# Post-Operative Ileus: a Pharmacological Perspective

Etienne Buscail[1] and Celine Deraison[2]

[1]University Hospital Centre Toulouse
[2]Inserm U1220

July 26, 2021

**Abstract**

Post-operative ileus (POI) is a frequent complication after abdominal surgery. The consequences of POI can be potentially serious such as bronchial inhalation or acute functional renal failure. Numerous advances in peri-operative management, particularly early rehabilitation, have made it possible to decrease POI. Despite this, the rate of prolonged POI ileus remains high and can be as high as 25% of patients in colorectal surgery. From a pathophysiological point of view, POI has two phases, an early neurological phase and a later inflammatory phase, to which we could add a "pharmacological" phase during which analgesic drugs, particularly opiates, play a central role. The aim of this review article is to describe the phases of the pathophysiology of POI, to analyse the pharmacological treatments currently available through published clinical trials and finally to discuss the different research areas for potential pharmacological targets.

*Br. J. Pharmacology.*

**Post-Operative Ileus: a Pharmacological Perspective**

Etienne Buscail[1,2*], Céline Deraison[1]

1- IRSD, INSERM, INRAE, ENVT, University of Toulouse, CHU Purpan (University Hospital Centre), Toulouse, France.

2- Department of digestive surgery, colorectal surgery unit, Toulouse University Hospital, Toulouse, France.

* **Corresponding Author:** Dr. Etienne BUSCAIL, MD, PhD, INSERM, UMR-1220, IRSD, Place du Dr. Baylac, CHU Toulouse Purpan, CS 60039, Toulouse 31024, Cedex 3, France;*etienne.buscail@inserm.fr*

**Word count** : 6891 words

**Potential competing interests:** no author has any conflict of interest to declare.

**Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Acknowledgements:** Thanks to Viktoria Milanova for her involvement in conception of Figure 2.

**Abstract**

Post-operative ileus (POI) is a frequent complication after abdominal surgery. The consequences of POI can be potentially serious such as bronchial inhalation or acute functional renal failure. Numerous advances in peri-operative management, particularly early rehabilitation, have made it possible to decrease POI. Despite this, the rate of prolonged POI ileus remains high and can be as high as 25% of patients in colorectal surgery. From a pathophysiological point of view, POI has two phases, an early neurological phase and a later inflammatory phase, to which we could add a "pharmacological" phase during which analgesic drugs, particularly opiates, play a central role. The aim of this review article is to describe the phases of the

pathophysiology of POI, to analyse the pharmacological treatments currently available through published clinical trials and finally to discuss the different research areas for potential pharmacological targets.

## Introduction

Postoperative ileus is a common condition occurring after abdominal surgery and reflecting a deceleration or complete arrest in intestinal motility (Venara et al., 2020). This complication is extremely frequent and varies according to the series, affecting between 10% and 25% of patients following abdominal surgery (Chapman et al., 2018). The postoperative ileus (POI) induces its own morbidity and prolongs the length of hospital stays. The costs associated with POI are considerable. In the USA, the annual total care costs for all paralytic ileus hospitalisations increased from 7.1 billion dollars in 2001 to 12.3 billion dollars in 2011 (Solanki et al., 2020). This review addresses current knowledge on mechanisms responsible for POI and the pharmacological strategies currently employed or under development to prevent or reduce POI.

## Pathophysiology of POI

### Definition

Postoperative ileus is an iatrogenic situation in abdominal surgery. Indeed, the opening of the peritoneal cavity and manipulation of the digestive tract trigger a chain reaction. This reaction involves many complex neurological, inflammatory, hydro-electrolytic and pharmacological mechanisms, all of which lead to transient paralysis of the digestive tract and a halt in peristalsis. Not all segments are affected to equal extent. Small intestine motility is disrupted within 24 hours, gastric motility from 24 to 48 hours and colonic motility from 48 to 72 hours post-surgery(Benson et al., 1994). The time difference to recovery of motor function explains why the passage of the first stool and gas is most frequently used to define the return to normal function. The complexity of the definition lies in the fact that the return of the migrating motor complex is not synonymous with a return to normal function, i.e. perception of peristalsis at auscultation is not indicative of a return to normal transit. Nevertheless, a recent literature review of 215 articles identified a total of 73 criteria defining the return of normal transit(Chapman et al., 2019). Thus, in decreasing order of frequency, we find: passage of the first gas (140 studies out of 217, 64.5%), passage of the first stools (69 studies out of 217, 31.8%) followed by the first intestinal movements (65 studies out of 217, 30%)(Chapman et al., 2019). The commonly accepted outcome to assess the pharmacological effects of POI treatment is the resumption of solid food combined with the first defecation (van Bree et al., 2014).

Several studies have been carried out to propose a definition and standardise the semiological and clinical framework of postoperative ileus. Recent works include the American Society for Enhanced Recovery After Surgery (ERAS) study and the Perioperative Joint Consensus which considered a more functional definition of POI and a grading system for postoperative gastrointestinal transit disorders(Hedrick et al., 2018). A classification was proposed on a pathophysiological and functional basis using the following criteria: tolerance of oral ingestion, nausea, vomiting, physical signs of ileus (Intake, Feeling nauseated, Emesis, physical Examination and duration of symptoms "I-FEED"). A three-category classification system was therefore established:

- Normal (I-FEED score of 0-2)

Patients in this category tolerate a symptom-free diet, but may experience transient feeding difficulties with postoperative nausea and vomiting (PONV). PONV are considered non-pathological in the first 24-48 hours following surgery.

- Post operative gastro-intestinal intolerance POGI (I-FEED score of 3-5)

These patients usually do well initially, but begin to experience nausea 48 hours after surgery. They present with nausea, small volume non-bilious vomiting and bloating. The majority of patients tolerate drinking and do not require a nasogastric tube.

- Postoperative gastrointestinal Dysfunction (POGD) (I-FEED score [?] 6)

POGD is the most severe form of impaired GI recovery and corresponds to what is considered ileus by most clinicians. These patients develop abdominal distension with tympany, anti-emetic resistant nausea and large volume bilious vomiting. This is associated with intolerance to oral ingestion. Specific treatment is required. Intravenous hydration and maintenance of fluid and electrolyte balance are necessary to maintain proper renal function. A nasogastric tube is also essential to prevent aspiration.

Secondary POI can also occur. This is defined by the same symptoms but is caused by a surgical complication such as anastomotic fistulae or another postoperative septic complication for which aetiological treatments based on the causal treatment of sepsis are administered (Chapman et al., 2018). Secondary ileus will not be dealt with here as it is usually managed surgically.

Pathophysiological studies have identified at least two phases in POI - an early phase involving neural pathways, known as the "neurogenic phase", and a later phase, characterised by inflammatory features.

A third pharmacological phase occurring "parallel" to the two previous phases is also apparent. This phase is essentially conditioned by the use of opioid. Opioids, often used as analgesics after different types of surgery, have a major impact on GI motility through the activation of μ-opioid receptors on myenteric fibres. This leads to inhibition of acetylcholine release from myenteric neurons and a reduction in GI transit (De Winter et al., 1997b; Holte and Kehlet, 2002). Interference with this mechanism by peripheral selective opioid antagonists will be discussed in detail later.

**The early neurogenic phase of POI**

Skin, muscle and peritoneal incision during laparotomy causes a neurological reflex arc via splanchnic afferent nerves that synapse in the spinal cord with adrenergic neurons. This signal activates efferent nerves in the direction of the digestive tract resulting in paralysis of the entire digestive tract(Fox and Powley, 1985; Barquist et al., 1996; Vergnolle and Cirillo, 2018). In the second neurological phase, when the bowel is manipulated and stimulated more intensely, additional pathways are activated by the brainstem(Fox and Powley, 1985). These pathways relay to hypothalamic and pontine-medullary nuclei such as the nucleus tractus solitarius and the paraventricular and supraoptic nuclei of the hypothalamus. It should be noted that these neural relays are also adrenergic in nature(De Winter et al., 1997a). Corticotrophin releasing factor (CRF) plays a central role in this activation pathway, leading to activation of the vagal nerve (Boeckxstaens et al., 1999; Browning et al., 2017). Intense stimulation of the splanchnic nerves activates another inhibition pathway of the digestive motor system via nitrergic (NO) and vipergic (VIP) synapses (Barquist et al., 1996; Boeckxstaens et al., 1999).

This neurological phase reaches its peak during the surgical procedure and in the immediate postoperative period. Once the abdomen is closed and stimulation by intestinal manipulation, traction of the abdomen for laparotomy and distension for laparoscopy have been completed, activation of these pathways will cease. An inflammatory cascade secondary to the tissue damage and local inflammation generated by the surgical procedure will then begin, which explains the potentially prolonged nature of the POI.

**The late inflammatory phase**

This involves activation of mast cells with secretion of histamine and proteases which, in turn, activate resident macrophages and leukocytes and alter intestinal barrier functions. All of these mechanisms trigger inflammation accompanying postoperative ileus and constitute potential pharmacological targets.

Mast cells (MCs) are involved in immunological phenomena, especially as effectors in allergic and anaphylactic processes (Galli et al., 2008). In the digestive tract, mast cells play a regulatory role in vascular and epithelial permeability and immune defence in particular. Indeed, studies in murine peritonitis models have shown that, in animals deficient in mast cells, mortality due to bacterial sepsis is increased (Echtenacher et al., 1996). In the intestine, the greatest number of mast cells are found in the mucosal and submucosal layers, whereas they are less represented in the muscular and serosal layers. Extrinsic afferent nerve endings as well as enteric neurons are in close contact with mucosal mast cells and about 70% of mucosal mast cells interact directly with nerve fibres, with an additional 20% located within 2 mm (Buhner et al., 2017). It

is a well-established fact that activation of mast cells generates epithelial and neuromuscular dysfunctions and promotes visceral hypersensitivity. Alteration in digestive motility is a direct consequence of these phenomena, potentially triggering postoperative ileus (The et al., 2008). De Jonge *et al* . investigated the administration of mast cell stabilisers such as Ketotifen and Doxantrazole in a murine model of ileus: pre-treatment of the mice with both molecules reduced inflammation (measured by myeloperoxidase immunodetection in the entire ileum wall and, more particularly, in the muscle layer) and reduced gastric emptying time (de Jonge et al., 2004).

The activation pathways of mast cells are multiple and a distinction can be made between immune and non-immune pathways. The classical stimulus for MCs activation is the cross-binding of cell surface-bound immunoglobulins E (IgE) to its high-affinity receptor FcεRI by an allergen in a sensitised individual (Galli et al., 2008). This leads to a cascade of phosphorylation and transcription of factors such as AP-1, MITF and STAT-5, and to degranulation and cytokine production (Rivera and Gilfillan, 2006) . MCs also express receptors for IgG (FcγRI), other Ig-associated receptors, complement fraction and toll-like surface receptors (Rivera and Gilfillan, 2006). Regarding non-immune pathways, MCs can be activated by neurotransmitters (acetylcholine, histamine, serotonin, dopamine, epinephrine) and neuropeptides such as substance P and calcitonin-related gene peptide (CGRP) (Wang et al., 2014). The latter two are involved in the inflammatory and motor response after a surgical procedure. Indeed, the use of a CGRP antagonist decreases transit recovery time in a murine model of ileus (Plourde et al., 1993; Zittel et al., 1994). These pathways are prospective pharmacological targets and will be discussed in detail in the "potential targets" section. MCs are also activated by growth factors such as nerve growth factor (NGF) (Barreau et al., 2004) or hormones such as CRF (Vanuytsel et al., 2014). MCs also play a role in the activation of nociceptive signals via bidirectional interactions with neurons of the enteric nervous system (Cenac et al., 2010). MCs activation leads to degranulation and release of newly synthesised (cytokines and lipid mediator) and stored (histamine, heparin, proteases) active substances (Wouters et al., 2016). These substances play a major role in regulating vascular and epithelial barrier function, the latter being a potential pathway for activation of resident macrophages. Epithelial permeability is an important element because its alteration results in the passage of bacteria into the lamina propria (Santos et al., 2001). This barrier function is partially regulated by interaction with the protease activated receptor-2 (PAR-2) on the basolateral part of the enterocytes (Hyun et al., 2008; Vergnolle, 2016). PAR-2 is also activated by chymase and tryptase - mediators secreted by MCs (Jacob et al., 2005). This results in redistribution of the tight junction and an increase in paracellular permeability to macromolecules (Martínez et al., 2012).

The resident macrophages and their activation pathway are the lynch pin of the inflammatory phase of the ileus (Asano et al., 2015). These macrophages are housed in the muscularis near the mesenteric plexus (Kalff et al., 1998). They play a central, predominant role in postoperative ileus despite the fact that there are still unknown areas regarding their activation pathway and the mechanisms they generate. In physiological conditions, outside of any inflammatory stress or infectious aggression, notably bacterial, they are quiescent (Kalff et al., 1999a).

The activation of resident macrophages leads to a cascade of reactions resulting in the production of chemokines (monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α)), pro-inflammatory cytokines (Tumor necrosis Factor alpha (TNFα), interleukin: IL1β, IL6) and integrins, and results in an up-regulation of cell adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), lymphocyte function-associated antigen-1(LFA-1)) in the endothelium (Türler et al., 2007). This results in the passage of pro-inflammatory cells, particularly leukocytes, into the intestinal muscularis by diapedesis (Kalff et al., 1999b). The invasion of these cells leads to up- regulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) resulting in increased nitric oxide (NO) and prostaglandin (PGs) production (Eskandari et al., 1999; Kalff et al., 2000; Kreiss et al., 2003). These phenomena inhibit contractile smooth muscle activity, which is further potentiated by the secretion of PG stimulating the afferent spinal nerves (Grant et al., 2007; Cenac et al., 2010; Forsythe, 2019).

The mechanisms and activation of the inflammatory pathway and resident macrophages (located in the

myenteric plexus between longitudinal and circular muscle layer) are multiple with varying levels of evidence. The initial neurological phase via intense activation of afferent fibres leads to the release of pro-inflammatory neuropeptides (Stakenborg et al., 2020). Numerous studies have highlighted the role of calcitonin gene-related peptide (CGRP) and substance P (SP) (Bueno et al., 1997; Rekik et al., 1997). Indeed, CGRP appears to activate resident macrophages and mast cells, although this pathway (mast cells) has been debated in the light of recent study (Glowka et al., 2015). The intestinal cholinergic pathways constitute another route of interaction between neurons and macrophages. There is proximity between enteric neurons and resident macrophages in the myenteric plexus (Stakenborg et al., 2020). The secretion of acetylcholine (Ach) by enteric neurons, stimulated by vagal efferences, leads to activation of α7-subtype of the nicotinic acetylcholine receptor (7αAChR) (de Jonge and Ulloa, 2007). Thus, activation of the 7αAChR 's leading to inhibition of TNF (Huston et al., 2006) production and induction of regulatory T cells (Rosas-Ballina et al., 2011).

Tissue damage and dehydration of intestinal tissue caused by intestinal manipulation led to the release of factors such as ATP, HMGB1 and IL-1alpha. Activation by damage-associated molecular patterns (DAMPS) during cellular damage is another pathway (Lotze et al., 2007). Finally, when the intestinal barrier is altered, bacterial invasion or their products such as liposaccharides interact with Toll-Like Receptors (TLR). All of these phenomena lead to activation of TLR and receptors for advance glycation end product (RAGE) (Hori et al., 2001). This generates an intracellular signalling pathway involving the activation of kinases (p38, JNK/SAP) causing phosphorylation of transcription factors such as nuclear factor kB (NF-kB), signal transducers and activator of transcription (STATS), and early growth response protein 1 (EGR-1) leading to the transcription of pro-inflammatory genes (Hommes et al., 2003; de Jonge et al., 2005; Wehner et al., 2009).

**Pharmacological factors**

The most commonly used drug for analgesia and anaesthesia is morphine, which is a central and peripheral $\mu$ receptor agonist (De Winter et al., 1997c). This central and peripheral action contributes to prolongation of the POI, but gastrointestinal receptors have a predominant role in inhibiting postoperative gut motility (figure 1). Morphine and other opioid analgesics inhibit the release of acetylcholine from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract (Schang et al., 1986; Delaney, 2004). There are several types of opioid receptors, the three main ones being μ, δ, and ϰ receptors, with each class also having several subtypes (Shahbazian et al., 2002). Opioid receptors are stimulated endogenously and exogenously (Gonenne et al., 2005; Becker and Blum, 2009). Exogenous opioids agonists such as such as morphine and codeine act primarily at μ-receptors which are present in the central and peripheral nervous system (Thomas, 2008). The μ-receptors of the enteric system are the main vectors for the effects on the gastrointestinal tract. The first level of action of opioids is inhibition of enteric nervous activity with inhibition of substance P, nitric oxide and acetylcholine secretion (Kowalski, 1998). This inhibits propulsive motor activity and leads to symptoms of the functional signs of ileus (digestive distension, inhibition of gastric emptying, etc.) (Ferraz et al., 1995). Previous studies on primate and clinical physiology investigating colonic myoelectrical activity have shown that, at a morphine dose range of 50 to 200 ug/l, there was an increase in the frequency of random, non-propagating bursts and contraction. Inhibition of colonic myoelectric activity and contraction were observed at higher doses (Frantzides et al., 1992; Ferraz et al., 1995). In addition, opioids are inducible nitric oxide synthase (iNOS) inducers, and the use of naloxone (mu-receptor antagonist) in murine models decreases NO production by resident macrophages (Kowalski, 1998).

**Non-Pharmacological Treatments**

There are several risk factors for postoperative ileus, however many of those identified in studies cannot be modified. Chapuis *et al* . conducted an observational study involving 2,400 patients undergoing colorectal cancer surgery. The independent predictors of POI were male gender, peripheral vascular history, history of respiratory pathology, emergency surgery, intraoperative transfusion, stoma placement and surgical procedure of over 3 hours' duration (Chapuis et al., 2013).

Numerous publications have shown the effectiveness of early rehabilitation measures on the post-operative course of abdominal surgery and on intestinal motility in particular (Vlug et al., 2011). The non-pharmacological measures used in these rehabilitation schemes, widely described in the literature, are not discussed in this paper. The broad outlines of these strategies can be described as a "simplification" of patient management. Firstly, there is no routine placement of a nasogastric tube because prophylactic emptying of the stomach has not highlighted any improvement in transit recovery (Vlug et al., 2012). This equipment allows the patient to be mobilised early, which is also a factor in the recovery of gut motility (Vlug et al., 2011). Another important aspect is the monitoring of the balanced fluid state in order to prevent visceral oedema that increases the risk of POI and anastomotic leakage (Shah et al., 2011). Finally, as shown in the LAFA trial involving 400 post-colectomy patients, the laparoscopic approach allows a median return to tolerate food one day earlier and a faster discharge from hospital with a median reduction of 1 day in the length of stay (Vlug et al., 2011).

**Pharmacological Treatments: "Mechanisms and Results of Clinical Trials"**

**Prokinetics**

Prokinetic agents are regularly used to treat nausea and vomiting in clinical practice. However, a Cochrane review of comparative clinical trials of 11 prokinetic agents and 39 randomised trials showed no improvement in postoperative ileus (Traut et al., 2008). One of the most widely used agents is metoclopramide, which has been approved by the FDA for the treatment of nausea and vomiting in gastroesophageal reflux disease and diabetic gastroparesis, and for the prevention of adverse effects of chemotherapy (Isola et al., 2021). Metoclopramide acts by antagonising central and peripheral dopamine-2 receptors. The mechanism involves a decrease in sensitivity of visceral afferent nerves that transmit from the gastrointestinal system to the vomiting centre in the postrema area of the chemoreceptor trigger zone (Harada et al., 2017). Metoclopramide also blocks the antiperistaltic effects of apomorphine, allowing metoclopramide to reduce the inhibition of gastric emptying by apomorphine (Ramsbottom and Hunt, 1970). This leads to acceleration of gastric emptying by increasing the amplitude and duration of oesophageal contractions. It also increases the resting tone of the lower oesophageal sphincter while simultaneously relaxing the pyloric sphincter, thereby increasing peristalsis in the duodenum and jejunum (Isola et al., 2021). In addition to antagonising dopamine and apomorphine, metoclopramide also acts against serotonin type 3 receptors, making it an attractive drug for the treatment of postoperative ileus. However, studies involving small patient cohorts in this context have not produced conclusive results (Seta and Kale-Pradhan, 2001; Chan et al., 2005).

A pharmacological alternative that could 'mimic' the action of the vagus nerve would be to stimulate the release of acetylcholine from enteric neurons along the digestive tract. This is one of the actions of selective 5HT4 agonists such as mosapride and prucalopride (Table 1). A cohort study comparing mosapride vs. placebo conducted by Narita*et al* . involving 40 patients who had undergone elective colectomy showed no improvement in the duration of transit recovery (Narita et al., 2008). However, the mosapride group had a significantly shorter hospital stay. Another cohort study of 30 patients who underwent elective colectomy showed a significant improvement in the time to first faltus and first defecation (Toyomasu et al., 2011). Interestingly, Tsuchida *et al.* (Gut 2011) showed in a mouse model that administration of mosapride prior to intestinal manipulation had anti-inflammatory properties via activation of acetylcholine secretion and thus activation of 7nAChR receptors on active macrophages(Tsuchida et al., 2011). Recently, Chapman *et al.* conducted a phase 2a clinical trial to assess the efficacy and safety of a novel 5HT-4 receptor agonist, TAK-954, in improving gastric emptying time in a cohort of mechanically ventilated patients with enteral feeding intolerance. The study group with TAK-954 administration was compared to a control group treated with metoclopramide. There was no difference in adverse events and TAK-954 improved the gastric emptying rate compared to metoclopramide (Chapman et al., 2021). A clinical trial is currently underway to test its efficacy on POI (NCT03827655).

Clinical studies involving prucalopride appear to show more promising results. A phase 2 study in a cohort of 110 patients receiving placebo (n=55) or prucalopride (2 mg/day; n=55) with initiation of treatment 24 hours post-surgery showed a significant reduction in the time to onset of the first gastrointestinal move-

ments and the arrival of the first gas (see Table 1 for detailed results)(Gong et al., 2016). Stakenborg *et al.* elegantly demonstrated the anti-inflammatory and prokinetic properties of prucalopride. In a cohort of 30 duodenopancreatectomy patients comparing a placebo group, a vagus nerve stimulation group and a prucalopride group, a reduction in the expression of pro-inflammatory genes in the duodenum and significantly faster transit recovery were observed in the prucalopride group compared to the other two groups. The authors also confirmed that the anti-inflammatory effect was mediated via α7nACh receptors by carrying out a comparative study in a α7nAChR Knock Out (KO) vs. Wild Type (WT) model, with prucalopride having no effect on postoperative ileus in α7nAChR KO mice(Stakenborg et al., 2019).

Discovered in 1999, ghrelin is a 28-amino acid peptide and an orexigenic hormone. Ghrelin is mainly produced by the P/D1-like cells of oxyntic gastric mucosa (Kojima et al., 1999). There is a gradual decrease in its production from the stomach to the colon (Dass et al., 2003). Ghrelin is also produced in smaller quantities in other tissues (pituitary gland, pancreas, heart, thyroid, kidney, liver, testicles, lung and immune system)(Lutter et al., 2008). The ghrelin receptor is a G protein-coupled receptor with two alternatively spliced variants (GHS-R1a and GHS-R1b)(Gutierrez et al., 2008). The level of ghrelin is regulated by meals, with a high pre-prandial level and a decrease after food intake (Cummings et al., 2001). Ghrelin was first described as a growth-releasing hormone and was later investigated for prokinetic functions because of its similarity to motilin(Janssen et al., 2011). This rationale was supported by the discovery of ghrelin receptors in the enteric nervous system through immunohistochemistry and mRNA expression studies (Gnanapavan et al., 2002). In addition, ghrelin receptors in the gastric vagal afferents play a role in regulating satiety (le Roux et al., 2005). The prokinetic properties of ghrelin and its agonists make this a promising route for the treatment of postoperative ileus. The first molecule used in clinical trials was TZP 101/Ulimorelin, an agonist with a high affinity for the GHSR1a receptor. As shown in Table 1, two phase IIb clinical trials were conducted to assess the efficacy and safety of ulimorelin. These studies have shown, over several doses (20 – 600 ug/l) of ulimorelin, an absence of adverse effects on the one hand and, on the other hand, faster transit recovery in the study group compared to the placebo group(Popescu et al., 2010; Bochicchio et al., 2012). Similar results were found by infusing a ghrelin analogue (15 pmol/kg/min, NeoMPS, Strasbourg France) before and after surgery (Falkén et al., 2013). However, two other phase III clinical trials (ulimorelin efficacy and safety studies, ULISES 007 n=332 patients, and ULISES 008 n=330 patients) did not show any significant improvement in transit recovery time or the prevention of morbidity inherent in postoperative ileus(Shaw et al., 2013). These negative results were correlated in a trial with another agonist, namely ipamorelin (Beck et al., 2014).

### Περιπηεραλ μ οπιοιδ ρεχεπτορ ανταγονιστς

As described above, one way of optimising the recovery of postoperative bowel function is to antagonise the peripheral opioid receptors without negating their central analgesic action. The main peripheral opioid antagonists used that do not cross the blood-brain barrier are alvimopan and methylnatrexone (figure1). Originally described in 1994 by Eli Lilly, alvimopan is a quaternary μ-opioid receptor antagonist with a high-molecular-weight zwitterionic form and polarity that restricts gastrointestinal absorption and prevents the drug from crossing the blood-brain barrier (Zimmerman et al., 1994; Schmidt, 2001). Alvimopan has an oral bioavailability of 6% resulting in predominantly gastrointestinal activity (Neary and Delaney, 2005). Since the early 2000s, randomised controlled trials have been conducted in North America on cohorts of patients who have undergone bowel resection and hysterectomy (Taguchi et al., 2001; Wolff et al., 2004; Viscusi et al., 2006; Ludwig et al., 2008; Delaney et al., 2012). Compared to placebo, patients treated with alvimopan had a significant reduction in time to transit recovery as evidenced by clinical functional signs such as first gas, first bowel movements or first stools (Jang et al., 2020). These results were confirmed by a combined analysis of three phase III trials (detailed in Table 2) with a significant reduction in the duration of hospitalisation and readmission to hospital in particular (Delaney et al., 2007). Alvimopan was approved by the FDA in 2008. It should be noted that adverse cardiovascular events have been reported, thereby limiting the indications for alvimopan (Erowele, 2008). A multicentre randomised clinical trial on a cohort of patients undergoing surgery after radical cystectomy also showed an improvement in the time taken to resume transit postoperatively (Lee et al., 2014). These encouraging results were not mirrored in

a European clinical trial involving 70 hospitals in 10 European countries (Austria, Belgium, France, United Kingdom, Germany, Greece, Poland, Portugal, Spain and Sweden) and New Zealand. In fact, no significant improvement in transit recovery time was observed in the alvimopan group (Büchler et al., 2008). The medico-economic evaluation of alvimopan treatment in a retrospective national cohort of 7050 postoperative patients undergoing open and laparoscopic bowel surgery showed a significant reduction in direct costs (-$2345, $p<0.0001$)(Delaney et al., 2012). These results have recently been reviewed with the expansion of minimally invasive techniques and the progression of early rehabilitation protocols (Keller et al., 2016). The latest retrospective cohort studies on the cost and efficiency of alvimopan are inconsistent(Keller et al., 2016; Nemeth et al., 2017; Hyde et al., 2019).

Methylnatrexone was developed at the University of Chicago in the 1980s. It is a quaternary derivative of naltrexone. The addition of a methyl group to nitrogen increases polarity, reduces lipid solubility and reduces crossing of the blood-brain barrier (Russell et al., 1982). Methylnaltrexone antagonises opioid binding to the opioid receptors in order of decreasing affinity: $\mu$ receptor (median inhibitory concentration IC50 = 70 nmol/L), $\varkappa$ receptor (median inhibitory concentration IC50 = 575 nmol/L) and negligible for the $\sigma$ receptor (Yuan and Israel, 2006). Despite its receptor antagonising properties, clinical trials, including a phase III trial, have not generated conclusive results (Table 2) (Yu et al., 2011; Viscusi et al., 2013).

**Non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclo-oxygenase (COX) 2 inhibitors**

As described above, the secretion of prostaglandins via COX 2 is a key element in the inflammatory phase. COX or prostaglandin G/H2 synthase allows the conversion of arachidonic acid into prostaglandin H2 and is the target of NSAIDs (Wallace, 2007). NSAIDs therefore appear to be attractive molecules for the prevention of ileus, particularly in its inflammatory phase. However, COX inhibitors, including selective COX 2 inhibitors, are responsible for adverse effects in the digestive tract (Wallace et al., 2000). These adverse effects include peptic ulceration or, in the case of gastrointestinal surgery, an increase in the rate of anastomotic fistula (Elia et al., 2005). They can be explained by the role of prostaglandin in the digestive tract. Indeed, they are notably secreted in the gastric mucosa and are one of the mediators for maintaining the integrity of the gastric mucosa. When the gastric mucosa is exposed to a toxic substance, prostaglandins help maintain gastric blood flow, the secretion of bicarbonates and mucus on the surface of the epithelial cells, thus preserving epithelial homeostasis (Wallace et al., 2004). Studies conducted in the 1980s have further defined the mechanism by which prostaglandins contribute to mucosal defence and the mechanisms by which NSAIDs impair the ability of the gastrointestinal mucosa to resist and respond to damage (Wallace, 2007). The studies have identified two COX isoforms, COX1, which allows the synthesis of protective prostaglandins in the gastrointestinal tract, and COX2, which is involved in inflammation (Xie et al., 1991). However, it appears that both isoforms are involved in the defence mechanisms of the gastrointestinal mucosa, although COX2 selective inhibitors generate fewer serious adverse effects than non-selective NSAIDs(Tanaka et al., 2001). A phase II multicentre randomised controlled clinical trial of 210 patients undergoing major abdominal surgery was conducted by Wattchow *et al.* in Australia. Patients were randomised to three groups and treated twice daily with celecoxib 100 mg, diclofenac 50 mg and placebo (Wattchow et al., 2009). The celecoxib group had significantly fewer patients with postoperative ileus (n=1) than the diclofenac (n=7) and placebo (n=9) groups (Wattchow et al., 2009). However, given the protective functions of COX and prostaglandins on mucosal healing, there are obstacles to the routine use of NSAIDs. Indeed, the literature reports inconsistent results, particularly on the rate of postoperative fistulae and the use of NSAIDs, leading to reluctance on the part of the surgical and anaesthetic teams (Gorissen et al., 2012; Saleh et al., 2014; Subendran et al., 2014). Nevertheless, in certain categories of patients with less risk of developing anastomotic fistula or septic complications, the results on transit time and pain control merit consideration of the administration of a selective COX2 inhibitor.

**Other treatments**

Another way to improve the postoperative period and reduce transit recovery time is to optimise analgesia and, more importantly, to obtain analgesia by reducing the administration of opiates. Lidocaine has been

studied to this end (Foo et al., 2021). Lidocaine is a local amino-amide anaesthetic. Intravenously, lidocaine is 60-80% protein-bound, mostly to a 1-acidic glycoprotein. Lidocaine crosses the blood-brain barrier by passive diffusion across membranes (Hermanns et al., 2019). The main mechanism of action of lidocaine as a local anaesthetic is blockade of voltage-gated sodium channels, resulting in reversible blockade of the propagation of action potentials (Cardoso and Lewis, 2018). Lidocaine acts on neuroinflammatory phenomena by controlling pain signals (Hermanns et al., 2019). It acts directly by blocking inhibitory sympathetic afferent and efferent pathways and prevertebral reflex arcs involved in the neurogenic phase of ileus (Hollmann and Durieux, 2000). In addition, *in-vitro* and animal model studies have shown that the administration of lidocaine reduces the production of pro-inflammatory cytokines such as TNFα IL-1β and IL6 (Wang et al., 2018). Numerous controlled trials have demonstrated a clinical benefit of intravenous lidocaine administration and these results have been confirmed by several meta-analyses (Sun et al., 2012). Thoracic epidural analgesia (TAE) is another interesting strategy for postoperative pain control. A controlled clinical trial compared a group of patients treated with intravenous lidocaine (n=16) to a group of patients with TAE (n=26) and found no difference in time to transit and food intake (Swenson et al., 2010). The efficacy of analgesics, therapeutics and strategies highlights the critical role of pain control in POI, and the relationship between the enteric nervous system and inflammation.

Daikenchuto (DKT) is a traditional Japanese preparation comprising three different herbs (dried ginger, ginseng and zanthox-ylum fruit) known for their effects on intestinal motility (Kubota et al., 2019). Animal model studies have shown a beneficial effect on POI via an anti-inflammatory effect by acting on nicotinic acetylcholine receptors. A recent meta-analysis comprising six controlled trials and one cohort study from Japan, included 1134 patients overall (588 DKT-treated patients). Three studies included colorectal cancer patients, two studies focused on gastric cancer patients and two on pancreatic resection cohorts. The analysis found a significant reduction in the rate of postoperative ileus in the DKT group (RR= 0.58, p=0.04, I2=48%)(Ishizuka et al., 2017). A 16-centre Phase 2 study in the US involving 69 patients with enrolment completed in June 2020 is currently underway to evaluate DKT (NCT02232893). Endo *et al.* recently identified Zingiberis Siccatum Rhizoma, a component of DKT, as an activator of the 7AChR alpha receptor via activation of transient receptor potential ankyrin 1(TRPA1 channels on enterochromaffin cells, resulting in stimulation of 5-HT4 receptors in the enteric nervous system(Endo et al., 2017).

## Cellular and molecular targets for potential future pharmacological approaches

### Mast cells

Several avenues of research and treatment have been and are being considered, depending on the pathophysiology and timing of ileus, with the initial focus on mast cells and their neuronal interactions (figure 2). The activation and degranulation of mast cells is a key point in the inflammatory phenomena of ileus as described above. An NGF antagonist is one of the first targets used to inhibit their activation. Indeed, mast cells are activated by NGF via the high-affinity NGF receptor, tropomyosin receptor kinase A (TrkA)(Marshall et al., 1990; Kawamoto et al., 2002). Berdun *et al.* showed in a mouse model that treatment with an NGF antagonist K252a prevented degranulation of mast cells and decreased the expression of inflammatory markers such as IL6 (Berdún et al., 2015b). Similarly, Jardi *et al.* suggested that NGF-TrkA-dependent pathways are involved in the colonic contractile alterations observed upon exposure to oral ovalbumin (OVA)-induced MCs hyperactivity in rats. They observed spontaneous colonic activity*in vivo* and *in vitro* modified by OVA, an effect prevented by K252a (Jardí et al., 2012). The same team studied the density of mast cells and their proteases, tryptases and chymase at several stages of the surgical procedure (Berdún et al., 2015a). There was a difference in chymase and tryptase concentration between the cholecystectomy group and the colectomy group suggesting a positive correlation between the invasiveness of the surgical procedure and mast cell activation. There was also a correlation between the peritoneal protease level and the occurrence of POI after colectomy(Berdún et al., 2015a).

Aggregation by the IgE antigen bound to its high-affinity receptor on mast cells triggers a complex series of biochemical events resulting in the release of inflammatory mediators. The essential role of the protein, tyrosine kinase Syk, in the degranulation of mast cells and activation of resident macrophages has

been described (Siraganian et al., 2010). Van Bree *et al.* studied the Syk inhibitor, GSK compound 143 (GSK143), in a mouse model of POI (figure2). Mice treated with GSK 143 had significantly faster transit. In addition,*in-vitro* studies showed that GSK 143 blocked substance P and decreased cytokine expression in lipopolysaccharide-treated macrophages (van Bree et al., 2013).

The interaction of mast cells with afferent neurons via receptor activity modifying protein 1 (RAMP1), calcitonin receptor-like (CALCRL) and their roles in inflammation have been highlighted in studies focusing on capsaicin and CGRP antagonists (figure 2) (Zittel et al., 1994). In addition, a capsaicin-mediated effect on the acceleration of gastric emptying has been described in mouse models (Plourde et al., 1993). More recently, a new CGRP receptor antagonist (BIBN 4096BS) has been studied in murine models, triggering a decrease in IL beta and IL6 mRNA expression in the muscularis externa 3 hours after surgery. In addition, the authors refer to the presence of CGRP receptors in resident macrophages (Glowka et al., 2015).

MCs stabilisation for the prevention of POI (figure 2) was assessed in a pilot clinical trial involving 60 patients undergoing abdominal surgery for gynaecological oncology and transit measurement by scintigraphy. Two groups were compared: a Ketotifen-treated group and a placebo group. Ketotifen is a second-generation H1-receptor antagonist/mast cell stabiliser with potent anti-anaphylactic and anti-histamine properties. It is almost completely absorbed after oral intake and has an approximate bioavailability of 50%. Patients were dosed at 12 mg and 4 mg on the basis of adverse events occurring at 20 mg. Results showed that Ketotifen significantly decreased gastric emptying time compared to placebo (12 mg (gastric retention: median 3% (1-7), P=0.01), 4 mg (gastric retention: 18% (3-45), P=0.6) compared to placebo (gastric retention: 16% (5-75)). There was no significant difference in colonic transit (The et al., 2009).

**Resident macrophages**

As described above, resident macrophages are a key element in the inflammatory response and in the reduction of gut motility. Each stage of their activation and the production of cytokines and chemokines present potential targets for the treatment of POI (figure 3). This activation could be prevented by acting on intestinal permeability, which is partly regulated by MCs.

*Targeting the vagal pathway*

The anti-inflammatory effect of the vagus nerve is part of a reflex whereby the brain detects inflammatory information at the periphery via the vagal afferents and then creates an integrated anti-inflammatory response via the vagal efferent fibres (figure 3). Studies of murine POI models have shown that vagus nerve stimulation decreases macrophage activation, reduces inflammation of the intestinal smooth muscle and is effective on POI (Tsuchida et al., 2011). Numerous studies have highlighted the timing and factors of cholinergic anti-inflammatory pathways (CAIP) (de Jonge et al., 2005; The et al., 2011; Matteoli et al., 2014). Vagus nerve involvement was first demonstrated by manipulating vagus nerve stimulation in mice. This stimulation resulted in a decrease in intestinal muscle inflammation, cytokine production and recruitment of inflammatory immune cells, leading to faster transit recovery (de Jonge et al., 2005). Matteoli *et al.* then showed that the protective effect of the vagal nerve on the POI was spleen-independent via local secretion of acetylcholine that inhibits resident macrophages by binding to 7αAChR (Matteoli et al., 2014). The vagus nerve only comes into indirect contact with immune cells in the intestinal wall. Indeed, vagal efferents only synapse with enteric neurons. However, anatomical studies have highlighted the proximity between cholinergic neuronal fibres and macrophages residing in the gut, both in the myenteric plexus and the lamina propria (Nemethova et al., 2013; Cailotto et al., 2014; Matteoli et al., 2014). Prokinetics such as prucalopride have shown promising results in animal models and in a patient cohort for controlling inflammation on the one hand and treating POI on the other hand (Gong et al., 2016). Other opportunities has been explored to stimulate CAIP. The efficacy of electrical abdominal vagal nerve stimulation on inflammation and transit time was recently demonstrated in preliminary studies in murine and porcine models. This electrical stimulation approach has been studied in a cohort of postoperative colorectal surgery patients. Eighteen patients were enrolled in the study and divided into three groups: one group without stimulation, one group stimulated with 5Hz and one with 20Hz. There was a significant decrease in IL6 and IL8 production in the stimulated groups compared

to the sham group (Stakenborg et al., 2017).

*Intracellular signalling*

Resident macrophages can also be stabilised by interfering with intracellular signalling (figure 3) (Wehner et al., 2009). Semapimod (CNI-1493, N, N-bis [3, 5diacethylphenyl] decanediamide tetrakis [amidinohydrazone]) is an inhibitor of p38MAK and NF-kB activation and COX2 induction by TLR ligands (Bianchi et al., 1995). Studies carried out by Wang *et al.* show that Semapimod desensitises TLR signalling via its effect on the TLR chaperone gp96(Wang et al., 2016). Work on the mouse model of POI has provided encouraging results via several routes of administration. Injection of semapimod (CNI-1493) into the cerebral ventricles is one route for pharmacological stimulation of the vagus nerve and for reproducing its anti-inflammatory and motor action on the digestive tract (The et al., 2011). Furthermore, intravenous (CNI-1403) and oral (CPSI-2364) administration of semapimod reproduces anti-inflammatory action in a murine model and reduces the suppressant effect of muscle contraction during POI (Wehner et al., 2012). MAPKs can be modulated by administering inhaled carbon monoxide (CO) or locally by intraperitoneal administration with promising results in mouse models of POI(De Backer et al., 2009; Van Dingenen et al., 2018). The mechanisms of CO action have been described and reviewed in depth by Babu *et al* . The mechanisms of action of CO on POI at MAPK level include suppression of ERK MAPK (extracellular signal-regulated kinases – mitogen activated kinase) phosphorylation via a soluble guanine cyclase (sGC)-dependent pathway and induction of haem oxygenase 1 (HO1) via phosphorylation of p38 MAPK (Babu et al., 2015). More recently, the direct induction of HO1 and its anti-inflammatory and POI-preventing action have been reported in mice following the intraperitoneal administration of Hemin (Van Dingenen et al., 2020).

The afore-mentioned studies using CO inhalation also revealed the significant temporal induction of IL10 in the external musculature during the inflammatory response after surgical manipulation of the intestine. In addition, CO significantly increased postoperative IL10 expression and work on an ileus model with IL10 KO mice highlighted a role for IL10 in the resolution of the inflammatory phase (Stoffels et al., 2009). However, these results have been challenged by recent studies which demonstrated a pro-inflammatory effect of IL10 (Stein et al., 2018). Finally, extravasation and diapedesis of leukocytes also play an important role in local inflammation. The et al showed that inhibition of adhesion molecules such as ICAM-1 with an antibody (ICAM antisense oligonucleotide ISIS 3082) reduces inflammation induced by intestinal manipulation in a murine model (The et al., 2005).

## Conclusion

In addition to the strategies commonly applied in clinical practice, it is interesting to study and develop new pharmacological approaches that target the intimate mechanisms of intestinal damage observed during POI, such as inflammation and alteration of intestinal permeability. The combined identification and study of new pharmacological agents will improve our understanding of the cellular and molecular mechanisms that govern postoperative ileus. The work must be continued and on-going progress is essential. Indeed, abdominal surgery has made progress to date with minimally invasive surgery and early rehabilitation protocols. However, recent progress in oncology now allows the tumour or tumour recurrence to be managed at advanced stages through often extensive surgery (Denost et al., 2020). These increasingly frequent treatments, such as cytoreductive surgery for peritoneal carcinomatosis or pelvic recurrence, for example, are a source of POI. New research avenues are essential to promote our understanding of this phenomenon and to develop new pharmacological treatments.

## Figure legends

### Figure 1:

Action of endogenous opioid (Met-enkephalin, leu-enkephalin, β-endorphin, and dynorphin), exogenous opioid (morphine and codeine) and peripheral opioid antagonists. Schematic representation of the mechanisms of action of opioids and peripheral opioid antagonists. A) In this situation, a patient is treated with opioids only (blue circle). Opioids act on mu-receptors (red receptors). The opioids have a central analgesic action

since they cross the blood-brain barrier, they also have a peripheral action by acting on the mu-receptors in the digestive tract and inhibit the motricity of the latter. B) Patient is treated with opioids (blue circle) and peripheral opioid antagonists (purple circle). Opioids have a central analgesic action since they cross the blood-brain barrier, whereas peripheral opioid antagonists do not entry into central nervous system and do not antagonize the analgesic action of opioids. Peripheral antagonists, on the other hand, bind on mu-receptors in the gastrointestinal tract thwarting the digestive motor slowing action of opiates.

**Figure 2:**

Schematic illustration of mast cell-nerve interactions, mast cell and intestinal barrier function elements interactions in gut and pharmacological targets. The classical stimulus for mast cells activation is the binding of immunoglobulins E (IgE) on its high-affinity receptor FcεRI cell surface prior to cross-linking by allergen in a sensitised individual. This leads to a cascade of phosphorylation, transcription of pro-inflammatory factors, and to cytokine production and to histamine degranulation notably. The protein tyrosine kinase Syk participates to this process through autophosphorylation and activation of intracellular signaling.*In-vitro* studies showed that GSK 143 (syk inhibitor) blocked substance P activation and decreased cytokine expression. MCs and nerve endings communicate bidirectionally and thus modulate peristalsis and visceral pain. The secretion of bioactive pro-inflammatory mediators by the MCs (such as histamin, leucotriens and proteases) results in numerous effects on neurons such as activation, sensitisation and recruitment of nociceptors to the cell membrane, neurogenic inflammation, thus increasing sensitivity and visceral pain. In the other direction the activation of neurons leads to the release of neuropeptides and neurotransmitters that activate the MCs. MCs are activated by NGF via the high-affinity NGF receptor, tropomyosin receptor kinase A. Its antagonist K252a prevented degranulation of mast cells and decreased the expression of inflammatory markers such as IL6. The interaction between the afferent neuron and the MCs can take place between the secretion of CGRP and substance P and their interaction on the MCs via RAMP-1, CALCRL (CGRP) and NK-1 receptors (substance P). The MCs interact with the intestinal barrier function, particularly at the level of the TJs via the activation of PAR-2 receptors.

Pharmacological targets:

- CGRP antagonist: BIBN 4096BS
- TRPV1 agonist: Capsaicin
- NGF antagonist: K252a
- Inhibitor of the protein tyrosine kinase Syk: GSK 143

Abbreviations:

TJ, tight junction; CRGP, calcitonin-related gene peptide; H1R, histamine receptor 1; IgE, immunoglobulins E; NK1, neurokinin 1 receptor; NGF, neuronal growth factor; PAR2, proteinase-activated receptor-2; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin 1; TrkA, receptor for nerve growth factor, PAR2, proteinase-activated receptor-2, RAMP1, receptor activity modifying protein 1; CALCRL, Calcitonin receptor-like; FcεRI, high affinity IgE receptor.

**Figure 3:**

Schematic representation of the proposed mechanism involved in the inflammatory response, resident macrophage activation, mechanisms underlying the Inhibition of the contractile activity of the smooth muscle of the intestine following abdominal surgery and potential pharmacological targets. Intestinal manipulation and increased intestinal permeability results in the passage of bacteria and liposaccharides on the one hand and increased tissue degradation products on the other. Binding to TLRs results in activation of intracellular signals with increased transcription of pro-inflammatory genes and release of cytokines (TNFα, IL1β, IL6) and chemokines (MCP1, MIP1α), including upregulation of endothelial adhesion molecules such as ICAM1. This leads to an influx of leukocytes into the muscularis externa, followed by increased production of NO and PGs (via upregulation of iNOS and COX2) by resident macrophages and leukocytes, inhibiting contraction of intestinal smooth muscle. The secretion of ACh by enteric neurons, stimulated by vagal efferences, leads

to activation of 7 αAChR receptors that inhibits TNF production.

Pharmacological targets:

- Inhibitor of p38MAK and NF-kB activation: Semapimod, CPSI 2634
- Inhibitor of MAP Kinase: Carbon Monoxide (CO)
- Inhibition of ICAM-1: ICAM antisense oligonucleotide ISIS 3082
- Stimulation of the release of acetylcholine from enteric neurons: selective 5HT4 agonists (mosapride and prucalopride).

Abbreviations:

TJ, tight junction; TLR, toll-like receptor; LPs, liposaccharide; 7αAChR α7-subtype of the nicotinic acetylcholine receptor; PAR2, proteinase-activated receptor-2; ICAM-1, intercellular adhesion molecule-1; LFA-1, lymphocyte function-associated antigen-1; MAP, Mitogen-activated protein; JNK, c-Jun N-terminal kinase; NF-kB, nuclear factor kB; STATS, signal transducers and activator of transcription; NO, nitric oxide; PGs, prostaglandin; Cox-2, cyclooxygenase 2 ; iNOS, inducible nitric oxide synthase; LFA-1, lymphocyte function-associated antigen-1.

## REFERENCES

Asano, K., Takahashi, N., Ushiki, M., Monya, M., Aihara, F., Kuboki, E., et al. (2015). Intestinal CD169(+) macrophages initiate mucosal inflammation by secreting CCL8 that recruits inflammatory monocytes. Nat. Commun. *6* : 7802.

Babu, D., Motterlini, R., and Lefebvre, R.A. (2015). CO and CO-releasing molecules (CO-RMs) in acute gastrointestinal inflammation. Br. J. Pharmacol. *172* : 1557–1573.

Barquist, E., Bonaz, B., Martinez, V., Rivier, J., Zinner, M.J., and Taché, Y. (1996). Neuronal pathways involved in abdominal surgery-induced gastric ileus in rats. Am. J. Physiol. *270* : R888-894.

Barreau, F., Cartier, C., Ferrier, L., Fioramonti, J., and Bueno, L. (2004). Nerve growth factor mediates alterations of colonic sensitivity and mucosal barrier induced by neonatal stress in rats. Gastroenterology *127* : 524–534.

Beck, D.E., Sweeney, W.B., McCarter, M.D., and Ipamorelin 201 Study Group (2014). Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. Int. J. Colorectal Dis. *29* : 1527–1534.

Becker, G., and Blum, H.E. (2009). Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. Lancet Lond. Engl. *373* : 1198–1206.

Benson, M.J., Roberts, J.P., Wingate, D.L., Rogers, J., Deeks, J.J., Castillo, F.D., et al. (1994). Small bowel motility following major intra-abdominal surgery: the effects of opiates and rectal cisapride. Gastroenterology *106* : 924–936.

Berdún, S., Bombuy, E., Estrada, O., Mans, E., Rychter, J., Clavé, P., et al. (2015a). Peritoneal mast cell degranulation and gastrointestinal recovery in patients undergoing colorectal surgery. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *27* : 764–774.

Berdún, S., Rychter, J., and Vergara, P. (2015b). Effects of nerve growth factor antagonist K252a on peritoneal mast cell degranulation: implications for rat postoperative ileus. Am. J. Physiol. Gastrointest. Liver Physiol. *309* : G801-806.

Bianchi, M., Ulrich, P., Bloom, O., Meistrell, M., Zimmerman, G.A., Schmidtmayerova, H., et al. (1995). An inhibitor of macrophage arginine transport and nitric oxide production (CNI-1493) prevents acute inflammation and endotoxin lethality. Mol. Med. Camb. Mass *1* : 254–266.

Bochicchio, G., Charlton, P., Pezzullo, J.C., Kosutic, G., and Senagore, A. (2012). Ghrelin agonist TZP-101/ulimorelin accelerates gastrointestinal recovery independently of opioid use and surgery type: covariate analysis of phase 2 data. World J. Surg. *36* : 39–45.

Boeckxstaens, G.E., Hirsch, D.P., Kodde, A., Moojen, T.M., Blackshaw, A., Tytgat, G.N., et al. (1999). Activation of an adrenergic and vagally-mediated NANC pathway in surgery-induced fundic relaxation in the rat. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *11* : 467–474.

Bree, S.H.W. van, Bemelman, W.A., Hollmann, M.W., Zwinderman, A.H., Matteoli, G., El Temna, S., et al. (2014). Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. Ann. Surg. *259* : 708–714.

Bree, S.H.W. van, Gomez-Pinilla, P.J., Bovenkamp, F.S. van de, Di Giovangiulio, M., Farro, G., Nemethova, A., et al. (2013). Inhibition of spleen tyrosine kinase as treatment of postoperative ileus. Gut *62* : 1581–1590.

Browning, K.N., Verheijden, S., and Boeckxstaens, G.E. (2017). The Vagus Nerve in Appetite Regulation, Mood, and Intestinal Inflammation. Gastroenterology *152* : 730–744.

Büchler, M.W., Seiler, C.M., Monson, J.R.T., Flamant, Y., Thompson-Fawcett, M.W., Byrne, M.M., et al. (2008). Clinical trial: alvimopan for the management of post-operative ileus after abdominal surgery: results of an international randomized, double-blind, multicentre, placebo-controlled clinical study. Aliment. Pharmacol. Ther. *28* : 312–325.

Bueno, L., Fioramonti, J., Delvaux, M., and Frexinos, J. (1997). Mediators and pharmacology of visceral sensitivity: from basic to clinical investigations. Gastroenterology *112* : 1714–1743.

Buhner, S., Barki, N., Greiter, W., Giesbertz, P., Demir, I.E., Ceyhan, G.O., et al. (2017). Calcium Imaging of Nerve-Mast Cell Signaling in the Human Intestine. Front. Physiol. *8* :.

Cailotto, C., Gomez-Pinilla, P.J., Costes, L.M., Vliet, J. van der, Di Giovangiulio, M., Némethova, A., et al. (2014). Neuro-Anatomical Evidence Indicating Indirect Modulation of Macrophages by Vagal Efferents in the Intestine but Not in the Spleen. PLoS ONE *9* :.

Cardoso, F.C., and Lewis, R.J. (2018). Sodium channels and pain: from toxins to therapies. Br. J. Pharmacol. *175* : 2138–2157.

Cenac, N., Altier, C., Motta, J.-P., Aldebert, E. d', Galeano, S., Zamponi, G.W., et al. (2010). Potentiation of TRPV4 signalling by histamine and serotonin: an important mechanism for visceral hypersensitivity. Gut *59* : 481–488.

Chan, D.-C., Liu, Y.-C., Chen, C.-J., Yu, J.-C., Chu, H.-C., Chen, F.-C., et al. (2005). Preventing prolonged post-operative ileus in gastric cancer patients undergoing gastrectomy and intra-peritoneal chemotherapy. World J. Gastroenterol. *11* : 4776–4781.

Chapman, M.J., Jones, K.L., Almansa, C., Barnes, C.N., Nguyen, D., and Deane, A.M. (2021). Blinded, Double-Dummy, Parallel-Group, Phase 2a Randomized Clinical Trial to Evaluate the Efficacy and Safety of a Highly Selective 5-Hydroxytryptamine Type 4 Receptor Agonist in Critically Ill Patients With Enteral Feeding Intolerance. JPEN J. Parenter. Enteral Nutr. *45* : 115–124.

Chapman, S.J., Pericleous, A., Downey, C., and Jayne, D.G. (2018). Postoperative ileus following major colorectal surgery. Br. J. Surg. *105* : 797–810.

Chapman, S.J., Thorpe, G., Vallance, A.E., Harji, D.P., Lee, M.J., Fearnhead, N.S., et al. (2019). Systematic review of definitions and outcome measures for return of bowel function after gastrointestinal surgery. BJS Open *3* : 1–10.

Chapuis, P.H., Bokey, L., Keshava, A., Rickard, M.J.F.X., Stewart, P., Young, C.J., et al. (2013). Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. Ann. Surg. *257* : 909–915.

Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E., and Weigle, D.S. (2001). A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes *50* : 1714–1719.

Dass, N.B., Munonyara, M., Bassil, A.K., Hervieu, G.J., Osbourne, S., Corcoran, S., et al. (2003). Growth hormone secretagogue receptors in rat and human gastrointestinal tract and the effects of ghrelin. Neuroscience *120* : 443–453.

De Backer, O., Elinck, E., Blanckaert, B., Leybaert, L., Motterlini, R., and Lefebvre, R.A. (2009). Water-soluble CO-releasing molecules reduce the development of postoperative ileus via modulation of MAPK/HO-1 signalling and reduction of oxidative stress. Gut *58* : 347–356.

De Winter, B.Y., Boeckxstaens, G.E., De Man, J.G., Moreels, T.G., Herman, A.G., and Pelckmans, P.A. (1997a). Effect of adrenergic and nitrergic blockade on experimental ileus in rats. Br. J. Pharmacol.*120* : 464–468.

De Winter, B.Y., Boeckxstaens, G.E., De Man, J.G., Moreels, T.G., Herman, A.G., and Pelckmans, P.A. (1997b). Effects of mu- and kappa-opioid receptors on postoperative ileus in rats. Eur. J. Pharmacol. *339* : 63–67.

De Winter, B.Y., Boeckxstaens, G.E., De Man, J.G., Moreels, T.G., Herman, A.G., and Pelckmans, P.A. (1997c). Effects of mu- and kappa-opioid receptors on postoperative ileus in rats. Eur. J. Pharmacol. *339* : 63–67.

Delaney, C.P. (2004). Clinical perspective on postoperative ileus and the effect of opiates. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *16 Suppl 2* : 61–66.

Delaney, C.P., Craver, C., Gibbons, M.M., Rachfal, A.W., VandePol, C.J., Cook, S.F., et al. (2012). Evaluation of clinical outcomes with alvimopan in clinical practice: a national matched-cohort study in patients undergoing bowel resection. Ann. Surg. *255* : 731–738.

Delaney, C.P., Wolff, B.G., Viscusi, E.R., Senagore, A.J., Fort, J.G., Du, W., et al. (2007). Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. Ann. Surg.*245* : 355–363.

Denost, Q., Solomon, M., Tuech, J.-J., Ghouti, L., Cotte, E., Panis, Y., et al. (2020). International variation in managing locally advanced or recurrent rectal cancer: prospective benchmark analysis. Br. J. Surg.*107* : 1846–1854.

Echtenacher, B., Männel, D.N., and Hültner, L. (1996). Critical protective role of mast cells in a model of acute septic peritonitis. Nature *381* : 75–77.

Elia, N., Lysakowski, C., and Tramèr, M.R. (2005). Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology *103* : 1296–1304.

Endo, M., Hori, M., Mihara, T., Ozaki, H., Oikawa, T., Odaguchi, H., et al. (2017). Zingiberis Siccatum Rhizoma, the active component of the Kampo formula Daikenchuto, induces anti-inflammatory actions through α7 nicotinic acetylcholine receptor activation. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *29* :.

Erowele, G.I. (2008). Alvimopan (Entereg), a Peripherally Acting mu-Opioid Receptor Antagonist For Postoperative Ileus. Pharm. Ther.*33* : 574–583.

Eskandari, M.K., Kalff, J.C., Billiar, T.R., Lee, K.K., and Bauer, A.J. (1999). LPS-induced muscularis macrophage nitric oxide suppresses rat jejunal circular muscle activity. Am. J. Physiol. *277* : G478-486.

Falkén, Y., Webb, D.-L., Abraham-Nordling, M., Kressner, U., Hellström, P.M., and Näslund, E. (2013). Intravenous ghrelin accelerates postoperative gastric emptying and time to first bowel movement in humans. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *25* : 474–480.

Ferraz, A.A., Cowles, V.E., Condon, R.E., and Schulte, W.J. (1995). Opioid and nonopioid analgesic drug effects on colon contractions in monkeys. Dig. Dis. Sci. *40* : 1417–1419.

Foo, I., Macfarlane, A.J.R., Srivastava, D., Bhaskar, A., Barker, H., Knaggs, R., et al. (2021). The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. Anaesthesia *76* : 238–250.

Forsythe, P. (2019). Mast Cells in Neuroimmune Interactions. Trends Neurosci. *42* : 43–55.

Fox, E.A., and Powley, T.L. (1985). Longitudinal columnar organization within the dorsal motor nucleus represents separate branches of the abdominal vagus. Brain Res. *341* : 269–282.

Frantzides, C.T., Cowles, V., Salaymeh, B., Tekin, E., and Condon, R.E. (1992). Morphine effects on human colonic myoelectric activity in the postoperative period. Am. J. Surg. *163* : 144–148; discussion 148-149.

Galli, S.J., Grimbaldeston, M., and Tsai, M. (2008). Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nat. Rev. Immunol. *8* : 478–486.

Glowka, T.R., Steinebach, A., Stein, K., Schwandt, T., Lysson, M., Holzmann, B., et al. (2015). The novel CGRP receptor antagonist BIBN4096BS alleviates a postoperative intestinal inflammation and prevents postoperative ileus. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *27* : 1038–1049.

Gnanapavan, S., Kola, B., Bustin, S.A., Morris, D.G., McGee, P., Fairclough, P., et al. (2002). The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J. Clin. Endocrinol. Metab. *87* : 2988.

Gonenne, J., Camilleri, M., Ferber, I., Burton, D., Baxter, K., Keyashian, K., et al. (2005). Effect of alvimopan and codeine on gastrointestinal transit: a randomized controlled study. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.*3* : 784–791.

Gong, J., Xie, Z., Zhang, T., Gu, L., Yao, W., Guo, Z., et al. (2016). Randomised clinical trial: prucalopride, a colonic pro-motility agent, reduces the duration of post-operative ileus after elective gastrointestinal surgery. Aliment. Pharmacol. Ther. *43* : 778–789.

Gorissen, K.J., Benning, D., Berghmans, T., Snoeijs, M.G., Sosef, M.N., Hulsewe, K.W.E., et al. (2012). Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. Br. J. Surg. *99* : 721–727.

Grant, A.D., Cottrell, G.S., Amadesi, S., Trevisani, M., Nicoletti, P., Materazzi, S., et al. (2007). Protease-activated receptor 2 sensitizes the transient receptor potential vanilloid 4 ion channel to cause mechanical hyperalgesia in mice. J. Physiol. *578* : 715–733.

Gutierrez, J.A., Solenberg, P.J., Perkins, D.R., Willency, J.A., Knierman, M.D., Jin, Z., et al. (2008). Ghrelin octanoylation mediated by an orphan lipid transferase. Proc. Natl. Acad. Sci. U. S. A.*105* : 6320–6325.

Harada, T., Hirosawa, T., Morinaga, K., and Shimizu, T. (2017). Metoclopramide-induced Serotonin Syndrome. Intern. Med. Tokyo Jpn.*56* : 737–739.

Hedrick, T.L., McEvoy, M.D., Mythen, M.M.G., Bergamaschi, R., Gupta, R., Holubar, S.D., et al. (2018). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Gastrointestinal Dysfunction Within an Enhanced Recovery Pathway for Elective Colorectal Surgery. Anesth. Analg. *126* : 1896–1907.

Hermanns, H., Hollmann, M.W., Stevens, M.F., Lirk, P., Brandenburger, T., Piegeler, T., et al. (2019). Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. Br. J. Anaesth. *123* : 335–349.

Hollmann, M.W., and Durieux, M.E. (2000). Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology*93* : 858–875.

Holte, K., and Kehlet, H. (2002). Postoperative ileus: progress towards effective management. Drugs *62* : 2603–2615.

Hommes, D.W., Peppelenbosch, M.P., and Deventer, S.J.H. van (2003). Mitogen activated protein (MAP) kinase signal transduction pathways and novel anti-inflammatory targets. Gut *52* : 144–151.

Hori, M., Kita, M., Torihashi, S., Miyamoto, S., Won, K.J., Sato, K., et al. (2001). Upregulation of iNOS by COX-2 in muscularis resident macrophage of rat intestine stimulated with LPS. Am. J. Physiol. Gastrointest. Liver Physiol. *280* : G930-938.

Huston, J.M., Ochani, M., Rosas-Ballina, M., Liao, H., Ochani, K., Pavlov, V.A., et al. (2006). Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. J. Exp. Med. *203* : 1623–1628.

Hyde, L.Z., Kiely, J.M., Al-Mazrou, A., Zhang, H., Lee-Kong, S., and Kiran, R.P. (2019). Alvimopan Significantly Reduces Length of Stay and Costs Following Colorectal Resection and Ostomy Reversal Even Within an Enhanced Recovery Protocol. Dis. Colon Rectum *62* : 755–761.

Hyun, E., Andrade-Gordon, P., Steinhoff, M., and Vergnolle, N. (2008). Protease-activated receptor-2 activation: a major actor in intestinal inflammation. Gut *57* : 1222–1229.

Ishizuka, M., Shibuya, N., Nagata, H., Takagi, K., Iwasaki, Y., Hachiya, H., et al. (2017). Perioperative Administration of Traditional Japanese Herbal Medicine Daikenchuto Relieves Postoperative Ileus in Patients Undergoing Surgery for Gastrointestinal Cancer: A Systematic Review and Meta-analysis. Anticancer Res. *37* : 5967–5974.

Isola, S., Hussain, A., Dua, A., Singh, K., and Adams, N. (2021). Metoclopramide. In StatPearls, (Treasure Island (FL): StatPearls Publishing), p.

Jacob, C., Yang, P.-C., Darmoul, D., Amadesi, S., Saito, T., Cottrell, G.S., et al. (2005). Mast cell tryptase controls paracellular permeability of the intestine. Role of protease-activated receptor 2 and beta-arrestins. J. Biol. Chem. *280* : 31936–31948.

Jang, J., Kwok, B., Zhong, H., Xia, Y., Grucela, A., Bernstein, M., et al. (2020). Alvimopan for the Prevention of Postoperative Ileus in Inflammatory Bowel Disease Patients. Dig. Dis. Sci. *65* : 1164–1171.

Janssen, S., Laermans, J., Verhulst, P.-J., Thijs, T., Tack, J., and Depoortere, I. (2011). Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. Proc. Natl. Acad. Sci. U. S. A. *108* : 2094–2099.

Jardí, F., Martínez, V., and Vergara, P. (2012). NGF is involved in oral ovalbumin-induced altered colonic contractility in rats: evidence from the blockade of TrkA receptors with K252a. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *24* : e580-590.

Jonge, W.J. de, The, F.O., Coelen, D. van der, Bennink, R.J., Reitsma, P.H., Deventer, S.J. van, et al. (2004). Mast cell degranulation during abdominal surgery initiates postoperative ileus in mice. Gastroenterology *127* : 535–545.

Jonge, W.J. de, and Ulloa, L. (2007). The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. Br. J. Pharmacol.*151* : 915–929.

Jonge, W.J. de, Zanden, E.P. van der, The, F.O., Bijlsma, M.F., Westerloo, D.J. van, Bennink, R.J., et al. (2005). Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nat. Immunol. *6* : 844–851.

Kalff, J.C., Buchholz, B.M., Eskandari, M.K., Hierholzer, C., Schraut, W.H., Simmons, R.L., et al. (1999a). Biphasic response to gut manipulation and temporal correlation of cellular infiltrates and muscle dysfunction in rat. Surgery *126* : 498–509.

Kalff, J.C., Carlos, T.M., Schraut, W.H., Billiar, T.R., Simmons, R.L., and Bauer, A.J. (1999b). Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate postoperative ileus. Gastroenterology *117* : 378–387.

Kalff, J.C., Schraut, W.H., Billiar, T.R., Simmons, R.L., and Bauer, A.J. (2000). Role of inducible nitric oxide synthase in postoperative intestinal smooth muscle dysfunction in rodents. Gastroenterology *118* : 316–327.

Kalff, J.C., Schraut, W.H., Simmons, R.L., and Bauer, A.J. (1998). Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann. Surg. *228* : 652–663.

Kawamoto, K., Aoki, J., Tanaka, A., Itakura, A., Hosono, H., Arai, H., et al. (2002). Nerve growth factor activates mast cells through the collaborative interaction with lysophosphatidylserine expressed on the membrane surface of activated platelets. J. Immunol. Baltim. Md 1950 *168* : 6412–6419.

Keller, D.S., Flores-Gonzalez, J.-R., Ibarra, S., Mahmood, A., and Haas, E.M. (2016). Is there value in alvimopan in minimally invasive colorectal surgery? Am. J. Surg. *212* : 851–856.

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., and Kangawa, K. (1999). Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature *402* : 656–660.

Kowalski, J. (1998). Augmenting effect of opioids on nitrite production by stimulated murine macrophages. Neuropeptides *32* : 287–291.

Kreiss, C., Birder, L.A., Kiss, S., VanBibber, M.M., and Bauer, A.J. (2003). COX-2 dependent inflammation increases spinal Fos expression during rodent postoperative ileus. Gut *52* : 527–534.

Kubota, K., Mase, A., Matsushima, H., Fujitsuka, N., Yamamoto, M., Morine, Y., et al. (2019). Daikenchuto, a traditional Japanese herbal medicine, promotes colonic transit by inducing a propulsive movement pattern. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *31* : e13689.

Lee, C.T., Chang, S.S., Kamat, A.M., Amiel, G., Beard, T.L., Fergany, A., et al. (2014). Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. Eur. Urol. *66* : 265–272.

Lotze, M.T., Zeh, H.J., Rubartelli, A., Sparvero, L.J., Amoscato, A.A., Washburn, N.R., et al. (2007). The grateful dead: damage-associated molecular pattern molecules and reduction/oxidation regulate immunity. Immunol. Rev. *220* : 60–81.

Ludwig, K., Enker, W.E., Delaney, C.P., Wolff, B.G., Du, W., Fort, J.G., et al. (2008). Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch. Surg. Chic. Ill 1960 *143* : 1098–1105.

Lutter, M., Sakata, I., Osborne-Lawrence, S., Rovinsky, S.A., Anderson, J.G., Jung, S., et al. (2008). The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. Nat. Neurosci. *11* : 752–753.

Marshall, J.S., Stead, R.H., McSharry, C., Nielsen, L., and Bienenstock, J. (1990). The role of mast cell degranulation products in mast cell hyperplasia. I. Mechanism of action of nerve growth factor. J. Immunol. Baltim. Md 1950 *144* : 1886–1892.

Martínez, C., Vicario, M., Ramos, L., Lobo, B., Mosquera, J.L., Alonso, C., et al. (2012). The jejunum of diarrhea-predominant irritable bowel syndrome shows molecular alterations in the tight junction signaling pathway that are associated with mucosal pathobiology and clinical manifestations. Am. J. Gastroenterol. *107* : 736–746.

Matteoli, G., Gomez-Pinilla, P.J., Nemethova, A., Di Giovangiulio, M., Cailotto, C., Bree, S.H. van, et al. (2014). A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut *63* : 938–948.

Narita, K., Tsunoda, A., Takenaka, K., Watanabe, M., Nakao, K., and Kusano, M. (2008). Effect of mosapride on recovery of intestinal motility after hand-assisted laparoscopic colectomy for carcinoma. Dis. Colon Rectum *51* : 1692–1695.

Neary, P., and Delaney, C.P. (2005). Alvimopan. Expert Opin. Investig. Drugs *14* : 479–488.

Nemeth, Z.H., Bogdanovski, D.A., Paglinco, S.R., Barratt-Stopper, P., and Rolandelli, R.H. (2017). Cost and efficacy examination of alvimopan for the prevention of postoperative ileus. J. Investig. Med. Off. Publ. Am. Fed. Clin. Res. *65* : 949–952.

Nemethova, A., Michel, K., Gomez-Pinilla, P.J., Boeckxstaens, G.E., and Schemann, M. (2013). Nicotine attenuates activation of tissue resident macrophages in the mouse stomach through the β2 nicotinic acetylcholine receptor. PloS One *8* : e79264.

Plourde, V., Wong, H.C., Walsh, J.H., Raybould, H.E., and Taché, Y. (1993). CGRP antagonists and capsaicin on celiac ganglia partly prevent postoperative gastric ileus. Peptides *14* : 1225–1229.

Popescu, I., Fleshner, P.R., Pezzullo, J.C., Charlton, P.A., Kosutic, G., and Senagore, A.J. (2010). The Ghrelin agonist TZP-101 for management of postoperative ileus after partial colectomy: a randomized, dose-ranging, placebo-controlled clinical trial. Dis. Colon Rectum*53* : 126–134.

Ramsbottom, N., and Hunt, J.N. (1970). Studies of the effect of metoclopramide and apomorphine on gastric emptying and secretion in man. Gut *11* : 989–993.

Rekik, M., Delvaux, M., Frexinos, J., and Bueno, L. (1997). The calcitonin gene-related peptide activates both cAMP and NO pathways to induce relaxation of circular smooth muscle cells of guinea-pig ileum. Peptides *18* : 1517–1522.

Rivera, J., and Gilfillan, A.M. (2006). Molecular regulation of mast cell activation. J. Allergy Clin. Immunol. *117* : 1214–1225; quiz 1226.

Rosas-Ballina, M., Olofsson, P.S., Ochani, M., Valdés-Ferrer, S.I., Levine, Y.A., Reardon, C., et al. (2011). Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science *334* : 98–101.

Roux, C.W. le, Patterson, M., Vincent, R.P., Hunt, C., Ghatei, M.A., and Bloom, S.R. (2005). Postprandial plasma ghrelin is suppressed proportional to meal calorie content in normal-weight but not obese subjects. J. Clin. Endocrinol. Metab. *90* : 1068–1071.

Russell, J., Bass, P., Goldberg, L.I., Schuster, C.R., and Merz, H. (1982). Antagonism of gut, but not central effects of morphine with quaternary narcotic antagonists. Eur. J. Pharmacol. *78* : 255–261.

Saleh, F., Jackson, T.D., Ambrosini, L., Gnanasegaram, J.J., Kwong, J., Quereshy, F., et al. (2014). Perioperative nonselective non-steroidal anti-inflammatory drugs are not associated with anastomotic leakage after colorectal surgery. J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract *18* : 1398–1404.

Santos, J., Yang, P.C., Söderholm, J.D., Benjamin, M., and Perdue, M.H. (2001). Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. Gut *48* : 630–636.

Schang, J.C., Hémond, M., Hébert, M., and Pilote, M. (1986). How does morphine work on colonic motility? An electromyographic study in the human left and sigmoid colon. Life Sci. *38* : 671–676.

Schmidt, W.K. (2001). Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am. J. Surg. *182* : 27S-38S.

Seta, M.L., and Kale-Pradhan, P.B. (2001). Efficacy of metoclopramide in postoperative ileus after exploratory laparotomy. Pharmacotherapy*21* : 1181–1186.

Shah, S.K., Uray, K.S., Stewart, R.H., Laine, G.A., and Cox, C.S. (2011). Resuscitation-Induced Intestinal Edema and Related Dysfunction: State of the Science. J. Surg. Res. *166* : 120–130.

Shahbazian, A., Heinemann, A., Schmidhammer, H., Beubler, E., Holzer-Petsche, U., and Holzer, P. (2002). Involvement of mu- and kappa-, but not delta-, opioid receptors in the peristaltic motor depression caused by endogenous and exogenous opioids in the guinea-pig intestine. Br. J. Pharmacol. *135* : 741–750.

Shaw, M., Pediconi, C., McVey, D., Mondou, E., Quinn, J., Chamblin, B., et al. (2013). Safety and efficacy of ulimorelin administered postoperatively to accelerate recovery of gastrointestinal motility following partial bowel resection: results of two randomized, placebo-controlled phase 3 trials. Dis. Colon Rectum *56* : 888–897.

Siraganian, R.P., Castro, R.O. de, Barbu, E.A., and Zhang, J. (2010). Mast cell signaling: the role of protein tyrosine kinase Syk, its activation and screening methods for new pathway participants. FEBS Lett. *584* : 4933–4940.

Solanki, S., Chakinala, R.C., Haq, K.F., Singh, J., Khan, M.A., Solanki, D., et al. (2020). Paralytic ileus in the United States: A cross-sectional study from the national inpatient sample. SAGE Open Med.*8* : 2050312120962636.

Stakenborg, N., Labeeuw, E., Gomez-Pinilla, P.J., De Schepper, S., Aerts, R., Goverse, G., et al. (2019). Preoperative administration of the 5-HT4 receptor agonist prucalopride reduces intestinal inflammation and shortens postoperative ileus via cholinergic enteric neurons. Gut*68* : 1406–1416.

Stakenborg, N., Viola, M.F., and Boeckxstaens, G.E. (2020). Intestinal neuro-immune interactions: focus on macrophages, mast cells and innate lymphoid cells. Curr. Opin. Neurobiol. *62* : 68–75.

Stakenborg, N., Wolthuis, A.M., Gomez-Pinilla, P.J., Farro, G., Di Giovangiulio, M., Bosmans, G., et al. (2017). Abdominal vagus nerve stimulation as a new therapeutic approach to prevent postoperative ileus. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc.*29* :.

Stein, K., Lysson, M., Schumak, B., Vilz, T., Specht, S., Heesemann, J., et al. (2018). Leukocyte-Derived Interleukin-10 Aggravates Postoperative Ileus. Front. Immunol. *9* : 2599.

Stoffels, B., Schmidt, J., Nakao, A., Nazir, A., Chanthaphavong, R.S., and Bauer, A.J. (2009). Role of interleukin 10 in murine postoperative ileus. Gut *58* : 648–660.

Subendran, J., Siddiqui, N., Victor, J.C., McLeod, R.S., and Govindarajan, A. (2014). NSAID use and anastomotic leaks following elective colorectal surgery: a matched case-control study. J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract *18* : 1391–1397.

Sun, Y., Li, T., Wang, N., Yun, Y., and Gan, T.J. (2012). Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. Dis. Colon Rectum *55* : 1183–1194.

Swenson, B.R., Gottschalk, A., Wells, L.T., Rowlingson, J.C., Thompson, P.W., Barclay, M., et al. (2010). Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: a randomized clinical trial. Reg. Anesth. Pain Med. *35* : 370–376.

Taguchi, A., Sharma, N., Saleem, R.M., Sessler, D.I., Carpenter, R.L., Seyedsadr, M., et al. (2001). Selective postoperative inhibition of gastrointestinal opioid receptors. N. Engl. J. Med. *345* : 935–940.

Tanaka, A., Araki, H., Komoike, Y., Hase, S., and Takeuchi, K. (2001). Inhibition of both COX-1 and COX-2 is required for development of gastric damage in response to nonsteroidal antiinflammatory drugs. J. Physiol. Paris *95* : 21–27.

The, F., Cailotto, C., Vliet, J. van der, Jonge, W.J. de, Bennink, R.J., Buijs, R.M., et al. (2011). Central activation of the cholinergic anti-inflammatory pathway reduces surgical inflammation in experimental post-operative ileus. Br. J. Pharmacol. *163* : 1007–1016.

The, F.O., Bennink, R.J., Ankum, W.M., Buist, M.R., Busch, O.R.C., Gouma, D.J., et al. (2008). Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus. Gut *57* : 33–40.

The, F.O., Buist, M.R., Lei, A., Bennink, R.J., Hofland, J., Wijngaard, R.M. van den, et al. (2009). The role of mast cell stabilization in treatment of postoperative ileus: a pilot study. Am. J. Gastroenterol. *104* : 2257–2266.

The, F.O., Jonge, W.J. de, Bennink, R.J., Wijngaard, R.M. van den, and Boeckxstaens, G.E. (2005). The ICAM-1 antisense oligonucleotide ISIS-3082 prevents the development of postoperative ileus in mice. Br. J. Pharmacol. *146* : 252–258.

Thomas, J. (2008). Opioid-induced bowel dysfunction. J. Pain Symptom Manage. *35* : 103–113.

Toyomasu, Y., Mochiki, E., Morita, H., Ogawa, A., Yanai, M., Ohno, T., et al. (2011). Mosapride citrate improves postoperative ileus of patients with colectomy. J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract *15* : 1361–1367.

Traut, U., Brügger, L., Kunz, R., Pauli-Magnus, C., Haug, K., Bucher, H.C., et al. (2008). Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. Cochrane Database Syst. Rev. CD004930.

Tsuchida, Y., Hatao, F., Fujisawa, M., Murata, T., Kaminishi, M., Seto, Y., et al. (2011). Neuronal stimulation with 5-hydroxytryptamine 4 receptor induces anti-inflammatory actions via α7nACh receptors on muscularis macrophages associated with postoperative ileus. Gut *60* : 638–647.

Türler, A., Schnurr, C., Nakao, A., Tögel, S., Moore, B.A., Murase, N., et al. (2007). Endogenous endotoxin participates in causing a panenteric inflammatory ileus after colonic surgery. Ann. Surg. *245* : 734–744.

Van Dingenen, J., Pieters, L., Van Nuffel, E., and Lefebvre, R.A. (2020). Hemin reduces postoperative ileus in a heme oxygenase 1-dependent manner while dimethyl fumarate does without heme oxygenase 1-induction. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. *32* : e13624.

Van Dingenen, J., Steiger, C., Zehe, M., Meinel, L., and Lefebvre, R.A. (2018). Investigation of orally delivered carbon monoxide for postoperative ileus. Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm. Verfahrenstechnik EV *130* : 306–313.

Vanuytsel, T., Wanrooy, S. van, Vanheel, H., Vanormelingen, C., Verschueren, S., Houben, E., et al. (2014). Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut *63* : 1293–1299.

Venara, A., Meillat, H., Cotte, E., Ouaissi, M., Duchalais, E., Mor-Martinez, C., et al. (2020). Incidence and Risk Factors for Severity of Postoperative Ileus After Colorectal Surgery: A Prospective Registry Data Analysis. World J. Surg. *44* : 957–966.

Vergnolle, N. (2016). Protease inhibition as new therapeutic strategy for GI diseases. Gut *65* : 1215–1224.

Vergnolle, N., and Cirillo, C. (2018). Neurons and Glia in the Enteric Nervous System and Epithelial Barrier Function. Physiol. Bethesda Md *33* : 269–280.

Viscusi, E.R., Goldstein, S., Witkowski, T., Andonakakis, A., Jan, R., Gabriel, K., et al. (2006). Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg. Endosc. *20* : 64–70.

Viscusi, E.R., Rathmell, J.P., Fichera, A., Binderow, S.R., Israel, R.J., Galasso, F.L., et al. (2013). Randomized placebo-controlled study of intravenous methylnaltrexone in postoperative ileus. J. Drug Assess. *2* : 127–134.

Vlug, M.S., Bartels, S. a. L., Wind, J., Ubbink, D.T., Hollmann, M.W., Bemelman, W.A., et al. (2012). Which fast track elements predict early recovery after colon cancer surgery? Colorectal Dis. Off. J. Assoc. Coloproctology G. B. Irel. *14* : 1001–1008.

Vlug, M.S., Wind, J., Hollmann, M.W., Ubbink, D.T., Cense, H.A., Engel, A.F., et al. (2011). Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann. Surg. *254* : 868–875.

Wallace, J.L. (2007). Building a better aspirin: gaseous solutions to a century-old problem. Br. J. Pharmacol. *152* : 421–428.

Wallace, J.L., McKnight, W., Reuter, B.K., and Vergnolle, N. (2000). NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. Gastroenterology *119* : 706–714.

Wallace, J.L., Muscará, M.N., Nucci, G. de, Zamuner, S., Cirino, G., Soldato, P. del, et al. (2004). Gastric tolerability and prolonged prostaglandin inhibition in the brain with a nitric oxide-releasing flurbiprofen derivative, NCX-2216 [3-[4-(2-fluoro-alpha-methyl-[1,1'-biphenyl]-4-acetyloxy)-3-methoxyphenyl]-2-propenoic acid 4-nitrooxy butyl ester]. J. Pharmacol. Exp. Ther. *309* : 626–633.

Wang, G.-D., Wang, X.-Y., Liu, S., Qu, M., Xia, Y., Needleman, B.J., et al. (2014). Innervation of enteric mast cells by primary spinal afferents in guinea pig and human small intestine. Am. J. Physiol. Gastrointest. Liver Physiol. *307* : G719-731.

Wang, J., Grishin, A.V., and Ford, H.R. (2016). Experimental Anti-Inflammatory Drug Semapimod Inhibits TLR Signaling by Targeting the TLR Chaperone gp96. J. Immunol. Baltim. Md 1950 *196* : 5130–5137.

Wang, L., Wang, M., Li, S., Wu, H., Shen, Q., Zhang, S., et al. (2018). Nebulized lidocaine ameliorates allergic airway inflammation via downregulation of TLR2. Mol. Immunol. *97* : 94–100.

Wattchow, D.A., De Fontgalland, D., Bampton, P.A., Leach, P.L., McLaughlin, K., and Costa, M. (2009). Clinical trial: the impact of cyclooxygenase inhibitors on gastrointestinal recovery after major surgery - a randomized double blind controlled trial of celecoxib or diclofenac vs. placebo. Aliment. Pharmacol. Ther. *30* : 987–998.

Wehner, S., Straesser, S., Vilz, T.O., Pantelis, D., Sielecki, T., Cruz, V.F. de la, et al. (2009). Inhibition of p38 mitogen-activated protein kinase pathway as prophylaxis of postoperative ileus in mice. Gastroenterology *136* : 619–629.

Wehner, S., Vilz, T.O., Sommer, N., Sielecki, T., Hong, G.S., Lysson, M., et al. (2012). The novel orally active guanylhydrazone CPSI-2364 prevents postoperative ileus in mice independently of anti-inflammatory vagus nerve signaling. Langenbecks Arch. Surg. *397* : 1139–1147.

Wolff, B.G., Michelassi, F., Gerkin, T.M., Techner, L., Gabriel, K., Du, W., et al. (2004). Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann. Surg. *240* : 728–734; discussion 734-735.

Wouters, M.M., Vicario, M., and Santos, J. (2016). The role of mast cells in functional GI disorders. Gut *65* : 155–168.

Xie, W.L., Chipman, J.G., Robertson, D.L., Erikson, R.L., and Simmons, D.L. (1991). Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proc. Natl. Acad. Sci. U. S. A. *88* : 2692–2696.

Yu, C.S., Chun, H.-K., Stambler, N., Carpenito, J., Schulman, S., Tzanis, E., et al. (2011). Safety and efficacy of methylnaltrexone in shortening the duration of postoperative ileus following segmental colectomy: results of two randomized, placebo-controlled phase 3 trials. Dis. Colon Rectum *54* : 570–578.

Yuan, C.-S., and Israel, R.J. (2006). Methylnaltrexone, a novel peripheral opioid receptor antagonist for the treatment of opioid side effects. Expert Opin. Investig. Drugs *15* : 541–552.

Zimmerman, D.M., Gidda, J.S., Cantrell, B.E., Schoepp, D.D., Johnson, B.G., and Leander, J.D. (1994). Discovery of a potent, peripherally selective trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonist

for the treatment of gastrointestinal motility disorders. J. Med. Chem. *37* : 2262–2265.

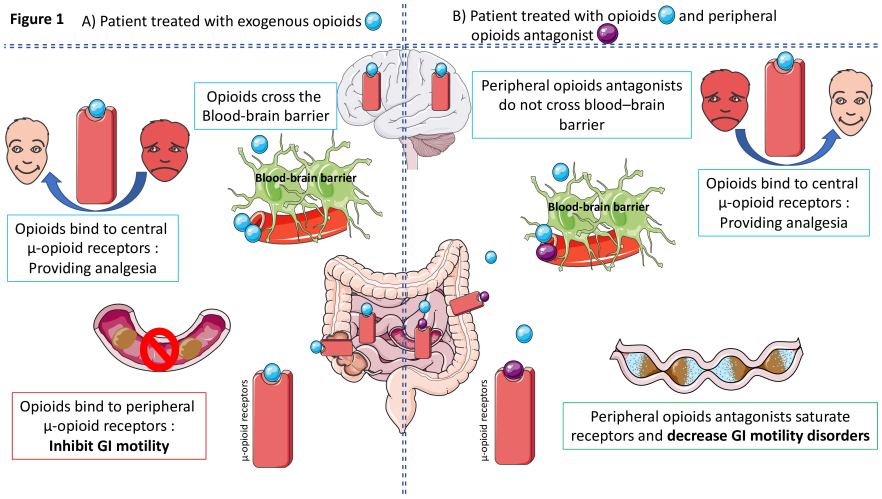
Zittel, T.T., Reddy, S.N., Plourde, V., and Raybould, H.E. (1994). Role of spinal afferents and calcitonin gene-related peptide in the postoperative gastric ileus in anesthetized rats. Ann. Surg. *219* : 79–87.

**Hosted file**

`Buscail et al BJP table 1.docx` available at https://authorea.com/users/427522/articles/531694-post-operative-ileus-a-pharmacological-perspective

**Hosted file**

`Buscail et al BJP table 2 .docx` available at https://authorea.com/users/427522/articles/531694-post-operative-ileus-a-pharmacological-perspective



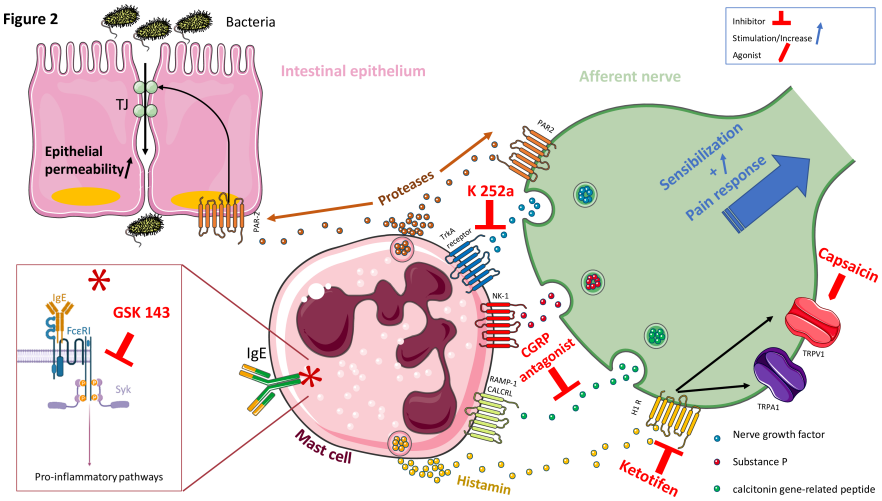



**Figure 3**