interactions with the reticular formation. In general, GI structures are not as organized as their somatic counterpart, although there is some evidence that different gut segments have specific regions of cortical representation as in the so-called homunculus described for somatic pathways[50]. Centres in the brainstem also communicate with regions such as the amygdala to integrate the pain signal with the autonomic nervous system and the hypothalamic–pituitary–adrenal axis[51].

Although visceral primary afferents running in the splanchnic nerves are the predominant fibres involved in GI pain processing, some nociceptive information is transmitted via the vagus nerve to the brainstem[52]. Vagal fibres might have a role in the central inhibitory modulation of pain, by activating regions of the brainstem, such as the periaqueductal grey and rostroventral medulla, that have a role in the descending modulation of pain[53] (FIG. 1). In addition, spinal cord neurons that are involved in pain processing receive inputs from the anterior cingulate cortex and other brain structures (which are part of descending pain control)[21,54]. This descending pain modulation can lead to either an increase in spinal transmission of pain impulses (that is, facilitation) or a decrease in transmission (that is, inhibition), and the balance between these states ultimately determines the quality and strength of the perceived pain signals. Indeed, shifting from inhibition to facilitation has been implicated in the transition from acute to chronic pain[55], and several studies have demonstrated the involvement of brainstem structures in the generation and maintenance of central sensitization and hyperalgesia in somatic and visceral pain[56]. Furthermore, dysfunctional descending pain control is associated with increased pain intensity in patients with IBS and in patients with chronic pancreatitis[57–59].

Sensitization and central reorganization also occur in brain regions implicated in visceral pain processing[31]. For example, plasticity of the insula occurs following

Box 2 | **The microbiota and GI pain**

- An interactive and multidirectional network exists between the microbiota, the host and the environment, whereby the integration of neural, endocrine and immunological signalling enables bidirectional communication between the gut and the brain[72,214,215].
- The microbiota is likely to be associated with gastrointestinal (GI) pain. Various animal models have shown that antibiotic administration early in life induces long-lasting effects on visceral pain responses[216] that can be normalized after postnatal microbial colonization of the gut[73]. Visceral hypersensitivity can also be transferred to rats by faecal transplantation from patients with irritable bowel syndrome (IBS)[217].
- In humans, disturbances in brain–gut communication are associated with intestinal inflammation and chronic abdominal pain syndromes. Both physical and psychological stressors enhance the perception of visceral pain[216], and stress alters the functioning of the autonomic nervous system and gut barrier, and results in changes in the microbiome[72,218]. In addition, the development of IBS after intestinal infections indicates that post-infectious plasticity of the nervous system is possible due to transient changes in gut bacteria[214]. Consistently, in patients with IBS, a systematic review reported an overall benefit of probiotics in reducing abdominal pain and bloating[73,219].

painful visceral stimulation in patients with chronic pancreatitis[60,61], and this plasticity is likely to contribute to the chronic pain state as was confirmed in later studies in which the neuronal networks were studied in detail[62]. Structural changes and abnormal neuronal fibre structures are also observed in these patients, predominantly in the limbic system such as the cingulate cortex[63,64]. Central changes have also been demonstrated in patients with pain associated with other GI diseases, particularly in those with functional disorders such as IBS[16].

***Autonomic symptoms and GI pain.*** As discussed earlier, patients with visceral pain often have autonomic symptoms, such as sweating and changes in blood perfusion, in addition to the pain sensation. These autonomic symptoms can, at least in part, be explained by the colocalization of visceral primary afferents with sympathetic and parasympathetic nerve fibres, which can allow local crosstalk between the nerve fibres[23]. The enteric nervous system is considered part of the autonomic nervous system and is also affected in painful GI diseases. For example, malfunction of bowel movements is frequently observed after, for example, surgery and acute pancreatitis, resulting in postoperative ileus and dysmotility[45,65,66]. The enteric nervous system has complex functions that may lead to pain disorders, such as communication with the microbiota (BOX 2). Changes in memory function particularly of enteric glia cells may also modulate pain perception through interactions with neurons and immune cells (reviewed in REFS[67–69]). By contrast, activation of nociceptive afferents can initiate local reflexes in the enteric nervous system between intrinsic pathways in the gut and associated ganglia, as well as spinal reflexes, and hence modulate gut function (FIG. 1). Descending pathways that originate in the brain also have some control over the enteric nervous system. The resultant changes from such modulation in enteric motor function may lead to GI dysmotility and as such contribute to the pain experience.

Another mechanism of GI pain-associated autonomic symptoms is the involvement of vagal afferent fibres. As mentioned above, vagal afferents are involved in the descending control of pain, but these fibres are also believed to mainly mediate non-noxious physiological sensations, such as satiety and nausea[70]. Indeed, together with the central autonomic network in the brain, the vagus nerve is involved in intestinal fluid transport, local visceral blood flow, gut motility, pancreatic exocrine and endocrine secretion, cardiac and respiratory rhythm generation and immune functions[51], and these diverse functions could explain the many sensory symptoms, such as nausea and general unpleasantness, that are associated with visceral dysfunction. Changes in the normal motility and barrier function of the gut can also affect the microbiota. Although beyond the scope of this Primer, changes in the microbiota can potentially lead to sensory symptoms such as pain and comorbidity[44,68,71–75] (BOX 2).

***Pain distribution and referred pain.*** In clinical practice, GI pain is often reported as diffuse pain that is poorly localized[76]. One reason for this distribution could be the termination of visceral primary afferents throughout several segments of the spinal cord in the rostral and caudal directions[77] (FIG. 1). This pattern is in contrast with the distribution of skin and muscle afferents that have a strict somatotopic organization. In addition, somatic fibres have limited terminal arborization in the dorsal horn, whereas visceral afferents extend across the superficial dorsal horn into deeper laminae of the spinal cord where the coding of pain is less site-specific[78]. However, if the peritoneum is affected by transmural inflammation, the pain becomes more localized and distinct than the 'typical' diffuse GI pain, as the peritoneum has somatic-like fibres.

GI pain is commonly referred to somatic structures; prototypical examples of this visceral pain phenomenon are referral of pain to the left arm during myocardial ischaemia, and right curvature and shoulder pain during gallstone attacks, but referred pain has been described for all organs and in several disease states. Although simplified, referred pain occurs due to convergence of visceral and somatic nerve fibres on the same neuron in the dorsal horn of the spinal cord[79,80] (FIG. 1). As the brain cannot localize the precise origin of the visceral pain stimulus, pain may be interpreted as originating from a somatic structure with the same segmental innervation.

In addition, pain and other sensory symptoms can also manifest in neighbouring organs that are not affected by disease or inflammation such as after surgery. Viscero-visceral hyperalgesia or cross-organ sensitization is a complex form of hypersensitivity that is probably explained by several mechanisms. Mechanisms implicated in preclinical studies include dichotomizing afferents (whereby different branches of a visceral primary afferent fibre enter the spinal cord at different levels), central convergence of afferents from two or more viscera on the same second-order neuron (FIG. 1) and indirect mechanisms related to inflammation, increased permeability of the mucosa and neurogenic inflammation[81] (FIG. 2). In addition, it is plausible that central sensitization plays an important part in cross-organ sensitization[82]. For example, studies in humans have shown

that oesophageal perfusion with acid and capsaicin can increase sensitivity in the rectum[83,84]. Besides changes at the spinal level, changes in the cortical processing of pain could be involved in these mechanisms[85]. Cross-organ sensitization could also explain the epidemiological findings that several clinical conditions show evidence of increased pain from other organs.

### *Subtypes of GI pain*

***Acute GI pain.*** Acute GI pain, such as in acute pancreatitis, is usually characterized by a deep pain in close proximity to the anatomical locations of the affected organs and associated somatic area, although localization of pain in the early stages of disease can be more difficult. Multiple interacting mechanisms might be involved in this type of pain, such as increased pressure in the pancreatic duct, activation of inflammation pathways, or ischaemia and tissue necrosis of the viscera and neighbouring organs, such as peripancreatic fat or complications of perforation (duodenum or colon)[30]. These mechanisms can all lead to peripheral sensitization, and in contrast to somatic pain in which longer-lasting stimulation is required, visceral stimulation may evoke central sensitization at the beginning of the painful event[86]. In the specific situation of digestive surgery (open or laparoscopic), pain can be due to organ resection, tissue dissection and cutaneous scar. Adverse effects of digestive surgery, such as bacterial translocation, organ insufficiency and postoperative ileus, can result in different pain presentations.

***Chronic GI pain.*** Chronic GI pain, such as in inflammatory bowel diseases, has the same mechanisms as other chronic pain disorders, including sensitization of the CNS and reorganization of brain centres involved in pain processing[56]. In addition, dysfunction of the normal descending pain modulatory system has been demonstrated in many GI diseases that are characterized by chronic pain, including IBS and chronic pancreatitis[56]. Clinically, features such as allodynia (painful sensation to stimuli that are not normally painful, such as air and faeces causing distension of the gut) and hyperalgesia are common epiphenomena[45].

***Neuropathic GI pain.*** Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system[87]. Although not included in the most recent taxonomy[2], neuropathic pain has been demonstrated in many GI diseases, such as chronic pancreatitis, and following chemotherapy and/or radiotherapy[30]. Pain after intestinal resections might be related only to damage of the visceral structures, but could also be a manifestation of neuropathic pain whereby lesions of somatic (and visceral) nerves contribute to the pain sensation[88]. Patients typically report a distinct set of symptoms with neuropathic pain, such as burning, shooting-like sensations and allodynia[88]. Similar to somatic pain, it is believed that neuropathic pain can be spontaneous or evoked by stimuli, such as gut motility and glandular activity[31]. Indeed, in patients with chronic pancreatitis who have neuropathic pain, food intake stimulates pancreatic glandular activity via neural and hormonal pathways. The resulting postprandial pain may reflect the allodynia that occurs in somatic disorders, in which pain can be provoked by light touch in the area of neuropathic pain[37,78]. Low pain thresholds to intestinal stimulation has been demonstrated in patients with diabetes mellitus, contrasting that the patients complained about GI symptoms[89]. Thus, as in somatic peripheral neuropathy, abnormal central sensory processing and hyperexcitability are likely to explain the symptoms[90].

***Functional (nociplastic or primary) GI pain.*** Chronic visceral pain, in the absence of any demonstrable sensorimotor abnormality (referred to as primary visceral pain in ICD-11)[2,91], is a central defining feature of many of the functional GI disorders, including IBS[92]. Although the origin and maintenance of chronic functional GI pain is incompletely understood, it can be conceptualized that aberrations occur at any level between the gut and brain[93]. As such, GI pain can arise as a peripheral augmentation of the afferent signals, sensitization of the spinal dorsal horn neurons, alterations in descending modulation or sensitization and reorganization of brain centres involved in pain perception[46].

***GI cancer pain.*** Pain in GI cancers often manifests as a composite of many pain mechanisms (such as nociceptive and neuropathic, among others). Pain is not always present, but it occurs in the majority of patients with some cancers, such as cancer of the pancreatic head[94]. In patients with pancreatic cancer, pain may be related to pressure on the ductal system, inflammation and direct tumour expansion or perineural invasion of splanchnic nerves. Indeed, cancer cells can penetrate the perineurium leading to damage to the perineural sheaths and immune cell infiltration that correlates with the severity of pain[95]. Back pain often indicates retroperitoneal or coeliac plexus infiltration[96]. In later stages, spread of pancreatic cancer to neighbouring organs and metastasis to other structures can alter pain presentation[33]. Finally, GI pain can also be related to treatment such as surgery, endoscopic procedures, chemotherapy or radiotherapy[97].

## Diagnosis, screening and prevention

### *Clinical characteristics*

During the early stages of GI pain, it is typically diffusely located, independently of the affected organ, and accompanied by autonomic symptoms[3] (BOX 1). As many inflammatory diseases can spread to neighbouring organs or can affect the peritoneum, the pain presentation often changes over time. For example, in acute appendicitis, pain is initially diffuse and vague, and is accompanied by autonomic symptoms such as sweating and nausea, whereas later in the disease process when the peritoneum is affected, the pain is localized to McBurney's point with the appearance of a somatic-like pain (that is, a distinct localization and sharp, intense pain sensation).

Pain referred to somatic structures can dominate the overall clinical picture, and in many cases the underlying visceral disease can be overlooked. Although typical referred pain patterns have been described for GI diseases, the specific location of the referred pain has considerable

inter-individual variability. For example, in one study, pain due to experimental stimulation of the stomach was referred to the epigastrium in most individuals, but referred to the retrosternal area and the back in some individuals[98]. In individuals with functional GI disorders, pain is often referred to atypical areas far away from the skin of the underlying organ in a manner that is also observed in functional somatic syndromes such as fibromyalgia[99]. Indeed, one study showed that in patients with functional dyspepsia, experimental distension of the stomach resulted in abnormal pain localization and an increase in size of the referred pain area[100]. In addition, trophic findings and changes in pain thresholds in underlying subcutaneous and muscular tissue can be found in people with some GI disorders, such as gallstone disease[101].

As previously mentioned, cross-organ sensitization can also change the manifestations of GI pain. The clinical manifestations of cross-organ sensitization have been described in a variety of functional visceral disorders, including IBS. This phenomenon may also be important in patients with organic diseases, such as those with coronary artery disease in whom pain from gallstones was more intense than in people without coronary artery disease, or in patients with inflammatory bowel disease, with symptom exacerbation in women with dysmenorrhoea compared with women without menstrual pain[102]. Additionally, effective treatment of one condition substantially improved symptoms of the other[85].

Organ dysfunction and complications of GI diseases may also confound the pain picture. For example, inflammation and fibrosis in individuals with chronic pancreatitis or Crohn's disease can affect the blood supply of neighbouring organs, change normal visceral reflexes and alter hormonal control with other organs[31]. These changes can lead to complications, such as peptic ulceration, motility disorders, small-intestinal bacterial overgrowth and organ ischaemia, among others, which can worsen pain[11] (FIG. 3).

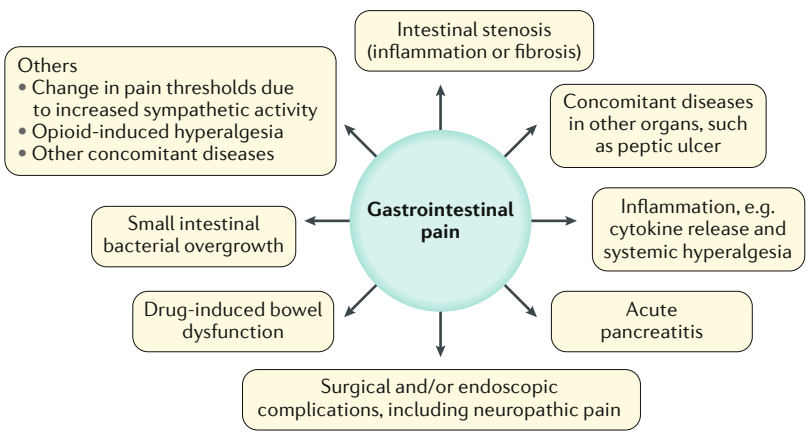


Fig. 3 | **Causes of pain in GI disorders.** Pain can have multiple causes in gastrointestinal (GI) disorders, such as in Crohn's disease. For example, pain can be caused by inflammation and/or fibrosis of the affected intestinal segment, resulting in stenosis, or by concomitant diseases of other organs that are dysfunctional due to the primary intestinal pathology. Inflammation can change the pain threshold in general, and pain can be associated with secondary motility changes and complications such as bacterial overgrowth in the small intestine. Finally, complications of medical and surgical therapy can result in pain, as can more rare complications such as ischaemia, among other factors.

### *Assessing GI pain*

Patients with acute onset pain and those with chest pain, as opposed to abdominal pain, may be more likely to seek medical care. By contrast, only a minority of patients with chronic abdominal visceral pain seek medical care for their symptoms, with symptom severity and impairment in quality of life (QOL) being predictive in this regard[103].

The primary goal of diagnostic work-up in patients presenting with GI pain is to establish a diagnosis and initiate treatment of the underlying condition. Appropriate clinical evaluation and investigations are mandatory and are specific for the individual GI disorder causing the pain. These tests can include various combinations of abdominal imaging (using, for example, CT or MRI) and laboratory tests, such as liver enzymes and amylase. Individuals with rare GI disorders (TABLE 1) often require specific laboratory tests. Pain management should always be directed against the specific diseases such as peptic ulcer. However, no definitive diagnosis can be reached in some patients, or the pain symptoms can persist despite successful treatment of the primary pain source. In these patients, a mechanism-orientated approach to GI pain can be useful whereby the underlying pain mechanisms are delineated using targeted treatment[104]. Additionally, several methods to assess and characterize GI pain exist, including questionnaires, quantitative sensory testing (QST) and methods for evaluating pain responses in the autonomic nervous system and CNS. However, many of these methods, although widely used in research settings, either are not validated for clinical use or are too cumbersome for routine clinical practice[105]. Consequently, many patients outside specialized centres do not undergo a thorough work-up for their GI pain complaints and are treated by a 'trial and error approach' that in many patients is unsuccessful and associated with adverse effects[106].

Validated questionnaires for organic GI pain are mostly lacking and therefore general pain questionnaires are often used in clinical practice. These questionnaires include simple assessments of pain intensity based on numeric rating scales or visual analogue scales[107], as well as more detailed pain questionnaires with documentation of the temporal profile of pain symptoms and the effect of pain on daily functioning and living, such as the McGill pain questionnaire[108] and the Brief Pain Inventory[109]. Some disease-specific questionnaires have been developed[19], such as a questionnaire for assessment of pain in chronic pancreatitis, which is under validation[110]. In addition, a large number of questionnaires have been developed for the assessment of symptoms of functional disorders, such as the IBS–Symptom Severity Scale, which includes broad measurements of pain-related aspects in patients with IBS and has been validated for use in these patients[111,112].

Although mainly used as a research tool, it has been suggested that QST may provide an objective means for assessment and characterization of GI pain in the future. QST involves standardized stimulation of visceral and somatic tissue and quantification of the evoked response, which reflects the output of the nociceptive system[19,58,113,114]. The most widely used method for QST

Table 1 | **Rare GI pain disorders**

| Condition or disease | Pathophysiology | Clinical context |
|---|---|---|
| Hereditary angioneurotic oedema | Mutations in complement protein inhibitors | Recurrent visceral pain that may be accompanied by swelling of the extremities, genitals, face, lips, larynx or gastrointestinal tract |
| Familial Mediterranean fever | Autoinflammatory disease caused by mutations in Mediterranean fever gene (*MEFV*) | Increased prevalence in the southern and eastern Mediterranean areas; pain often accompanied by serositis |
| Acute porphyria | Mutations in genes encoding haem synthesis enzymes, with accumulation of pyrrole-containing intermediates | May involve symptoms from the gastrointestinal (GI) tract and cardiovascular system, as well as neuropsychiatric symptoms; often precipitated by medications, alcohol or other external factors |
| Median arcuate ligament syndrome | Compression of the coeliac artery and the coeliac ganglia by the median arcuate ligament | Pain may be associated with postural changes, worsen during the postprandial period and can be associated with mild gastric emptying delay |
| Superior mesenteric artery syndrome | Compression of the third portion of the duodenum between the aorta and the overlying superior mesenteric artery | Extremely lean persons predisposed; postprandial pain, nausea and vomiting relieved when the patient is in the knee-to-chest position or in the prone (face down) position |
| Abdominal migraine | Intestinal ischaemia | Mostly seen in children; intermittent and often associated with nausea and vomiting |
| Henoch–Schönlein purpura | IgA-mediated vasculitis | Mostly seen in children and typically presents with purpura of the lower extremities; ~50% experience abdominal pain |
| Abdominal cutaneous nerve entrapment[a] | Entrapment of abdominal cutaneous nerves | Positive Carnett's sign |
| Ehlers–Danlos syndrome[a] | Hereditary non-inflammatory disorder of connective tissue | Visceral pain accompanied by joint hyperextensibility and musculoskeletal symptoms |
| Hernias[a] | Entrapment of nerves or intestine | Past surgery predisposes to incisional hernias; clinical examination, but Spigelian hernias may be difficult to identify |
| Radicular pain[a] | Compression of spinal nerve roots | History of back pain and radicular pain |

[a]Myofascial syndrome.

in GI pain is the rectal barostat with balloon distension, which has been commonly used for assessment of lower abdominal pain in IBS, mainly in the research setting[115]. However, evidence for the value of QST in general is weak[105] and many patients find visceral QST unpleasant. To circumvent this problem, QST of somatic tissue can provide information on the nociceptive system. For example, QST of the skin overlying the upper abdominal region can be used to assess the presence of sensitization of the central pain system by nociceptive input from the pancreas[113,116,117], owing to the convergence of these afferent fibres in the spinal cord. Sensitization will manifest as a segmental lowering of the pain threshold to QST of the skin and deep tissue. This approach can be combined with indirect assessment of descending inhibition, as explained above, as well as central sensitization (for details, see REF.[117]). Until now, relatively few studies have used somatic QST in patients with GI pain, but these methods could hold promise for the future.

Responses to painful stimuli can also be measured in the autonomic nervous system and the CNS. Within the autonomic nervous system, cardiometrically derived time and frequency domain parameters of heart rate variability are frequently used as clinical standards, although the temporal resolution is poor[118]. Within the CNS, several techniques including electroencephalography and evoked brain potentials, functional MRI and PET have been used to study spinal and cerebral responses to GI pain[119,120]. Overall, these methods have good reliability, but their use has been limited to the research setting given their complexity[61,121,122].

### *GI pain as a complication of other GI disorders*

Chronic visceral pain is a common component of a number of GI disorders that might not be painful per se, such as active and quiescent inflammatory bowel disease and motility disorders (such as in IBS and gastroparesis)[123,124], and when pain predominates it can lead to misclassification and maltreatment. In addition, there is a marked association between pain and physiological sensations from the GI tract, including diarrhoea, constipation, bloating, nausea and early satiety[16]. International consensus with respect to the optimal management of chronic visceral pain in the aforementioned disorders is currently lacking, and there is a paucity of high-quality randomized controlled trials of therapeutic interventions.

### *Rare disorders and pitfalls in GI pain*

Several disorders are associated with GI pain and must be considered in patients in whom a routine clinical examination and work-up has not revealed any explanation for their complaints. These comprise a heterogeneous group of disorders with varying prevalence and distinct clinical presentations. Common disorders associated with GI pain are myofascial syndromes including hernias, radicular pain, abdominal wall pain syndrome and Ehlers–Danlos syndrome[125–127]. At the other end of the spectrum, rare inherited diseases, such as familial Mediterranean fever[128], intestinal and vascular compression syndromes[129,130], and disorders of the complement system (hereditary angioneurotic oedema)[131] and the haem synthesis pathways (acute porphyria)[132], must be considered (TABLE 1).

## Management

The treatment of GI pain can include pharmacological, endoscopic and surgical therapies, as well as cognitive behavioural therapy (CBT). Whenever possible, treating the causative disorder is sufficient for pain reduction. Specific analgesics may be warranted for some GI disorders. Indeed, pain due to acute pancreatitis can require fast-acting opioids at hospitalization, whereas non-specific acute pain can be treated with paracetamol (especially when combined with codeine) and NSAIDs for which the number needed to treat is ~2.5 for one patient to achieve 50% pain relief[133,134]. In addition, when gut spasms are suspected, antispasmodics such as hyoscine are often better than analgesics[135]. An overview of pharmacological management of acute pain in general has been published[136].

Management of chronic visceral pain is best undertaken in a multidisciplinary environment. First, the individual pain mechanisms involved (according to clinical manifestations) should be identified, and other causes of pain should be excluded to develop management that is mechanistically tailored[11]. We propose that chronic GI pain should be treated in a stepwise fashion commencing with analgesics that have the least (in number and severity) adverse GI effects (FIG. 4). Management needs to be individualized depending on the patient's preferences, local resources and access to medications. In addition, assessing the degree of comorbid anxiety and/or depression (which are present in up to 40% of patients) is useful to ascertain whether patients could respond to psychological interventions such as CBT. Opioids should be used carefully, and often non-pharmacological treatments such as behavioural interventions are more beneficial in patients with GI pain[137–139]. Neurostimulation, complementary therapies and non-analgesic drugs (such as antipsychotics and benzodiazepines) can be considered in some patients[11]. In specific patient groups, such as those with pain related to visceral malignancy, the approach is more aggressive and neurolytic procedures, among other treatments, can be used (for useful reviews, see REFS[33,140]). It should be noted that placebo has a strong effect on visceral pain[141,142]. Indeed, for surgery and other invasive treatments for various chronic pain conditions, >50% of patients may benefit from sham interventions, and this finding is probably also true for diseases associated with GI pain, such as chronic pancreatitis[143].

### *Pharmacological principles*

No pharmacological treatments have been approved specifically for GI pain, and clinicians often use the same medications as for other types of pain (such as musculoskeletal or neuropathic pain) or rely on suggestions from expert consensus statements[144–146]. Indeed, most evidence for the treatment effects of analgesics is based on studies of somatic pain. On the other hand, the variability is greater between individual patients than between different organic pain syndromes (such as chronic pancreatitis and low back pain), which reflects the notion that pain mechanisms and the subsequent effects of management are based to a higher degree on the individual than on the involved organs and structures[147]. In addition, practical guidelines with pedagogical flow charts can guide clinicians to the optimal management.

The WHO analgesic ladder was originally developed for the treatment of cancer pain but has now been extended to the treatment of chronic visceral pain, including GI pain. The WHO analgesic ladder suggests the oral administration of drugs in the following order until pain relief is achieved: non-opioids (such as aspirin and acetaminophen); then, as necessary, mild opioids (such as codeine); then strong opioids (such as morphine)[106]. The analgesics can be given sequentially or in combination, and can be tailored to the individual patient and their responses. To treat concomitant anxiety, additional drugs should be used (for example, antidepressives). A top-down approach might be used in a subset of patients[106], such as those with severe pain, as it may be necessary to begin with strong opioids in these patients[144].

***Non-opioids.*** NSAIDs can be used for the treatment of GI pain; however, no strong evidence supports the use of these drugs for this indication[106]. Acetaminophen (paracetamol) is widely used for GI pain as it has analgesic and antipyretic effects through central and peripheral non-opioid mechanisms, although the precise mechanisms have not been fully elucidated[106]. In contrast to NSAIDs, acetaminophen has no anti-inflammatory characteristics, although this drug is preferred over NSAIDs for the treatment of chronic GI pain owing to the limited adverse effects associated with it, and treatment is often continued when stronger analgesics are required. In patients with chronic GI pain that is secondary to, for example, other GI processes such as changes in motility, bacterial overgrowth or bloating, pharmacological agents directly targeting these symptoms are needed (for example, propulsive drugs or antibiotics, which can be associated with pain reduction)[146].

***Opioids.*** Non-opioid pharmacological therapies are often insufficient to relieve GI pain to a satisfactory level; therefore, opioids are widely used for the management of severe pain (for example, in cancer)[144], but may also be needed in patients with disabling pain such as those with chronic pancreatitis. However, evidence supporting the effectiveness of opioids for short-term use in chronic

non-cancer pain is mainly related to musculoskeletal pain, and the evidence of analgesic efficacy in GI pain is sparse[138]. In general, the long-term effects have not been studied. More recently, with the recognition of the dangers of chronic opioid use (such as addiction and hyperalgesia), they are not routinely recommended for chronic abdominal pain[138,139,148], and in patients with centrally mediated chronic visceral pain they can be associated with allodynia[149]. When opioids are used for GI pain, strategies to manage opioid misuse, risk–benefit profiles including reduced pain-related disability and addiction are used[11]. Recommendations for opioid use in general are available[137].

***Adjuvant analgesics.*** Evidence is growing that as the chronicity of pain increases, brain changes can result in pain amplification owing to central sensitization, anxiety and depressive symptoms. Adjuvant analgesics may dampen or reverse central sensitization and should be considered in an early stage of pain management in both functional and organic GI pain disorders[106,149]. For example, gabapentin and pregabalin have demonstrated analgesic effects in patients with pancreatitis, IBS or inflammatory bowel diseases, and can also help abdominal wall pain and comorbid fibromyalgia[138,150,151]. Interestingly, these effects are thought to be mediated by effects in the CNS. In addition, the off-label use of non-opioid pain-relieving agents, such as tricyclic antidepressants (TCAs) or serotonin–noradrenaline reuptake inhibitors (SNRIs), are used in the management of chronic GI pain[138] particularly for the treatment of functional disorders. With respect to GI pain, the exact

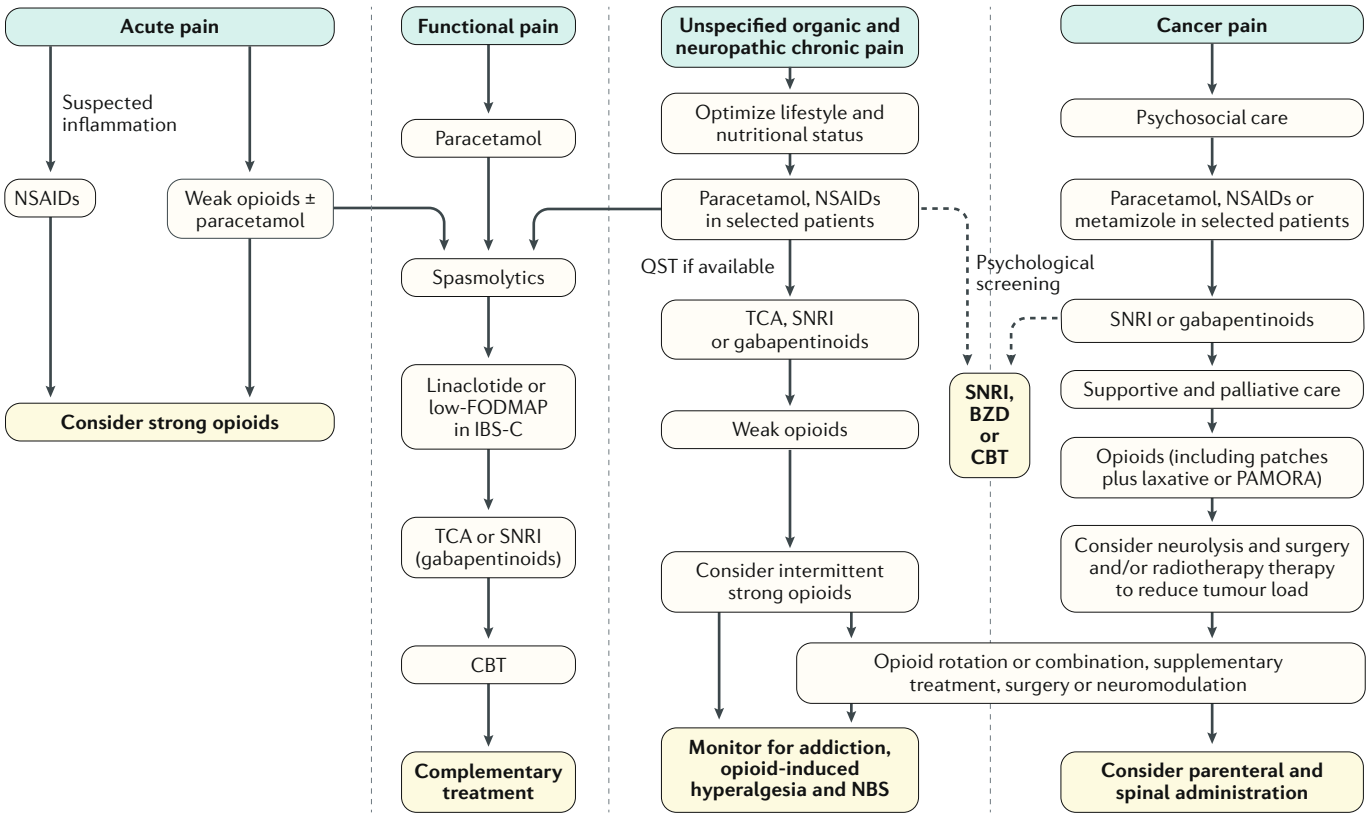


Fig. 4 | **Pharmacological management of GI pain.** No evidence-based management exists for sequential and multiple treatments for gastrointestinal (GI) pain and, as such, this figure presents what is found in current guidelines[11,16,33,106] and the view of the authors. Treatment of acute pain is dependent on the pain intensity and nature; if possible, opioids should be avoided as they can induce adverse GI effects that may worsen symptoms. Management of functional (primary) pain is disease-dependent[16]; patients often respond to antidepressants in low doses or gabapentinoids in those with concomitant anxiety, and alternative treatments and behavioural therapies can be useful in some patients. Management of chronic pain overlaps with treatment of neuropathic pain, and often the conditions coexist. Often lifestyle changes, cessation of smoking and alcohol use will improve symptoms. Simple analgesics are often more easily tolerated and psychological screening (dashed arrows) may be needed to guide treatment with drugs that have both antidepressant and analgesic effects. The efficacy of adjuvant analgesics is best documented in neuropathic pain. Patients with severe pain may need opioids, but owing to their adverse effects, these drugs should be restricted whenever possible. Opioid rotation may be needed as well as patch formulation when malabsorption is suspected. Patients with cancer pain are often treated more aggressively than patients with other forms of pain, especially when curative therapy is not possible; treatment should always be multidisciplinary and supportive or palliative care should be offered. Patients with cancer are prone to develop opioid-induced constipation and should be monitored accordingly. Neurolytic procedures and irradiation therapy may be optional, and in end-stage disease parenteral analgesics may be useful. The order of treatment can change according to patient preferences; hence, neuromodulation or supplementary treatment may be tried before strong opioids (supplementary treatment includes medication such as ketamine, antipsychotics and cannabinoids). BZD, benzodiazepines; CBT, cognitive behavioural therapy; IBS-C, constipation-predominant irritable bowel syndrome; low-FODMAP, diet low in fermentable oligo-, di- and mono-saccharides and polyols; NBS, narcotic bowel syndrome; PAMORA, peripherally-acting μ-opioid receptor antagonists; QST, quantitative sensory testing; SNRI, serotonin–noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

Box 3 | **GI factors that influence drug absorption**

**Gastric emptying**
- Altered release of active pharmaceutical ingredient (API) from controlled-release formulations
- Altered time to effective plasma concentration

**Gastric pH**
- Altered release of API from controlled-release formulations

**Intestinal transit time**
- Altered amount absorbed

**Surface area**
- Altered amount absorbed

**GI intraluminal pH**
- Altered absorption

**Pancreatic insufficiency, bile insufficiency and/or altered secretory function**
- Altered release of API from controlled-release formulations on lipid-based matrices

**Drug transporter expression**
- Altered absorption

**Dysmotility**
- Altered absorption due to reduced luminal water content (opioid-induced constipation) or due to altered enteric microbiota (diarrhoea)

**Bacterial overgrowth and/or altered enteric microbiota**
- Altered release of API from controlled-release formulations on water-swellable matrices
- Altered absorption due to bacteria-induced changes in gastrointestinal intraluminal pH

GI, gastrointestinal.

mechanism of action of these agents is incompletely understood, but they have been postulated to influence nociceptive signalling and/or processing in the GI tract, spinal cord and brain[152] and TCAs have been suggested to influence descending inhibitory pathways and may have anti-inflammatory properties[153]. However, intolerability of the adverse effects of these medications often limits their use at their maximal efficacious dose range. There is no evidence to support the use of selective serotonin reuptake inhibitors (SSRIs) for GI pain directly, but these drugs can improve comorbid anxiety and depression[145]. Tetracyclic antidepressants (such as mirtazapine or mianserin) and trazodone can be helpful for symptoms that occur with GI pain, such as early satiety, nausea, vomiting and weight loss, but there is little evidence that they help in relieving pain directly[154].

***Unconventional pharmacological treatment.*** Unconventional pharmacological treatments — including antispasmodics, clonidine, quetiapine, bupropion, azapirones (buspirone), benzodiazepines, antipsychotics or cannabinoids — have also been used experimentally in the treatment of chronic GI pain disorders, often as part of augmentation strategies. Given the close association between physiological sensations and chronic GI pain, many drugs that modulate these sensations also have moderate analgesic efficacy[145]. Other evaluated molecules include peppermint oil, antispasmodics, 5-$HT_3$ receptor antagonists (such as ramosetron and ondansetron) and guanylate cyclase-c agonists (such as plecanatide and linaclotide)[155]. Cannabinoids are being actively investigated for their analgesic effects in certain types of abdominal pain, but there is only weak anecdotal evidence for such effects[156,157]. However, cannabinoids may increase appetite and decrease gastric and colonic motility, and as such have an effect in treatment[158].

***Absorption challenges in visceral diseases.*** Altered GI physiology and function in visceral diseases can lead to alterations in the bioavailability of orally delivered analgesics[159]. Although the effect of GI variables on drug absorption is still not fully understood, the release of drugs from controlled-release formulations, dissolution of solid dosage forms and drug absorption from the GI tract are known to be affected in some GI disorders (BOX 3).

GI secretion and motility are necessary for disintegration and dissolution of solid drug forms[160]. Controlled-release drug formulations are widely used, and are designed to release the active ingredient at a predefined rate throughout the GI tract and, theoretically, a dysfunctional GI tract could adversely affect drug release, if, for example, gastric pH, gastric emptying time or lipase, enzyme or bile secretion is altered. However, only a few studies in small populations have addressed the effects of, for example, short bowel syndrome, bariatric surgery or diabetes mellitus on the net absorption of drugs[159,161], and no studies have investigated how drug release from different controlled-release formulations are affected in different GI disorders.

Given that most medications are absorbed in the small intestine, delayed gastric emptying, such as in diabetes mellitus, will slow the time to peak concentration and delay the onset of the action of a drug[162]. In addition, in some patients with GI pain such as those with Crohn's disease, part of the intestine may be removed surgically or some patients may have a malfunctioning mucosa, resulting in decreased expression of drug transporters and enzymes that can affect drug release and absorption[159]. In other patients with GI pain, such as those with chronic pancreatitis, exocrine pancreatic insufficiency is associated with changes in intestinal pH resulting in fat malabsorption[163], which might affect drug release from the lipid-based matrices. In addition, pancreatitis and associated diabetes mellitus can cause dysmotility and small-intestinal bacterial overgrowth[161,163,164], which can affect pH and, therefore, drug release from water-swellable matrices and drug absorption.

Other pharmacokinetic factors may also be affected in patients with GI pain, as multimorbidity is frequent. For example, ischaemic heart disease and renal or hepatic dysfunction may affect drug distribution, metabolism and excretion. Many patients receive treatments for these comorbidities. Some medications can affect the GI tract and, therefore, can affect absorption of other drugs, For example, opioids increase GI fluid absorption and decrease water availability for drug dissolution[163,165].

In summary, extensive disease of the GI tract will have consequences for the absorption of orally administered drugs[166]. Indeed, 55% of patients who failed to respond to oral opioids had previously been given a diagnosis associated with GI symptoms, motility disturbances and possibly nutritional malabsorption[167],

whereas after 30–90 days of non-oral opioid treatment, all patients attained sufficient pain relief[167]. This finding demonstrates that non-oral drug administration should be considered in individuals with altered GI physiology; for example, opioids are available as transdermal administrations for which bioavailability is independent of diseases in the gut[168].

***Adverse effects specific to the gut.*** The use of NSAIDs is frequently associated with damage to the GI tract in the form of peptic ulceration and enteropathy; thus, NSAIDs should be used in combination with proton pump inhibitors (which reduce the production of gastric acid) in those with GI diseases. A drug that prevents or treats NSAID-induced enteropathy has not yet been developed, and further investigations are needed to elucidate the pathogenesis of such enteropathy and develop suitable treatment strategies.

Opioids exert their effects throughout the GI tract by binding to opioid receptors in the enteric nervous system which can cause dysmotility, reduced secretions and increased sphincter tone; these effects are collectively known as 'opioid-induced bowel dysfunction' (OIBD)[169]. OIBD-related symptoms include nausea, vomiting, constipation, abdominal distension, spasms and gastro-oesophageal reflux[144], which can all adversely affect drug absorption[165]. Laxatives are used for prophylaxis or management of OIBD, although these drugs do not affect all underlying mechanisms so that inadequate response to laxative treatment is prevalent[170]. Thus, other medication strategies (for example, peripherally acting μ-opioid receptor antagonists) can be considered[171]. Chronic opioid use can also cause paradoxical hyperalgesia (for example, opioid-induced hyperalgesia or narcotic bowel syndrome) due to CNS changes, as well as other negative effects in the enteric nervous system. Hence, repetitive monitoring of the risk–benefit ratio is important in pharmacological management of visceral pain.

### *Non-pharmacological management*

Several non-pharmacological strategies can be used for the treatment of GI pain. In those with pain due to obstruction of the biliary tree or main pancreatic duct, extracorporeal shock wave lithotripsy and/or endoscopic procedures may be effective[11]. The latter typically include sphincterotomy and biliary or pancreatic duct stenting. These procedures are believed to restore normal duct pressure and relieve pain based on the assumption that pain is generated from ductal hypertension[172]. Notwithstanding the effectiveness of endoscopic procedures in many patients, the relationship between ductal hypertension and pain is not linear. Surgery may be an option in selected patients with chronic pancreatitis, although the rationale for its use and its efficacy have been disputed[143]. Biliary and digestive stenting are also useful in those with GI cancers, in whom biliary stenting alleviates nausea and pruritus in patients with cholestasis, and intestinal stenting improves digestive spasmodic pain and vomiting[33]. Revascularization, either by arterial stenting or surgery, is the preferred treatment for chronic intestinal ischaemia in the presence of a dominant vascular stricture[173].

The assessment of nutritional status is important and nutritional support should be considered in all patients with GI pain and potential malnutrition. This is of particular salience as malnutrition and vitamin deficiencies can promote asthenia (lack of energy) and pain through oxidative stress and by decreasing the tolerance threshold to pain[174]. In addition, malnutrition also reduces tolerance to oncological treatments such as chemotherapy and radiotherapy[175]. For some GI diseases, a specific diet can be used as one of the primary treatment modalities. For example, a diet low in fermentable oligo-, di- and mono-saccharides and polyols (that is, the low FODMAP diet) can improve symptoms and QOL in patients with IBS[176]. Moreover, for more refractory pain, non-pharmacological procedures including transcutaneous, spinal cord and brain electrical stimulation[177,178], vagus nerve simulation and coeliac neurolysis[179] can be used in selected patients. Invasive neurostimulation procedures are used more often in the USA than in other countries, but their use is highly dependent on local expertise and traditions, among other factors.

### *Multimodal treatments*

As previously mentioned, chronic pain is associated with changes in brain regions involved in emotional and cognitive processing[180,181] resulting in depression, anxiety, fear, hyperarousal, catastrophic thinking and avoidant coping[124,182]. These secondary pain manifestations further amplify pain[183,184]. In addition, life stress and trauma, and socioeconomic and cultural factors can further adversely influence pain intensity and related suffering and disability[185]. Thus, addressing these secondary pain manifestations with multimodal treatment that includes behavioural interventions is critical.

CBT, hypnosis and mindfulness meditation are the behavioural therapies with the most empirical support in reducing pain intensity and related dysfunction in patients with chronic GI pain, including disease-related pain or pain of functional origin[186–189]. The evidence base for the efficacy of CBT for visceral pain is largest in functional GI disorders such as IBS[186,190]. Hypnosis potentiates the natural capacity of humans to dissociate, and has been associated with significant and lasting reductions in GI pain and associated symptoms[191–193]. In mindfulness meditation, the emphasis is on focusing attention on the present moment and accepting thought, behaviours and bodily sensations without judgment; this meditative state has been associated with reduced pain severity in several GI conditions, such as IBS and pancreatitis[16,194,195].

## Quality of life

Chronic GI pain is associated with several difficulties that can impair QOL, such as loss of function, anxiety, depression, disturbed sleep and impaired cognition. Instruments that examine broad dimensions of health, including physical, mental, emotional and social functioning, are increasingly used in research and clinical settings. Of these factors, QOL is generally accepted as one of the most important measures in the assessment of pain and its response to management, as it includes a number of benchmark measures such as mood and

global impression of change[196]. In addition, QOL is negatively correlated with GI pain[197].

Various general QOL questionnaires have been used to evaluate QOL in patients with GI pain, such as the Short-Form Health Survey 36 (SF-36) and its shorter form (SF-12)[198]. In addition, several questionnaires have been developed for specific diseases, including the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 for pancreatic cancer, and the Pancreatitis Quality of Life Instrument (PANQOLI) for pancreatitis[199,200]. Questionnaires have also been developed for GI disorders that are characterized by primary pain, such as the Irritable Bowel Syndrome–Quality of Life Measure (IBS-QOL)[16]. A more generalized instrument is the Gastrointestinal Quality of Life Index (GIQLI), which comprises 36 questions and can be used in patients with a range of different GI diseases[201].

Owing to the complexity of visceral pain that is often associated with malnutrition and psychosocial problems, multidimensional QOL questionnaires are highly relevant in the assessment of disease severity. In clinical settings, multidimensional QOL questionnaires have also be used to monitor management strategies, such as the effect of pharmacological therapies, endoscopy and surgery[202–204]. In addition, QOL has also been shown to be a major determinant in the assessment of efficacy of therapies with probiotics and dietary modifications, and as such the value of QOL assessment has been proven in areas where conventional pain assessment may not be optimal[205].

## Outlook

### *Individualized pain management*

A major problem in GI pain management is the lack of knowledge about what treatment is effective at the individual patient level. As the underlying mechanisms of this pain are being increasingly understood, treatments targeting specific and relevant mechanisms based on phenotyping of an individual patient's unique pain profile may hold promise for the future[104]. Indeed, such individualized pain management has been studied for years and has led to some, albeit slow, progress in both somatic and visceral pain conditions[104,147]. Individual patient phenotyping can be performed in several ways[147]; for example, QST has been used to characterize pain processing and to predict the analgesic effect of pregabalin in individual patients with chronic pancreatitis who had long-lasting abdominal pain[109,113]. In this study, patients with lower pain thresholds to electrical stimulation of abdominal skin areas that shared spinal innervation with the pancreatic gland were likely to benefit from pregabalin treatment. These findings suggest that sensitization of convergent neurons in the spinal cord (segmental central sensitization) is associated with pregabalin efficacy. Such phenotyping of patients could be used to tailor pain treatment in the future, and is, therefore, a step towards individualized pain management.

### *Assessing therapeutic benefit and risk*

Considering therapeutic analgesic effects in conjunction with adverse effects is important during the evaluation of treatments for visceral pain. Several approaches have been used for this task, such as the efficacy index[206], in which therapeutic effect is regarded as gross profit (benefit) and adverse effects as cost (harm), and the utility function, which was developed to provide a mathematical means for an integrated evaluation of benefit versus harm. The utility index was originally based on population pharmacokinetic–pharmacodynamic models[207,208]; however, since this method is dependent on drug plasma concentrations, it is often not applicable for use in the clinical setting. Thus, a pragmatic utility function was recently constructed based on measurements of benefit and harm, but without making assumptions about the underlying pharmacokinetics[209]. The two binary outcomes could, for example, be pain relief and a combination of the recorded adverse effects, and a graph showing the utility function over time for a given treatment may be clinically applicable in illustrating that adverse effects will appear but may decrease over time, while the analgesic effect increases.

### *Future treatments*

Novel targeted therapies for somatic pain conditions are in development, and could also be effective for visceral pain. For example, tanezumab, an anti-nerve growth factor monoclonal antibody that can relieve pain in patients with osteoarthritis[210] may also be effective in people with chronic pancreatitis or other GI disorders, as nerve growth factor is upregulated in, for example, chronic pancreatitis and has a pivotal role in peripheral sensitization[31]. Other visceral analgesic drugs in development include ibodutant, a neurokinin 2 receptor antagonist, and ebastine, a histamine H1-receptor antagonist, both of which have demonstrated promising results in phase II trials of their use in the treatment of IBS[211,212]. Transcutaneous stimulation of the vagus nerve has also been shown to reduce visceral pain through neuromodulation. Indeed, one study has demonstrated a reduction in pain scores in children with chronic visceral pain using percutaneous electrical nerve field stimulation applied to the external ear in the area innervated by the auricular branch of the vagus nerve[213]. Owing to these promising results, further studies are warranted in adults.

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### Author contributions

Introduction (A.M.D. and E.S.); Epidemiology (S.S.O. and A.D.F.); Mechanisms/pathophysiology (A.M.D. and V.R.); Diagnosis, screening and prevention (A.M.D., S.S.O. and A.D.F.); Management (A.E.O., E.S., V.R., S.S.O. and A.M.D.); Quality of life (E.S. and S.S.O.); Outlook (S.S.O., A.M.D. and A.E.O.); Overview of Primer (A.M.D.).

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