Prevention and treatment strategies for post-operative ileus after colorectal surgery

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ABSTRACT

Aim

Prolonged postoperative ileus (PPOI) is one of the most common and difficult to manage complications following colorectal surgery. This thesis aims to examine the healthcare cost of PPOI, to validate the use of a predictive scoring system for PPOI (the “I-Score”), and to analyze currently available methods to prevent or treat PPOI, including non-steroidal anti-inflammatories (NSAIDs) and gastrografin. Finally, we will assess whether prucalopride improves postoperative gut dysmotility after elective colorectal surgery.

Methods

A retrospective review was undertaken to assess the economic impact of PPOI using a strict and modern definition. A large multi-center cohort study was conducted to prospectively assess the validity of the I-Score, a prediction tool for PPOI development. A systematic review and meta-analysis of randomized control trials was conducted to assess whether NSAIDs reduce PPOI and improve postoperative gut function. A pooled analysis of 2 randomized control trials that compared gastrografin to placebo for PPOI treatment was conducted. Finally, a multicenter double-blind randomized control trial was undertaken using a novel serotonin-4 receptor agonist, prucalopride. The purpose of the trial was to determine if prucalopride was able to improve postoperative recovery of gut function and prevent PPOI after elective major colorectal surgery.

Findings

This thesis found that PPOI leads to a significant economic burden across all areas of the healthcare system, and nearly doubles the cost of admission. The I-Score did not accurately predict PPOI development in a large cohort study, but the study found new risk factors for POI development. A systematic review found that NSAIDs confer a modest benefit in time to passage of flatus, stool, and time to tolerance of diet after elective colorectal surgery. Furthermore, gastrografin given at the onset of PPOI may improve time to tolerate an oral diet postoperatively but did not significantly improve time to PPOI resolution. Prucalopride significantly improved time to passage of stool for patients undergoing elective colorectal

surgery within an ERAS setting. Prucalopride did not improve time to tolerate diet or reduce rates of PPOI or length of stay in our series. However, in patients who underwent laparoscopic surgery, prucalopride improved their time to gut recovery by around 24 hours.

Conclusions

PPOI carries a significant economic burden. NSAIDs may reduce postoperative gut dysmotility, but gastrografin is likely ineffective as a treatment for PPOI. Prucalopride did not reduce the rate of PPOI in our study, but may improve postoperative gut function in a subset of patients who undergo laparoscopic surgery. Further studies are required to refine the prediction of PPOI, and allow better selection of high-risk patients to target with future interventions.

DEDICATION

This thesis is dedicated to my wife, Sarah, and my children Grant and Eva for their support, patience, and understanding.

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Chapter 1 Introduction

Postoperative ileus (POI) refers to the obligatory period of pan-intestinal dysmotility that occurs following major abdominal surgery.[1-4] POI affects the entire gastrointestinal tract, and causes nausea and vomiting, distension, inability to pass flatus or stool, and inability to eat. For around 24% of patients who undergo elective colorectal surgery, for both benign disease and colorectal cancer, POI persists for 4 or more days postoperatively, and this is referred to as prolonged postoperative ileus (PPOI).[2] Consequently, patients with PPOI have a significantly longer postoperative hospital stay and are at a significantly increased risk of developing further complications. Studies report PPOI in between 10-30% of patients, which makes it one of the most common complications to occur after elective colorectal surgery.[5] Prolonged hospital stay and increased patient morbidity translates to increased costs for our healthcare system, and estimates of the financial burden of ileus place spending over 1 billion dollars annually in the US alone.[6] The prediction, prevention and management of PPOI is a key target for future research as defined by the American Society of Colon and Rectal Surgeons (ASCRS).[7] This chapter will outline the burden of PPOI in patients undergoing elective colorectal surgery, examine the definitions of “ileus” used in the literature and define the pathophysiology and risk factors of ileus. This chapter will also examine current tools used to predict and treat ileus.

1.1 Defining postoperative ileus

Postoperative ileus (POI) refers to pan-intestinal dysmotility after surgery, and it results from an interplay of multiple factors including autonomic nervous system activity, inflammation and opioid induced inhibition of gut motility. [8] Recent definitions refer to POI as a “transient cessation of coordinated bowel motility after surgical intervention”. [9, 10] An international Delphi survey of experts across multiple countries found that postoperative ileus is regarded as physiological, and is expected to some degree postoperatively.[11] POI is therefore seen as obligatory, unavoidable or inevitable.[10, 12] Investigation is not usually warranted unless another postoperative complication is suspected, although there is a lack of consensus on the need for radiological imaging in the diagnosis of POI.[11] The term POI may be referenced based on whether there is a perceived cause or not. “Primary” POI is described as a delay in postoperative gut motility with no precipitating condition, whereas a “secondary” POI occurs due to the presence of another complication (such as an intra-abdominal abscess or anastomotic leak). In this setting, an abdominal CT scan is the most

accurate modality used to distinguish between primary POI and secondary POI, or to rule out an early postoperative small bowel obstruction.[13]

Early studies reporting on postoperative recovery of gut function indicated that small bowel recovered first (within 24 hours), the stomach at 48 hours, and colon at 48-72 hours.[14] However, there is significant disagreement in the previous literature about how POI should be defined, whether there is an “obligatory” and “pathological” or “prolonged” POI, and when POI should be considered resolved. This is an important distinction, as a “normal” POI that resolves within the first 24-72 hours, and requires no intervention, is unlikely to negatively impact patient recovery. However, a prolonged POI (PPOI) that lasts for more than 4 days after an operation leads to significantly increased patient morbidity, length of stay and healthcare spending, as will be addressed later in this thesis. A recent Delphi survey of 35 international experts defined POI as “a temporary inhibition or gastrointestinal motility after surgical intervention due to non-mechanical causes and prevents sufficient oral intake”.[11] Most international experts would state that POI lies on a spectrum of delayed postoperative gut recovery that includes early events such as PONV (postoperative nausea and vomiting).[11] Unfortunately, the terms POI and PPOI are often used interchangeably in the literature, with POI being the most commonly described term relating to adverse patient outcomes. This section will assess the different definitions of POI given in the literature and explain the rationale for separating POI from PPOI.

Historically, a number of terms have been used to define the idea of POI: “uncomplicated ileus”, “pathologic paralytic ileus”, “adynamic ileus” or “prolonged ileus lasting >3 days after surgery”.[15] It is, therefore, difficult to compare the results of studies that report POI due to variability in how POI is defined. A systematic review by Wolthius *et al* (2016) sought to determine the incidence of POI and to collate different definitions of POI used in the literature.[16] They found a significant heterogeneity in both the criteria for POI diagnosis, and the day at which POI became a pathological (prolonged) process. The review found that studies commonly defined POI as nasogastric tube (NGT) insertion or focused on a cut-off for time to first bowel motion after surgery.[16] There was significant variability in when studies defined POI based on day of first bowel motion, ranging from postoperative days 3-7.[16] Many studies report POI as a duration until an expected end-point is achieved: time to first flatus, stool or tolerance of diet. Early series suggested return of bowel sounds postoperatively could be used to determine resolution of POI, but current evidence suggests that they are unlikely of clinical value.[11] In fact, bowel sounds do not correlate with time to flatus, stool or tolerance of oral intake in the postoperative period.[17]

The duration of POI is therefore entirely dependent on the endpoint used and may vary based on the type of surgery a patient has. Passage of flatus and stool has often been the most commonly reported criteria for POI resolution, and less attention has been put on ability to tolerate an oral intake.[11] However, POI is a pan-intestinal disease, and recording only one component of intestinal recovery (time to stool) is an oversimplification. Peters *et al* (2016) defined POI as lack of tolerance of diet and passage of flatus or stool for at least 24 hours on postoperative day 5,[18] and a more modern definition to time to gut recovery would include the "time from surgical intervention to passage of flatus or stool and initiation of adequate oral intake that is tolerated and maintains hydration".[12] However, studies still determine a cut-off for when recovery of gut function should happen, and this cut-off may be defined differently for patients undergoing laparoscopic surgery (i.e. recovery by postoperative day 3) or open surgery (i.e. recovery by postoperative day 5),[12, 19] or the need for NG tube insertion in the absence of mechanical obstruction.[20] Normal recovery is often described as occurring within the first 72 hours postoperatively, after elective colorectal surgery, and this is supported in the literature.[21]

A systematic review of outcome measures for return of postoperative gut function by Chapman *et al* (2019) found reports of 73 different reported outcome measures for postoperative gut function, which highlights the degree of heterogeneity within the literature about how to define POI.[3] Importantly, clinical outcome measures make up the majority of POI definitions used (86-92%).[3] Whereas, radiological outcome measures make up only 8% of outcome measures for POI.[3] There is significant variability in the definition of postoperative ileus and prolonged postoperative ileus.[3] Most studies have focused on measures of lower gastrointestinal recovery (80%) and relatively fewer have included measures of upper gastrointestinal recovery (41%).[3]

Composite endpoints for recovery of postoperative gut function have been described. Ludwig *et al* (2008) described a composite end-point called GI-2 for resolution of postoperative ileus, it involves the time taken for a patient to both tolerate a solid diet without significant nausea or vomiting, and pass a bowel motion (whichever occurs later).[22] The volume of food was not specified in their study, and the authors noted that GI-2 was mostly determined by time to passage of stool.[22] However, GI-2 provides an important continuous outcome marker for return of gut function that includes both upper gastrointestinal and lower gastrointestinal recovery. A separate outcome measure "GI-3" was defined as the time until both tolerance of food and passage of either flatus or stool.[22]

Van Bree *et al* (2014) assessed the clinical markers of gut recovery in relation to scintigraphy, to find the most reliable clinical markers of gut recovery, and sought to determine normal and prolonged cut-offs for GI-2 and GI-3 in patients undergoing elective colorectal surgery.[23] Patients who had a segmental colonic resection for colon cancer between 2005-2009 were allocated to laparoscopic or open surgery and separated into fast track or standard recovery pathways. Patients underwent a solid gastric emptying study 24 hours postoperatively using a technetium-99 labelled pancake, and then on postoperative days 2 and 3 they underwent an indium-111 labelled colonic transit study. Time to solid food was determined as time to solid food intake with no significant nausea or vomiting. They found that every patient who did not have passage of radioactive tracer into their colon by postoperative day 3 required NGT insertion. These patients were defined as having POI, and their median length of stay was 21.8 days.[23] Conversely, only 5 out of 77 patients in whom the tracer reached the colon by postoperative day 3 required NGT insertion (6.5%).[23] They compared the clinical outcomes of GI-2 and GI-3 to intestinal motility based on scintigraphy, and found that GI-2 was the strongest correlator to return of gut function postoperatively with an AUC of 0.87, and was much more sensitive than GI-3.[23]

POI can be defined using dichotomous outcomes as well. As a simple measure, insertion of NGT is viewed as a suitable definition of PPOI.[16] Wolthius *et al* (2016) proposed that NGT insertion should be the criteria for PPOI, as NGTs are routinely omitted in the era of enhanced recovery after surgery (ERAS) pathways.[16] NGT is not a perfect measure of PPOI, however, and in a recent Delphi survey, only 78% of international experts agreed that NGT insertion should be mandatory as part of a definition for PPOI.[11]

Importantly, while NG tube insertion is very rare in patients who do not develop PPOI, the incidence of NG insertion for patients who satisfy a more rigorous definition of PPOI is only 71%.[2, 24] NG insertion as solitary diagnosis for PPOI therefore leads to a significant underestimate in the true incidence of PPOI. Vather *et al* (2013) conducted a systematic review and global survery to clarify the terminology and definition of POI and PPOI.[2] The most common definitions of POI involved absence of flatus or stool, and the most common criteria for resolution of POI were passage of flatus (68% responders) and tolerance of diet (61% responders).[2] The most common criteria for prolonged postoperative ileus were inability to tolerate oral diet (82%) and absence of flatus (71%).[2] Interestingly, only 77% of international experts were able to provide a definition for PPOI in this study.[2] POI was defined as time until tolerance of diet and passage or flatus or stool, and should occur before day 4 postoperatively.[2] Based on an international survey, Vather *et al* (2013) defined PPOI as 2 or more of the following criteria on or after postoperative day 4 without prior resolution

of POI: nausea or vomiting, inability to tolerate oral diet over 24 hours (<25% of preoperative meal volume), absence of flatus over 24 hours, abdominal distension, radiological confirmation of ileus.[2]

Venara *et al* (2017) further sought to refine the definition of POI based on a DELPHI survey including 22 different international contributors.[18] Their hypothesis was that a specific cut-off day for PPOI was not required, and that PPOI should be graded instead on the outcome for the patient. They used the definition described by Vather *et al* (2013),[2] but it was assessed on each postoperative day instead of postoperative day 4. POI resolution was defined as tolerance of diet (the ability to eat half of a hospital meal) and passage of stool (time until GI-2). Venara defined the following grades of POI: A- no consequence, B- symptomatic measures required only (antiemetics, prokinetics, decreased meals), C- NGT insertion or readmission, D- severe consequences (such as pneumonia, atrial fibrillation, intensive care unit admission), E- death.[18] The conclusions that we can draw from this research are that POI and PPOI lie on a spectrum. Venara *et al* (2017) attributed grades A and B of POI as causing minimal impact on the patient's postoperative recovery, and grade C and above as causing a more significant impact. Similarly, based on international consensus, Vather *et al* (2013) described postoperative day 4 as a cut-off for when POI becomes PPOI. The implications of these 2 conclusions are the same: after a point, POI (or PPOI) becomes a burden for the patient and a pathological process, rather than just a physiological process.

Recently, some authors have sought to define POI and PPOI as a spectrum of symptoms that can be factored into a prospective scoring system, such as the I-FEED model of ileus.[25] The I-FEED score rates patient symptoms such as oral intake (tolerance or intolerance), levels of nausea, vomiting, abdominal distension and the duration of symptoms (0-24 hours, 24-72 hours, or >72 hours), in order to triage patients postoperatively into groups.[25] The proposed implication of this score is that patients with high scores (>=6/15) should be managed as per patients who satisfy a definition of PPOI (NGT insertion and IV fluids), and those with moderate scores (3-5) can be managed less intensely with a clear liquid diet and anti-emetics.[25] A number of other techniques have been employed to characterise the clinical and physiological changes that occur with POI. Scoring systems, such as the Gastroparesis Cardinal Symptom Index (GCSI) have been designed and validated as tools to measure patient-reported symptoms of gastroparesis.[26, 27] The GCSI has been used recently to assess postoperative levels of gastroparesis after upper GI surgery for delayed gastric emptying,[28, 29] and it may be an effective score to characterise postoperative changes in gastric function relating to POI. Researchers have also employed

smart pill systems and automated bowel sound detectors as possible means to detect or define POI, with limited success.[30-32]

Currently, POI and PPOI is defined based on clinical outcome measures, and how they are defined has a signifciant impact on the burden of POI for both patients and the healthcare system. The focus of this chapter is do demonstrate the impact, prediction, treatment and prevention of PPOI (the pathological form of POI), and therefore we will reference PPOI alone in this thesis. The next section will discuss the incidence of PPOI and highlight its association with the definition used.

1.2 The burden of PPOI

1.2.1 Incidence

PPOI is incredibly common. However, there is significant variability in the rate of PPOI reported in the literature, with incidences suggested between 3-32% after colorectal surgery.[18, 19, 33-36] A meta-analysis on the incidence of PPOI after colorectal surgery assessed 54 studies, and found a rate of PPOI of around 10% across observational studies and randomized control trials.[16] Amongst the included studies the majority defined PPOI as requirement for NGT insertion,[16] which we have shown leads to an underestimate of the true rate of PPOI. Much of our understanding PPOI incidence relies on large observational, retrospective series that use clinical coding data.[10] This is inherently prone to bias, and underestimates the problem. Large retrospective series reporting clinical coding data for POI demonstrate rates of 4.1-19.2%.[12, 37] Furthermore, clinical coding data is unable to provide the exact definition of PPOI used.

There is a large difference in PPOI rates based on whether data is collected retrospectively compared to prospectively. An estimated PPOI rate of 8.5% was described by Delaney *et al* (2006).[12] When prospective trials report PPOI rates, the incidence is significantly higher. NGT insertion of 15.9-23.1% have been reported in recent prospective series.[18, 21, 33, 38] One study showed that only 68% of patients with PPOI required a NGT insertion,[39] which means the true PPOI incidence in these series could be between 30-35%. The incidence of PPOI may be lower in some ERAS cohorts (down to 8.6% in once series),[40] or up to 38.4% in series reporting on open colorectal surgery.[18, 41]

The definition used to define PPOI is integral to describing its incidence postoperatively. When PPOI rates after ileostomy closure were described in a recent systematic review, the

more robust the definition of PPOI used, the higher the reported PPOI incidence.[42] The reported incidence of PPOI between studies that used a pre-defined definition and those that did not was doubled: 12.5% compared to 6.7% respectively.[42] Furthermore, only 8 out of the 67 studies identified in this systematic review were deemed to use a robust definition of POI.[42] Vather *et al* (2015) applied their strict and prospective definition of PPOI, based on international consensus, to a cohort of 327 patients who underwent elective colorectal surgery at a tertiary referral hospital in New Zealand and found a rate of PPOI of 26.9%.[43] We believe that this is a true estimate of the incidence of PPOI after elective colorectal surgery, making PPOI one of the most common complications that patients suffer after bowel resection and stoma reversal.

1.2.2 PPOI increases postoperative complications

Patients with PPOI suffer nausea and vomiting, abdominal bloating, reduced mobility and have a significantly worse quality of life. PPOI significantly prolongs patient length of stay, which may be double that of those who recover normally, an additional 4-9 days of inpatient stay.[6, 12, 33, 37, 44, 45] In a large retrospective series, PPOI was directly attributed to a 29% increase in hospital length of stay on multivariate analysis, even when adjusting for other postoperative complications and risk factors.[37] In addition, patients with PPOI were much less likely to be discharged home, rather than to another health institution or home healthcare facility, and were much more likely to be readmitted to hospital within 30 days.[37]

In addition to prolonged length of stay, PPOI also increases the rate of other postoperative complications, reoperation, and mortality.[44] Mortality rates are increased 4 fold in patients with PPOI, and 59% of patients with PPOI develop at least one other adverse outcome.[44] A large multicenter retrospective review by Scarborough *et al* (2017) of 26,682 patients who underwent colectomy found that patients who developed PPOI (11.8%) had a relative risk of end-organ dysfunction of 3.8 (95% CI 3.23-4.45) and a relative risk of 2.57 (95% CI 1.94-3.41) for mortality within 30 days.[46] Aside from anastomotic leak, ileus, bleeding and pneumonia made up the largest contributing factors to poor patient outcomes.[46] PPOI was attributable to 32% of end-organ dysfunction post colectomy, 22.6% of 30-day mortality, 25.6% of the prolonged length of stay and 10.9% of the hospital readmissions.[46] Another series found that the rate of other postoperative complications for patients with PPOI was 50%, compared to 21% for those who didn't develop PPOI, and they had a 17% readmission rate compared to 9%.[44] For example, the risk of postoperative DVT is up to 7 fold greater in patients with PPOI (7.1% vs 1.1%, p=0.026, Odds Ratio (OR) 7.06).[20] The overall

postoperative complication rate for patients with PPOI is approximately doubled (54.8% compared to 32.4% after abdominal surgery), as is the risk of additional major complications (23.3% compared to 12.2%).[45] 30-day readmission rates after elective colorectal surgery were 3.6% in patients with PPOI but only 0.2% in patients without PPOI.[12]

PPOI therefore affects patients at all levels of their inpatient hospital stay and their postoperative course as well. For patients, the implications of double the risk of complications and double the inpatient stay is a significant burden. This burden is also carried by the healthcare system, through increased medical staff time, investigations, treatments, and prolonged patient stay leads to bed shortages in hospital.

1.2.3 The economic burden of PPOI

It makes sense, therefore, that PPOI places a significant financial drain on the healthcare system worldwide. In the USA alone, healthcare costs attributed to PPOI are estimated to be between Costs attributed $1.14-$1.5 billion per year.[6, 12] It was estimated that PPOI accounts for 6.24% of all health costs in the USA.[47] Goldstein *et al* (2007) retrospectively assessed the economic burden of patients coded as having PPOI across 160 US hospitals over a single year (2002), and included patients undergoing laparotomy, endoscopic procedures, orthopaedic, thoracic and non-abdominal surgery.[6] They found that patients coded as having PPOI cost twice as much to the healthcare system (US $18,877 vs $9,460).[6] They found that 91% of the increased cost was directly related to the costs of inpatient postoperative stay.[6]

Subsequent studies on the economic impact of PPOI in colorectal patient cohorts show similar results. Iyer *et al* (2009) found a mean hospitalization cost of US $25,089 for patients with PPOI compared to $16,907 following colectomy ($p<0.001$).[37] Research by Asgeirsson *et al* (2010) confirmed earlier findings that PPOI doubles the cost of hospital care after colectomy (US $16,612 vs. $ 8,316).[48] US Medicare data would suggest that 161,000 patients undergo major intestinal surgery per year which translates to 1.8 million patients days in hospital and an estimated yearly cost of US 1.75 billion.[49] The burden of PPOI persists after discharge for many patients, with signfiicantly reduced quality of life scores reported by patients who develop POI compared to those who don’t, even for those who had PPOI as their sole postoperative complication.[50] The financial burden of PPOI persists after discharge, and estimates of the overall healthcare and societal costs at 3 months postoperatively were 38.47% higher for patients with PPOI.[50]

If approximately 20-25% of patients develop PPOI after elective colorectal surgery, and cost twice as much to the healthcare system, that places a phenomenal burden on the health sector. An important limitation to the data presented is that it largely relies on retrospective review, using clinical coding data. This introduces significant bias and uncertainty in the true cost of PPOI. An accurate portrayal of the costs of PPOI, therefore, requires prospectively collected patient data and the use of a standardized PPOI definition.

1.2.4 Complications postoperatively and the consequences

There is some evidence that postoperative complications lead to poorer long term oncological and survival outcomes after surgery for colorectal cancer. An analysis of postoperative complication severity, using the Clavien-Dindo grading system for complications,[51] showed that any major complication postoperatively (grade 3 of higher) led to poorer long term disease-specific survival.[52] Certainly, infective complications, which can be increased in PPOI, impaired overall and disease-free survival in one series.[53] There is an interaction between PPOI and anastomotic leak after bowel resection that is not fully understood,[34] and further research is required to determine whether patient outcomes longer than 30 days postoperatively are impacted by PPOI.

1.2.5 Summary

PPOI is one of the most common complications to occur after elective colorectal surgery and it leads to signficiant patient morbidity and financial strain on our healthcare system. Research into PPOI prediction, prevention and treatment is a prioroty target for international healthcare institutions.[7] The use of a strict and prospective definition of PPOI actually leads to an increase in its incidence, and the majority of what we understand about PPOI risk factors and burden is based on historic data that relies on clinical coding, a system prone to significant bias. In order to understand how we can develop future treatments or preventative measures for PPOI, we must understand the pathophysiology of PPOI development. The following section will cover what we currently understand to be the mechanisms behind PPOI in animal and human models.

1.3 Ileus pathophysiology

The concept of “postoperative ileus” has been around since the 1970s,[54] however the mechanism of its action has only recently become a target of research. It is important to understand that a degree of intestinal dysmotility due to surgery is inevitable and is

considered normal. The majority of what we understand about the pathophysiology of ileus is based upon animal models, and there is little human data to correlate to findings in animal models. Observations on changes in intestinal motility in animal models focus on the normal intestinal response to surgery, and this will be referred to as “ileus”. There is limited data from animal models on what happens in the gastrointestinal tract in states of PPOI. Ileus and PPOI likely exist on a spectrum, and share a common pathophysiological process, but in PPOI that process is markedly increased and prolonged. Nevertheless, our understanding of how ileus develops in rats and mice has formed the physiological basis for all current ileus interventions. The physiological period of ileus begins at the time of opening of the peritoneal cavity, and with intestinal manipulation.[1] There are two distinct phases to postoperative ileus, the early neurogenic phase, and the late inflammatory phase.[5, 8] There is emerging evidence that a third phase of ileus, involving neuronal signaling, plays an important role in the prolongation of ileus. The pathophysiology of ileus and how it relates to PPOI will be discussed below.

1.3.1 Early neurogenic phase

The neurogenic phase of ileus likely involves adrenergic and non-adrenergic inhibitory reflexes.[55] These reflexes are stimulated by noxious cutaneous signals,[56] and by incision through the peritoneum.[5] Activated adrenergic and noradrenergic pathways act via a spinal reflex loop that travel along afferent and efferent splanchnic nerves.[5] The sympathetic nervous system (SNS) is thought to be the primary source of adrenergic signaling in the early phase of ileus,[57] and noradrenaline release directly inhibits the motor function of enteric neurons via presynaptic alpha-2 adrenergic receptors.[12, 55] SNS fibers from the thoracic and lumbar cord (levels T5-L2) reach the gastrointestinal tract via splanchnic nerves. Signaling via spinal reflex loops also leads to release of nitric oxide (NO), somatostatin, glucagon and gastric inhibitory polypeptide (GIP) that immediately reduce gut motility.[12] Animal studies show that plasma and tissue catecholamine levels return to normal prior to return of gut function, which makes catecholamines the likely initiator for the early phase of ileus.[12] Furthermore, depletion of adrenergic neurons prior to intestinal manipulation ameliorates the early phase of ileus in mice,[1] as does splanchnicectomy (division of the splanchnic nerves).[56] In a rodent model of ileus, the use of guanethidine (a non-selective adrenergic blocking agent) and yohimbine (a selective alpha-2 adrenergic receptor antagonist) led to improved colonic motility in rats who underwent laparotomy and intestinal manipulation.[58] Interestingly, beta-adrenergic blockade by propranolol did not improve postoperative gut motility in this study, nor did direct nicotinic receptor blockade using hexamethonium.[58] Non-adrenergic pathways, including the vagus nerve, also play a

role.[5] In the early phase of ileus, the vagus nerve may act to inhibit gut motility as well by releasing NO and vasoactive intestinal peptide (VIP) that inhibit enteric neurons.[1]

This initial neural effect on gut transit is short lived, and only lasts for 30-90mins after the onset of surgery.[1] However, the degree of gut dysmotility depends on the degree of surgical insult. In addition to spinal reflexes involving sympathetic neurons, the early neurogenic phase of ileus may also involve supraspinal hypothalamic and ponto-medullary pathways that are affected by corticotrophin-releasing hormone activity.[1] These supraspinal, high-threshold, adrenergic pathways are only activated by more noxious stimulation to the gut, further impairing gut motility.[59] In animals, caecal manipulation results in the release of corticotropin-releasing factor in the hypothalamus and dorsal vagal complex, which inhibits gastrointestinal motility via vagal and SNS pathways.[12] Current theory suggests that the neurally-mediated phase of ileus should resolve once the nociceptive triggers are gone.[1] The early phase of ileus can be impacted by anaesthetic drugs, but this effect is considered short lived.[1] However, when intensely activated, afferent neurons release pro-inflammatory neuropeptides, such as substance P and calcitonin gene-related peptide.[59] Release of these pro-inflammatory mediators due to a severe surgical insult starts a cascade of inflammation that leads to a prolonged phase of ileus, and involves complicated immune cell interactions. The following phase is termed the “late inflammatory phase” and is discussed below.

1.3.2 Late inflammatory phase

After the initial phase of ileus, induced by intestinal manipulation, gut motility returns to normal for up to 3-6 hours.[60] However, there is a second phase of ileus that develops, that may last more than 24 hours.[60] Early research found that the duration of this second phase of ileus was related to the site of surgery: colonic resection in dogs and sheep led to a shorter period of dysmotility (6 hours) than small bowel resection (48-72 hours).[60] When first reported in 1978, the cause of this delayed second phase of ileus was unclear. Subsequently, researchers have discovered that the delayed phase of ileus is related to intestinal inflammation. The current theory is that PPOI is a manifestation of a significantly prolonged inflammatory phase of ileus. The inflammatory response of the gut to surgery relies on a complex interplay between neuronal mechanisms, the innate and the adaptive immune system. Intestinal immune cells are designed to detect markers of damage or infection, as part of the innate immune system. They detect pathogen-associated molecular patterns (PAMPs) such a lipopolysaccharide (LPS), and damage-associated molecular patterns (DAMPs) such as ATP or uric acid.[61, 62] Immune cells express toll-like receptors

that bind PAMPs and DAMPs, which leads to the initiation of the inflammatory cascade.[62] The key mediators of this inflammatory response are resident intestinal macrophages, dendritic cells, and mast cells.[63-66] There are 3 likely triggers to the inflammatory response to surgery: intestinal mucosal barrier dysfunction leading to translocation of bacteria (or LPS) into the gut wall and lymph, surgical trauma leading to release of DAMPs (damage-associated molecular patterns) from damaged cells into the extracellular space, and mechanosensation (i.e. a direct response of intestinal immune cells to intestinal manipulation via mechanosensitive ion channels).[66] The exact timing of when individual mediators of ileus play their role is unclear, but they appear to act synergistically in ileus development.

1.3.3 The role of mast cells

Mast cells play an integral role in the development of ileus. Mast cells in the gut are intimately related to blood vessels and enteric afferent neurons, within the mesentery and serosa.[66] Mast cells degranulate in response to triggers induced by intestinal manipulation or injury. One such trigger is substance P,[14] which is directly released by enteric neurons in response to prolonged stimulation.[59] When activated, mast cells release proinflammatory mediators such as histamine, tryptase, TNF-α, cytokines and proteases.[12, 65]

The response is rapid, and mast cell mediators can be detected immediately in the peritoneal fluid of patients undergoing abdominal surgery.[65] These mediators act locally and also spread throughout the intestine via mesenteric vessels.[67, 68] The action of mast cell degranulation is pan-intestinal.[68] The net effect of mast cell degranulation is an immediate increase in gut mucosal permeability, phagocyte infiltration and increased gut lymphatic flow.[67] One hypothesis is that resident gut bacteria also translocate into the gut muscularis as a response to surgical trauma, and increased mucosal permeability, and act synergistically with the body's inflammatory response to promote ileus.[67] Animal models demonstrate the importance of mast cells in the inflammatory phase of ileus. Preoperative mast cell stabilization in animal models reduced the expected delay in postoperative gastric emptying using ketotifen fumarate.[64, 69] Furthermore, mice deficient in mast cells do not demonstrate impaired epithelial barrier function due to intestinal manipulation.[8] Again, the degree of inflammation seems proportional to the degree of surgical insult. Mast cell degranulation much less after cholecystectomy than after colectomy,[9] and is believed to be significantly less after laparoscopic surgery.[65] Increased mucosal permeability may then

lead to exposure of resident innate immune cells in the gut muscularis to bacterial related PAMPs, causing further immune cell activation.

1.3.4 The role of intestinal macrophages and dendritic cells

Dendritic cells form part of the innate immune system of the gut, and act as antigen presenting cells (APCs). Resident macrophages lie within the myenteric plexus (within the muscularis) and within the serosa of the gut and detect bacteria-related ligands such as lipopolysaccharide.[70, 71] Intestinal macrophages express Toll-like receptors that bind to bacterial cell wall components.[59] Enteric macrophages and dendritic cells are normally quiescent, but when activated (by factors such as intestinal manipulation) they start an inflammatory cascade that begins around 3-4 hours after the onset of surgery.[1, 61, 72] Early animal studies showed that surgical manipulation leads to activation of resident macrophages,[61, 70, 72] and upregulation of iNOS (inducible nitric oxide synthase) and COX-2.[73] Induction of iNOS leads to reduced intestinal motility in rat models of ileus.[74] More recent evidence suggests that resident dendritic cells are probably the first cells in the gut to identify and present antigens associated with surgical trauma.[66] Activated intestinal dendritic cells release IL-12, activating resident macrophages, and stimulate T-helper cells (Th1) to release IFN-gamma, which further potently stimulates macrophages.[75] Mast cells, macrophages and dendritic cells likely act synergistically in the early inflammatory phase of ileus.

The resulting inflammatory profile from macrophage activation is similar between animal models and in human studies: predominantly upregulation of cyclo-oxygenase 2 (COX-2), IL6, and iNOS)[69, 72] Sections of human small bowel taken during laparotomy show that within 1 hour of incision, the gut muscularis is infiltrated densely with resident macrophages.[76] Macrophages are also found in large numbers around mesenteric vessels, in an inactive state, but become progressively more activated during the course of surgery.[76] Activated macrophages release proinflammatory cytokines (IL-1b, IL-6, TNF-α) and chemokines to attract circulating leukocytes.[1, 12, 65, 77] Activated macrophages also induce expression of adhesion molecules such as ICAM-1, which leads to further leukocyte recruitment into the gut wall.[78] Leukocyte infiltration in the muscularis continues from 3 hours post onset of surgery to a peak at 24 hours.[61, 78] Inflamed intestinal tissue demonstrates impaired motility, though the exact mechanism for this is unclear. The magnitude of the inflammatory response is thought to be related to the duration and magnitude of surgery.[1] Human studies show higher levels of plasma IL-1b, IL-6 and IL-8 after open abdominal surgery compared to laparoscopic surgery.[79] Increased COX-2

expression in animals models of ileus leads to reduced smooth muscle contractility.[80] The effect of intestinal manipulation on gut motility was lessened in COX-2 knockout mice,[80, 81] and pharmaceutical COX-2 inhibition also lessens the degree of ileus.[61, 67, 69, 80, 81] The importance of leucocyte infiltration was demonstrated by studies that showed blockage of white-cell adhesion molecules prevented impaired gut motility induced by intestinal manipulation.[12, 61, 64, 69, 82] Finally, the adaptive immune response becomes activated. This occurs due to the direct activation of Th1 cells by enteric dendritic cells.[66] Th1 cells propagate throughout the entire gastrointestinal tract and activate further immune cells to continue to process of intestinal inflammation, and they are found in the circulation within 1 hour of patients undergoing abdominal surgery.[75]

1.3.5 Opioids in ileus

Opiates act on several specific receptors throughout the gut. Stimulation of peripheral mu-opioid receptors in the gut reduces ACh secretion and leads to disorganized gastrointestinal motility.[59, 83] Mu-opioid receptors are expressed throughout the whole gastrointestinal tract, most commonly in the small intestine.[84] Human studies show that morphine results in short, non-migrating clusters of colonic activity.[85] Interestingly, the disorganized colonic motility in response to morphine was only seen from postoperative day 3 onwards, and not in the earlier postoperative period.[85] Opiates are not only exogenous (administered to the patient). Endogenous opioids are actually produced as part of the stress response to surgery.[12] Opioids may potentiate NO synthase induction and this may increase NO release from phagocytes, which impairs gastrointestinal motility and plays a role in the initiation of the inflammatory phase of ileus.[12] Opioids therefore may act as an exacerbating factor in the pathophysiology of ileus.

1.3.6 Pan-intestinal inflammation and dysmotility

Pan-intestinal dysmotility caused by localized surgical trauma is referred to as the “GI field effect”.[8, 59] Ileus is characterized by the pan-intestinal upregulation of inflammatory mediators.[67, 68, 86] In animals, selective jejunal manipulation in rats leads to widespread intestinal hypomotility, and increase in IL-6, cyclooxygenase-2 (COX-2) and TNF-α production across the whole intestinal tract.[47] Surgical specimens taken at time of small bowel resection in patients who required a reoperation within 24-48 hours postoperatively show significantly diminished contractile ability and reduced responsiveness to muscarinic stimulation.[76] Inflammatory mediators such as NO (produced by macrophages) or LPS from bacterial translocation lead to impaired gut motility.[71, 73] Until recently, this pan-

intestinal prolonged inflammatory response was thought to be solely related to immune cell activation. However, current evidence suggests that neural pathways in the gut once again become involved, and trigger the wide-spread changes in gut motility characterized by PPOI.[64, 81, 87, 88] In fact, prolonged bowel handling leads to increased activity in the specific areas of the brain, such as the nucleus of the solitary tract and in the area postrema, the so-called “vomiting center” of the brain.[79, 87] In mice, inflammatory-mediated impaired smooth muscle contraction lasts for 3 days after surgery, then returns to normal.[88] However, for up to 10 days postoperatively in mice, enteric neurons demonstrate reduced responsiveness to stimulation and reduced expression of cholinergic and NO receptors.[88] There are structural changes in spinal afferent neurons in response to intestinal manipulation, including increased expression of the proto-oncogene Fos.[81] These neuronal alterations are not seen in animal models of ileus where only minimal bowel handling has occurred.[81] Interestingly, these neuronal structural changes may be blocked by COX-2 inhibition.[81, 87] The role of pan-intestinal inflammation and neurological dysfunction certainty leads to a significant alteration in intestinal motility. The following figure 1-1 is from Wells *et al* (2022), adapted from Vather 2014, and provides an overview of the complicated mechanisms at play in the development of PPOI, reproduced with permission.[4, 89]

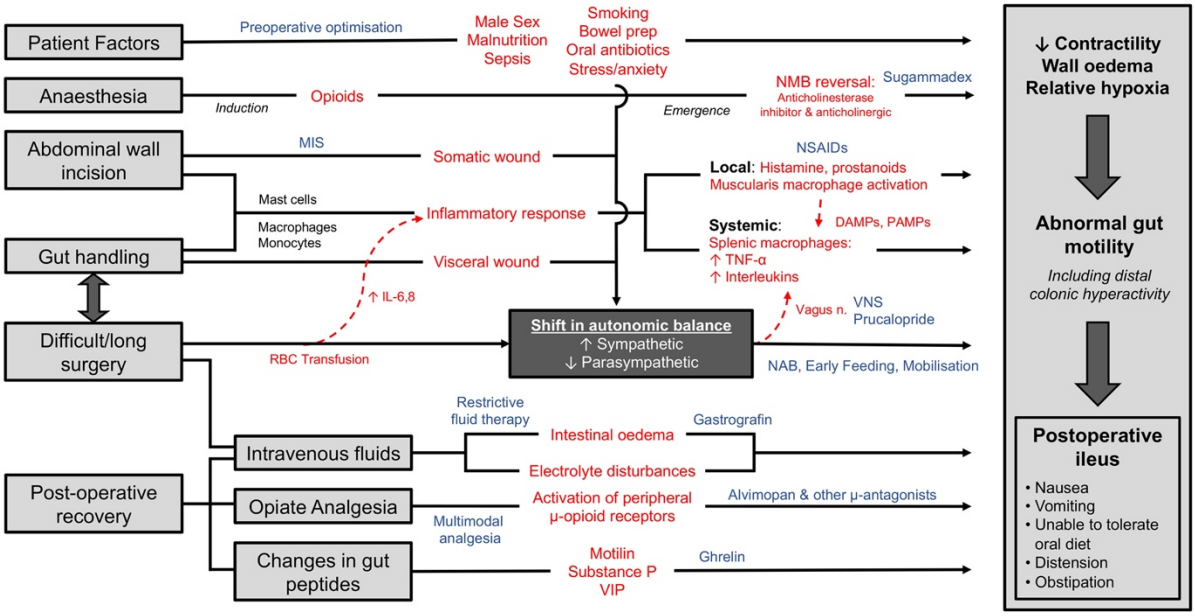

Figure 1-1: Pathophysiological mechanisms of PPOI

1.3.7 Motor patterns associated with ileus

Researchers initially suspected that the motility patterns of ileus and PPOI solely involve a reduction in motor activity, however, it is more complicated than that. We will now explore the evidence for how gut motility changes postoperatively. As explained, much of what we understand about postoperative gut dysmotility comes from animal models and in vitro studies. These studies show reduced gut motility and reduced intestinal smooth muscle contractility in the postoperative period. Recently, use of manometry techniques has shed more light onto the true, in vivo, patterns of gut motility in the postoperative period. Postoperative colonic manometry actually shows that motor and electrical activity persists after surgery, but it is abnormal and disorganized.[90] Low-resolution manometry, combined with pressure monitoring using barostats, shows an increased colonic motility index and increased colonic tone in patients after left-sided colonic resection, not a decrease in tone as would be expected.[91] Colonic tone actually increases across postoperative days 1-3.[91] Studies that used high-resolution colonic manometry after right hemicolectomy show that surgery may actually increase cyclical motor activity in the distal colon for at least 16 hours postoperatively.[90, 92]

Clinical studies certainly demonstrate a difference in gut recovery for patients who undergo right versus left sided colonic resection: right hemicolectomy leads to increased rates of PPOI compared to left sided resections, and a significantly slower recovery of GI-2 in those who do not develop PPOI.[42, 93] A recent systematic review found that the OR for PPOI in right hemicolectomy was 1.78 (95% CI 1.32-2.39) compared to left hemicolectomy, although the mechanism for this is not understood.[94] Left-sided colonic cyclical motor patterns actually propagate in a retrograde fashion, and it is hypothesized that this increase in cyclical motor activity in the rectosigmoid region results in a “brake” on colonic motor propagation.[95, 96] The implications of the “rectosigmoid brake” on postoperative recovery are uncertain, but may lead to new targets for PPOI treatment and prevention in the future.[97] Studies using prolonged manometry show a gradual recovery of normal colonic motor activity over 3-6 days, with recovery in the proximal colon first and then distal colon last.[90] However, these studies are based solely on low-resolution manometry techniques, which have been shown to significantly misinterpret true motility patterns in the colon.[98]

1.3.8 Resolution of PPOI

PPOI eventually resolves. It is proposed that an increase in vagus nerve activity after surgery reduces intestinal inflammation and eventually restores normal intestinal motility.

This is referred to as the “resolution phase” of ileus.[57] The nicotinic alpha-7 acetylcholine receptor (a7AChR) plays a key role in this vagus-mediated anti-inflammatory pathway, and will be discussed later in this review.[57, 66] Vagal nerve activity, and release of ACh, actually inhibits intestinal macrophages via activation of the Jak2-STAT3 transcription factor pathway.[77] The vagus nerve acts via an intermediate neuronal signaling pathway of enteric neurons in the muscularis of the gut, that in turn inhibit resident macrophage activation.[99] Direct stimulation of enteric neurons using electrical field stimulation directly inhibits intestinal macrophage activation.[99] Anti-inflammatory mediators such as IL-10 may play a role in reducing the effects of ileus.[66] Mice with IL-10 deficiency have an increased inflammatory response to intestinal manipulation and higher levels of IL-6, IL-12, NO and prostaglandin release.[100] In one study, recombinant IL-10 in mice led to a significant reduction in postoperative gut inflammation, and restored jejunal smooth muscle contractility in response to manipulation.[100] The resolution phase of ileus may be impacted by lipid mediators called resolvins.[101] Resolvins are produced by infiltrating monocytes, and lead to increased production of protectins, and return of gut motility.[101]

1.3.9 Conclusion

The pathophysiology of ileus is complicated. There are several key mediators to ileus development that could be amenable to targeted interventions, such as COX inhibition, stimulation of the vagus (parasympathetic) nerve, and antagonism of the effects of opioids on the gut. As stated previously, an important limitation to our understanding of the pathophysiology of ileus is that our understanding of the complex interplay between neuronal and inflammatory mediators are based on animal models.[59] Animal models are, in turn, based on standardized protocols of intestinal manipulation, and not on actual bowel resection, anastomosis or stoma reversal.[59] Animal models of ileus behave in a standardized way, and there is no ability to categorize animals into “ileus” and “PPOI” groups. Ileus is considered normal after bowel surgery in animals and humans, but PPOI is not. The implication, therefore, is that we assume PPOI is a prolonged, or more pronounced, manifestation of ileus that occurs in some patients. This may not be the case. We will now consider risk factors for PPOI and explore PPOI prediction.

1.4 Ileus risk factors

There are multiple risk factors for PPOI. Understanding these risk factors, and how me might mitigate them, may help develop better preventative strategies for PPOI, or highlight areas targets for future prevention of treatment. Risk factors can be separated into

preoperative/patient factors, intraoperative/surgical factors, and postoperative/patient care factors. This section will summarize our current understanding of risk factors for PPOI.

1.4.1 Preoperative factors

There are multiple preoperative "patient" factors that are associated with an increase in rate of PPOI. Male sex is the most commonly reported PPOI risk factors across a number of studies, although the mechanism for this is unclear.[35, 37, 38, 43, 102-104] The OR for PPOI in males is 2.2 compared to females.[33] One study reported a PPOI rate in males as around 50% higher than females (31.9% males vs. 20.4% females).[43] Higher patient comorbidity increases the risk of PPOI: presence of peripheral vascular disease, cardiac, renal and respiratory disease all increase the risk of PPOI.[43, 102] Patient comorbidity can be categorized based on the American Society of Anaesthesiologists (ASA) classification system,[105] and any patient with severe systematic disease (ASA grade 3+) has a higher risk of PPOI.[18, 43, 102, 103, 106] Elevated body-mass index (a measure of obesity) also increases PPOI risk.[43, 106, 107] Elderly patients (defined by some as age >70 years old) have a higher risk of developing PPOI in some series,[38, 42, 103, 106] however, this finding is not consistently agreed upon in the literature.[15, 43] Furthermore, studies infrequently report an age cut-off for what is considered elderly. Relatively few studies report on ethnic differences in rates of PPOI, with one series showing no difference,[43] and another found European patients to be at a higher risk.[108]

Interestingly, preoperative psychiatric illness and use of antidepressants or antipsychotics are independent predictors of POI, although the mechanism for this is unclear.[109] Similarly, chronic preoperative use of opiates has been shown to increase PPOI rates, in particular daily usage of opiates for the 30 days prior to admission.[20] Acute operations have a higher risk of PPOI,[37, 102] especially if patients have preoperative septic complications.[103] There may be a higher risk of PPOI in patients who have undergone previous abdominal surgery.[20] Low preoperative albumin has been suggested as a risk factor for PPOI, although studies have reported significant variations in threshold values of albumin. Preoperative albumin of less than between 34g/L and 39g/L are risk factors for PPOI.[20, 43, 103, 110] of particular note, normal values for serum albumin range from 3.4-5.4g/L and Hypoalbuminaemia is classically defined as $\leq$30g/L,[111, 112] which means that even modest hypoalbuminaemia or a "normal" albumin level may still predispose a patient to developing PPOI.[113] Preoperative malnutrition is a marker of increased patient morbidity and length of stay after colorectal surgery.[114] However, the role of albumin as a marker of

nutrition is uncertain, and low albumin levels are likely a reflection of a degree of chronic inflammation in patients who undergo surgery.[115, 116] There is currently no evidence for preoperative correction of albumin leading to improved patient outcomes. Smoking is a risk factor for PPOI,[45, 103, 106] as is COPD.[107] When the above risk factors are considered, there are relatively few that are correctable. Smoking and BMI are perhaps the only risk factors that are amenable to change in the preoperative period, but in oncological surgery there is often insufficient time to allow patients meaningful changes to preoperative weight.

1.4.2 Operative factors

It is often said that the magnitude of surgery affects the resulting degree of PPOI. Intraoperative decisions, techniques and complications can predispose patients to develop PPOI. Colorectal surgery is much more likely to lead to PPOI development than other forms of abdominal surgery.[45] Open surgery compared to laparoscopic surgery has a much higher incidence of PPOI, including when laparoscopic procedures are converted to open.[18, 38, 43, 45, 104, 106, 117] The proposed mechanism is that open surgery leads to a greater degree of postoperative inflammation than laparoscopic surgery.[8, 79, 118-120] Wolthius *et al*, in 2 separate series, found a significant difference in the incidence of PPOI between patients who had laparoscopic vs open surgery (5.8-7.4% vs 12.4-24.1% respectively, p=0.007).[16, 33] A subsequent study by the same group found an OR of 4.3 for PPOI in patients who underwent open surgery, and an OR of 6.2 for patients who had a laparoscopic converted to open procedure.[33] The type of operation impacts the risk of PPOI, with higher rates in patients who undergo right hemicolectomy, total colectomy, reversal Hartmann's, end ileostomy formation compared to other procedures.[43, 106] Right sided colonic resections may prolong gastrointestinal recovery compared to left-sided resections,[21, 93] and in particular, the length of right hemicolectomy specimen correlates with the degree of delayed gut recovery.[93] Stoma formation increases risk of ileus in retrospective series.[35, 102, 117] After open rectal surgery, patients who had a defunctioning ileostomy were significantly more likely to develop POI with an OR of 4.96 (95% CI 1.02-24.03).[117]

A more difficult operation leads to prolonged operative time and more bowel handling. Surgeon-perceived operative difficulty increased the risk of PPOI in one series,[43] and the degree of bowel handling,[43] duration of operation (in particular operations longer than 180 minutes),[16, 102, 103, 108] and length of wound have all been reported as PPOI risk factors.[43, 45] Perioperative transfusion is a risk factor for PPOI,[102] and intraoperative blood loss >500mL also increases it incidence.[15, 45, 121, 122] A meta-analysis of

perioperative blood transfusion administration showed that blood transfusion leads to worse postoperative outcomes, and poorer patient cancer-specific and overall survival.[123] The exact mechanism for how perioperative transfusion increases PPOI rates is unclear, but may be related to an increase in systemic inflammation due to transfused blood products.[123] Interestingly, a large RCT published in the Lancet, showed no reduction in requirement for intraoperative blood transfusion for anaemic patients undergoing major abdominal surgery, allocated to preoperative iron infusion or placebo.[124] Patients with spinal and epidural regional anaesthesia had a higher incidence of PPOI in one study,[121] but this was not seen on multivariate analysis which means that epidurals may have been used more readily in patients already at high risk of PPOI (such as elderly patients undergoing open surgery).[43] Intraoperative fluid administration correlates with PPOI risk. One study found non-compliance with strict intraoperative IV fluid protocols was a predictor of PPOI.[121] The recommended intraoperative fluid volume replacement was defined as 3mL/kg/hr for laparoscopic surgery and 5mL/kg/hr for open surgery in this study.[121] Furthermore, patients who received more than 3L of intraoperative fluid are much more likely to develop PPOI.[125]

Aside from preferential use of laparoscopic surgery, and careful management of the volume of intraoperative IV fluid given, there are few modifiable risk factors for PPOI in the intraoperative period. The role of intraoperative risk factors is largely in predicting patients who have a high risk for developing PPOI.

1.4.3 Postoperative factors

Postoperative risk factors for PPOI are likely the most easily modifiable, and accounting for them is often part of a standard ERAS protocol. Higher doses of postoperative IV fluid in the first 3 days after surgery increases the risk of PPOI with an OR of 1.55 per liter of crystalloid given.[43] Postoperative weight gain is usually attributed to the volume of IV fluid given, and patients who gain more than 2.5kg by postoperative day 2 had an OR of 1.82 (95% CI 1.02-3.52) for PPOI.[126] Postoperative weight gain of >2.5kg on postoperative day 2 was found to be an independent predictor of PPOI on multivariate analysis.[125] Similar to intraoperative transfusion, postoperative blood transfusion leads to delayed gut motility,[43] as does delayed day of first mobilization (inability to mobilize on postoperative day 1).[43] Postoperative opioid usage correlates well with incidence of PPOI, with higher dosage of opiate leading to significant delays in return of gut function.[15, 127, 128] Total postoperative opiate dose is a key predictor of delayed return of gut function.[15] A study by Barletta *et al* (2011) of 279 patients undergoing elective colorectal surgery, within an ERAS framework,

showed on multivariate analysis that a dose of opiate equivalent to 2mg hydromorphone per day correlated directly with increased PPOI risk and with prolonged length of stay.[40] The number of postoperative days of opiate usage also significantly correlated with PPOI rates.[40] Postoperative infectious complications, especially intra-abdominal sepsis or anastomotic leak, increase the risk of PPOI.[38, 104]

Therefore, careful use of postoperative IV fluids, restrictive use of postoperative opiates and blood transfusion, and early mobilization are modifiable risk factors for PPOI prevention. As discussed before, the pathophysiology of PPOI likely develops in the intraoperative and early postoperative period. While postoperatively, we can try to minimize the impact of PPOI by encouraging mobilization and reducing the dose of IV fluids and opiates, in real-life practice some patients are unable to mobilize for a myriad of reasons and require larger amounts of opiate due to severe postoperative pain. The most important implication of risk factors for PPOI is to develop accurate ways to predict high-risk patients and target them with either novel treatment strategies for PPOI or preventative strategies or medications. The ability to predict PPOI occurrence will be discussed in the following section. Table 1 summarizes the common risk factors for PPOI.

Table 1-1: Risk factors for PPOI

Preoperative	Intraoperative	Postoperative
Males	Open surgery	IV fluid administration
Patient comorbidity	Type of surgery	Opioid usage
Elderly	Stoma formation	Blood transfusion
Chronic opiate use	Blood transfusion	Delayed mobilization
Low albumin	IV fluid administration	Infectious complications
Smoking		
Sepsis		

1.5 Ileus prediction

The risk factors for PPOI have been well established in the current literature, however translating these risk factors into predictive scores for PPOI is still in its early stages. Kronberg *et al* (2010) found that patients aged 60 years or older, preoperative chronic narcotic use (daily use for at least 30 days preoperatively) and previous abdominal surgery

were independent predictors of PPOI on multivariate analysis.[20] By assigning a score of 1 point to each, patients with 0 risk factors had a risk of POI of 2.7%, 1 point had a risk of 9.4%, 2+ points had a risk of 18.3%.[20] The study focused only on laparoscopic partial colectomy, but used retrospective data collected from a prospectively maintained database. PPOI was defined as "absence of bowel function for 5 or more days" postoperatively or NGT insertion, absence of adequate bowel function was not further defined.[20] All rectal and pelvic surgery was excluded, as were patients who required conversion to open, and there was no reference to an ERAS protocol.[20] This means it is difficult to generalize the results of their study.

Hain *et al* (2018) conducted a retrospective assessment of a prospectively collected database on patients who underwent laparoscopic or converted-to-open colorectal surgery within an ERAS setting.[38] PPOI was defined as NGT insertion due to abdominal distension, nausea and/or vomiting.[38] On multivariate analysis of 428 patients, they found that males, patients aged >70 years old, conversion to open, and intra-abdominal infection were key risk factors for PPOI. If none were present, the overall risk of PPOI was only 5%, but this increased to 11%, 28% and 54% with 1, 2, $\geq$3 risk factors respectively.[38] We know, however, that NGT insertion is prone to underestimate the true incidence of PPOI, and that retrospective studies may be more likely to overestimate risks compared to prospective studies and RCTs.[129]

Rencuzogullari *et al* (2017) published a 10 point nonogram to predict PPOI risk after colectomy.[103] The followiing multivariate risk factors were used: open approach, preoperative albumin <35g/L, sepsis, ASA grade, male sex, oral antibiotic prep preoperatively, type of operation, smoking status and operative time.[103] The nomogram demonstrated a risk prediction of ileus with a concordance rate of 0.687.[103] Patients with all criteria had a risk of PPOI of 80%.[103] This study used a large retrospective review of the US ACS-NSQIP database, comprising 29,201 patients. PPOI was defined by clinical coding, making it less reliable than prospective definitions.

Vather *et al* (2015) devised a simple scoring system for PPOI called the "I-Score" based on prospective data collected from 327 patients who underwent elective colorectal surgery at a single institution. The I-Score comprised a 6-point scoring system with fair predictive capacity for PPOI within an ERAS setting, with an area under the curve (AUC) of 0.742.[43] Importantly, they used a strict definition of PPOI,[2] and the definition was applied prospectively to their patient cohort. The I-Score was calculated immediately postoperatively and comprised the following risk factors, based on multivariate analysis: male gender,

preoperative albumin <34g/L, operative difficulty >=8, open or converted technique, wound size >10cm, and requirement for blood transfusion.[43] Patients with a low risk (score 0-1) had a PPOI incidence of 6.6%, moderate risk (score 2) had an incidence of 26.3% and high risk individuals (score >=3) had a risk of 48.5%, representing a 7 fold increase in PPOI risk between low and high risk groups.[43] This study was the first time that PPOI was pre-defined and applied prospectively to an inclusive cohort of patients who underwent colorectal surgery. Both laparoscopic and open cases were included, and patients were not excluded based on pathology (benign or malignant). Sugawara *et al* (2018) conducted a similar study, using the same definition as Vather *et al* (2013), and analyzed 841 patients who underwent major abdominal surgery in an ERAS setting.[45] They devised a simple nomogram to predict PPOI risk: males, open operations and colorectal surgery were the main factors.[45] Lack of any of these risk factors led to a risk for PPOI of 2.5% and 3 risk factors led to a risk of 19.6%, with an AUC of 0.71 (95% CI 0.66-0.77).[45]

Studies have attempted to determine whether preoperative and postoperative inflammatory marker profiles (in particular using IL-6, TNF-α, and IL-1b) are effective in predicting PPOI.[130] One report found that CRP levels were higher on POD1-4 in patients who developed PPOI, as well as higher levels of IL-6, IL-8 and IL-10 on postoperative days 1-2.[50] However, while elevated inflammatory markers can certainly predict postoperative septic complicatications after colorectal surgery, their role in PPOI prediction has not been determined.[130]

Ultimately, there are a multitude of risk factors for PPOI, but these risk factros are largely based on retrospective data. Our understanding of whether these risk factors are truly causative is unclear. There would be significant clinical utility for an accurate and validated predictive score for PPOI. Such a score must use a robust definition within a contemptorary ERAS cohort, such as the I-Score defined by Vather *et al* (2015).[43] The benefits of accurate PPOI prediction would allow clinicians to better counsel their patients at high-risk of PPOI, initiate early treatment, and allow researchers to design future studies on interventions targetting high-risk patients. Targetted studies on high-risk patients would signifciantly increase the yield and benefit for the patients who need it the most, compared to low-risk patients who will recover quickly anyway. The following section will deal with the current evidence for PPOI prevention, including the aspects of ERAS care and the evidence for targeted medication interventions on PPOI.

1.6 Ileus prevention

There are several strategies to improve postoperative gastrointestinal function and reduce PPOI. These strategies primarily revolve around ERAS principles, such as early oral feeding, minimizing postoperative opioids, early mobilization, and use of minimally invasive surgery.[8] There are published guidelines for the components of ERAS in the literature.[131] Outside of common ERAS components, there is no consensus on which pharmacological interventions should be routinely used, and the widespread use of targeted pharmacological interventions for POI is still relatively uncommon.[21] This section will examine the evidence behind standard ERAS components, and discuss the evidence for targeted pharmacological treatments for PPOI prevention.

1.6.1 ERAS

Enhanced recovery after surgery (ERAS), also known as enhanced recovery pathways (ERPs), or “fast-track” surgery, has become the gold standard in the perioperative and postoperative management of patients undergoing abdominal surgery.[132, 133] The introduction of ERAS has led to a 1-4 day reduction in length of stay after abdominal surgery, and has been shown to be effective in patient undergoing either laparoscopic or open surgery.[132] The key ERAS principles consist of targeted interventions in the preoperative, operative and postoperative period. Preoperative interventions include patient counselling, omission of bowel prep, a preoperative carbohydrate drink and a reduced duration of fasting prior to surgery.[131] Patient optimization prior to surgery is also encouraged. This includes assistance with smoking cessation and avoidance of alcohol abuse, optimization of perioperative nutritional status, treatment of preoperative anaemia, and preemptive management of postoperative nausea and vomiting.[131] Unfortunately, the strength of evidence for “prehabilitation” (interventions to improve the patient’s physical status prior to surgery) is weak.[131] For malnourished patients, additional enteral nutrition for 7-10 days prior to surgery may lead to a reduction in anastomotic leak, infectious complications and a shorter length of stay.[134] Whether preoperative optimization improves postoperative gastrointestinal function, or reduces PPOI, is unclear.

Operative interventions include selective use of thoracic epidural, restricted use of intraoperative fluids, avoidance of NGT or removal of NGT prior to extubation, prevention of intraoperative hypothermia, and omission of abdominal drains. Finally, postoperative interventions include early mobilization, early removal of urinary catheter, and early oral intake. Intraoperatively, ERAS protocols encourage IV fluid replacement to maintain

normovolaemia only.[131] ERAS guidelines recommend avoidance of NG tube unless absolutely necessary.[131] Studies have found that routine use of NG tube does not confer any benefit to the patient, does not reduce the incidence of postoperative nausea and vomiting and does not improve time to intestinal recovery.[135] In fact, routine use of NG tube postoperatively prolongs the time to flatus and stool, and significantly increases postoperative length of stay.[136] Routine use of an NGT increased postoperative pulmonary complications in one systematic review.[137] Early mobilization and early time out of bed are essential. Current recommendations aim for 2 hours out of bed on the day of surgery, and 6 hours out of bed each subsequent postoperative day.[138] Interestingly, studies on ERAS compliance show that early postoperative mobilization is the least adhered to within an ERAS framework, with only 27.5% reported in one large prospective series.[107]

ERAS is now thought to be the primary means of PPOI prevention for patients who undergo elective colorectal surgery. Studies prove that adherence to ERAS leads to significantly lower rates of PPOI on multivariate analysis in patients who are highly compliant with ERAS ($\geq$85% overall compliance) and significantly higher rates of PPOI in those who have <85% compliance.[107] ERAS compliance was found to be the sole multivariate predictor of PPOI in one series.[107] A systematic review and meta-analysis of ERAS/ERP in colorectal surgery assessed 6 RCTs and 452 patients, and found that patients adhering to ERAS had significantly shorter stay compared to standard care by 2.5 days.[83] The 30-day morbidity was 50% less in the ERAS cohort than in the standard care cohort, and there was no difference in readmission rates.[83, 133] ERAS is beneficial in elderly populations (age $\geq$65) as well Although relatively few studies have assessed the benefit of ERAS specifically in elderly populations, a meta-analysis suggests that elderly patients spend between 2.5-4 days shorter in hospital if they undergo surgery in an ERAS setting.[139] ERAS compliance is equivalent in elderly patients compared to younger patients.[139] While elderly patients may have a more difficult time achieving early mobilization than younger patients, and have prolonged duration of urinary catheterization, elderly patients still stand to significantly benefit from ERAS.[139]

The proposed mechanism for the beneficial effects of ERAS involves maintenance of normal body homeostasis, and a reduction in the systemic inflammatory response to surgery. Studies that compare the inflammatory response to colorectal cancer surgery in ERAS patients, compared to traditional care, show a reduction in mucosal COX-1 and COX-2 expression, and reduced prostaglandin D and E synthase activity.[140, 141] Interestingly, prostaglandin synthesis and COX-2 activity were not significantly different between patients who had laparoscopic or open surgery in this study, but they were significantly correlated

with patients' overall ERAS compliance.[140] The need for strong compliance, therefore, is both a strength and a weakness of the ERAS protocol. ERAS is dependent on a multimodal bundle of care provided to patients at all stages of their perioperative and postoperative stay, rather than a single aspect of their care (such as operative technique). The main issue is that maintaining adherence to ERAS is difficult in patients who develop PPOI. Studies that report annual PPOI incidence have failed to show a significant reduction in PPOI rates over time, comparing data from pre and post ERAS adoption.[142] This may relate to the definition of PPOI used, which has certainly also changed over time, more so than a lack of beneficial effect of ERAS on PPOI rate. The evidence for the most impactful aspects of ERAS is discussed below.

1.6.2 Early enteral feeding

Historically, patients were kept nil by mouth until "resolution of their postoperative ileus".[143-145] In the late 1990s, researchers began to assess whether starting patients on an early oral intake was safe.[144] Initial studies permitted patients to drink clear fluids or free-fluid diet postoperatively, and found no difference in the incidence of nausea, vomiting or need for NGT insertion compared to patients who were kept nil by mouth.[143-145] Early enteral feeding did not increase patient complication rates after abdominal surgery.[135, 136, 143-150] In fact, early feeding improves time to passage of flatus and stool, and some studies suggest that early enteral feeding may improve time to hospital discharge.[136, 147] More recent series have allowed return to low residue or full diet after surgery, and found that that early commencement of a regular diet was superior to clear fluids in relation to patients rate of postoperative nausea, time to flatus and length of stay.[150] Feeding patients orally is safe, even after major upper GI surgery. A large series of 453 patients after major upper GI surgery allocated to either routine nil by mouth or enteral tube jejunostomy feeding vs normal enteral food.[151] There was no difference in complication rates or mortality in the enterally fed group, and enteral feeding significantly improved time to return of bowel function.[151] Enteral feeding led to significantly fewer major complications and reduced length of stay, as well as a reduced rate of post discharge complications.[151]The evidence for early enteral nutrition after gastrointestinal surgery has been assessed in 3 Cochrane systematic reviews, last updated in 2018.[152, 153] In the most recent Cochrane review, including 17 RCTs and 1437 patients, Herbert *et al* (2018) found that patients allocated to early enteral feeding showed no difference in overall postoperative complications rates, and no difference in postoperative mortality, but had a 1.95 day mean difference shorter time in hospital (95% CI, -2.99 to -0.91 days, $p<0.001$).[153] In fact, a recent neural network meta-analysis of 48 trials on ileus prevention found that early enteral feeding was the most

beneficial treatment to improve time to tolerance of diet after colorectal surgery.[154] One limitation of this research is that trials are unable to blind patients to early diet or not, which may lead to a significant risk of bias.[153] However, while considered low quality evidence, early enteral feeding has become a cornerstone of ERAS protocols.[5]

Enteral nutrition is required to ensure adequate intestinal mucosal cell proliferation, and it plays a role in maintenance of intestinal bacterial homeostasis.[155] Enteral nutrition activates the autonomic nervous system by stimulating release of neuroendocrine hormones, which may have prokinetic and anti-inflammatory effects.[8] Dietary lipids, in particular, may reduce intestinal mast cell activation by stimulating release of cholecystokinin.[8, 156-158] In rats, ingestion of dietary fat stimulates cholecystokinin (CCK) receptors that lead to increased vagus nerve activity that reduces intestinal inflammation.[159] Reducing mast cell activation and increasing vagus nerve stimulation may reduce PPOI, as discussed previously. In animal models, lipid rich feeding prior to induction of intestinal inflammation reduces intestinal mast cell degranulation.[156] Lipid rich enteral feeding also reduces neutrophil migration into the gut wall, and reduces levels of peritoneal IL-6 and TNF-α in rats.[158] Unfortunately, the large multi-center randomized SANICS-II trial failed to demonstrate a beneficial role for lipid-rich enteral feeding in reducing postoperative complications after colorectal surgery, in particular, it showed similar rates of PPOI between both groups.[160]

The implications of enteral nutrition and early feeding go beyond simply starting an oral diet. Abrisqueta *et al* (2014) conducted an RCT on patients prior to ileostomy reversal. The intervention was feeding the distal ileostomy limb using a mixture of 500mL saline and Nestle Resource, compared to no feeding.[161] Patients pre-treated with 2 weeks of daily distal ileostomy limb feeding recovered significantly faster from surgery, tolerated diet over 1 day faster (1.06 days vs 2.57 days, $p=0.007$), and passed stool over 24 hours faster (1.14 days vs 2.85 days, $p<0.001$) than the controls.[161] Furthermore, the rate of POI was only 2.85% in the ileostomy feeding group compared to 20% in the control group.[161] Enteral feeding therefore is necessary to ensure adequate intestinal mucosal function and may reduce the inflammatory phase of PPOI. Research into the effects of early enteral feeding has also led to the idea that sham feeding, and direct or indirect vagus nerve stimulation may reduce PPOI. [8]

1.6.3 Minimizing perioperative fluids

Restrictive use of perioperative fluids is a key epithet of the ERAS protocol, and current management of perioperative fluid status involves minimal impact on patient physiology. Patients are encouraged to drink a clear carbohydrate drink 2-3 hours preoperatively, with avoidance of excessive IV fluids and a trend towards a "zero-balance" approach to fluid therapy.[162] This may include avoidance of preoperative bowel prep, to ensure the patient reaches theatre in a euvolaemic state.[162] Lobo *et al* (2002) found, prior to ERAS, that fluid volume and sodium restriction (≤2L per day, compared to ≥3L per day) after colon cancer surgery led to faster gastric emptying rates on postoperative day 4, faster time to passage of flatus and stool and a shorter hospital stay.[163] This randomized trial comprised only 10 patients per arm, but laid the groundwork for many subsequent studies on the importance of restricted IV fluid postoperatively. Subsequent studies have confirmed that restrictive intraoperative IV fluid regimens (on average 1L versus 2L) are safe, and do not increase short or long term complications.[164, 165] Examples of restrictive fluid regimens compared to liberal regimens include intraoperative IV fluid of 1L versus ≥2L and perioperative fluid volumes (intraoperatively and 24 hours postoperatively) of only 3.7L compared to 6.1L.[164, 165] Optimal fluid therapy perioperatively may reduce postoperative complications by up to 50%.[166] Permissive oliguria is appropriate in the early postoperative course, and recent RCT evidence from Pucket *et al* (2017) showed that a urine output of 0.2mL/kg/hr was not inferior to a traditional urine output of 0.5mL./kg/hr in terms of postoperative creatinine, glomerular filtration rate and markers of renal stress.[167] Retrospective series suggest that the volume of peri and postoperative IV crystalloid correlated directly with PPOI incidence, and those patients who received a volume of IV crystalloid in the upper quartile had a risk of PPOI of 39.2%.[168]

There are different means of assessing perioperative fluid requirements. Goal directed fluid therapy (GDFT) refers to optimizing fluid delivery based on markers of cardiac output, using the Frank Starling curve.[169] This can include transoesophageal doppler to assess the flow signal from the descending thoracic aorta, analysis of arterial pulse contour, and transpulmonary thermodilution techniques.[169, 170] RCT level evidence suggests similar rates of PPOI between patients who receive standard ERAS fluid therapy perioperatively and GDFT in patients undergoing elective laparoscopic colorectal surgery.[170] GDFT in an ERAS setting has not been shown effective in randomized trials, compared to standard ERAS restrictive fluid administration.[171, 172] A meta-analysis of GDFT showed no benefit in PPOI rates or length of stay across 12 RCTs. Subgroup analysis showed that GDFT was only superior in reducing ileus rates when compared with standard therapy and in non-ERAS

patients.[169] A further Meta-analysis of restrictive, goal-directed and standard fluid therapy, in patients undergoing colorectal surgery, showed that restrictive and GDFT significantly reduced overall postoperative morbidity across 9 RCTs.[173] The OR of morbidity was 0.41, 95% CI 0.22-0.77 for restrictive or GDFT vs standard,[173] meaning that restrictive perioperative fluid is the key.

1.6.4 Minimally invasive surgery

Laparoscopic surgery, or minimally invasive surgery, has become the standard of care for elective colorectal surgery, where possible. Early trials found faster return to eating and passage of stool for patients who underwent laparoscopic colorectal surgery compared to open surgery.[174] Additionally, large retrospective series in the US of 500 hospital and 32,733 patients have found a reduction in length of stay with laparoscopic colorectal surgery compared to open surgery by approximately 24 hours.[175] Perioperative complications may be more common in patients undergoing open colectomy compared to laparoscopic.[176] There may be a significantly higher rate of postoperative mortality after open colorectal surgery (4.9% vs 0.8%), surgical site infection, pneumonia, and renal impairment.[176] It should be noted that these early studies were prior to widespread adoption of ERAS. A Cochrane review in 2005 of 25 RCTs, largely using “traditional” postoperative care models, found that laparoscopic surgery led to faster return of postoperative gut function by approximately 24 hours.[177] Vlug *et al* (2011) conducted a multicenter trial of patients (The LAFA-Study) assessing the benefit of laparoscopic surgery compared to open surgery in patients both within an ERAS and a standard care framework.[178] Total hospital stay for laparoscopic ERAS surgery was a median of 5 days, significantly faster than 7 days in the open ERAS surgery (median 7 days), and laparoscopic and open surgery in a standard care framework (median 6 and 7 days respectively).[178] However, it should be noted that the risk of anastomotic leak was relatively high in the LAFA trial, and that the rate of reoperation was also considerably higher than expected (10-18%) in the literature.[178] Laparoscopic surgery has a significant benefit on recovery of postoperative gastrointestinal function. Colonic transit is significantly faster in patients who undergo laparoscopic compared to open surgery, within an ERAS framework.[179] Laparoscopic surgery provides additional benefits in an ERAS setting, with studies showing faster postoperative colonic motility based on scintigraphy, compared to laparoscopic surgery in patients with a “traditional” postoperative care protocol.[180]

While laparoscopic surgery clearly offers benefits to patients who undergo elective colorectal surgery, there is insufficient evidence to support its use in the acute setting.[181]

Furthermore, despite widespread uptake of ERAS protocols in colorectal surgery, a significant number of patients in ERAS-based institutions still undergo open surgery for a variety of reasons. Up to 51% of patients in one recent cohort study using ERAS principles underwent open or converted-to-open colorectal resection or stoma reversal.[21]
A meta-analysis of laparoscopic versus open transverse colectomy found a mean improvement in time to first bowel motion of 1.57 days compared to open surgery, and a shorter hospital stay.[182]

The magnitude of intestinal inflammation generated by a surgical procedure corresponds to the magnitude of the surgical insult. This is the proposed mechanism for why laparoscopic surgery leads to reduced rates of PPOI. Mouse models of PPOI show a minimal intestinal inflammatory response after laparoscopic intestinal manipulation compared to laparotomy, and a reduced duration of PPOI.[183] Studies in humans show that serum IL-6 levels are lower after laparoscopic surgery compared to open surgery,[118, 119, 184, 185] and open surgery leads to higher levels of postoperative CRP, IL-1b, IL-8 and TNF-α.[119, 185] Veenhof *et al* (2012) compared the impact of an ERAS pathway on postoperative inflammation, and found that surgical technique, rather than postoperative care, was the most important predictor of the magnitude of inflammatory response to surgery in the first 72 hours.[118] Laparoscopic surgery may improve postoperative recovery and wound healing. Wound exudate in patients who underwent laparoscopic surgery showed increased levels of VEGF, an angiogenic factor, postoperatively compared to open surgery.[120] Cortisol levels, however, are not significantly different between laparoscopic and open surgery cohorts.[118, 184]

1.6.5 Management of perioperative electrolytes

Postoperative electrolyte disturbances or imbalances may predispose patients to PPOI.[186] Studies suggest a correlation with low serum potassium levels and ileus, with resolution of hypokalaemia leading to resolution of ileus.[187] In 1975, a study of 18 patients who underwent hysterectomy, bowel resection or urological surgery found that PPOI associated with hypokalaemia significantly improved after correction of serum potassium levels.[188] The authors acknowledged that hypokalaemia was only uncommonly associated with small and large bowel dilatation on radiological studies in a further 32 patients, and therefore that electrolyte disturbances may be an exacerbating factor rather than a causative factor in PPOI.[188] Patients with ileus have lower mean levels of calcium in some series, and lower trough levels of potassium.[20] There is limited evidence about the role of hyponatraemia and hypomagnesaemia on PPOI,[187] and when postoperative electrolyte disturbances

were assessed by Vather *et al* (2015), there was no statistical correlation between preoperative or postoperative levels of sodium, potassium, magnesium or calcium on risk of PPOI.[43] A subsequent study assessed the impact of electrolyte disturbances on models of Interstitial Cells of Cajal (ICCs) activity, the pacemaker cells of the gut, and enteric smooth muscle cells.[24] They found that postoperative day 1 calcium and postoperative day 3 chloride and sodium were lower in patients who developed PPOI.[24] In particular, patients who developed PPOI were more likely to have had a greater change in their preoperative and postoperative sodium and chloride concentrations.[24] Changes in serum sodium levels were also correlated with higher incidence of other complications.[24] The mathematical models of ICC and smooth muscle models showed that jejunal slow-wave activity was most impacted by alterations in serum chloride levels.[24] In the clinical setting, correction of serum electrolytes postoperatively is recommended and would be considered a key part in PPOI management.[186] However, we lack real evidence to suggest that strict electrolyte control reduces the incidence of PPOI.

1.6.6 Thoracic epidural

Thoracic epidurals are advocated as part of ERAS care, in patients undergoing open abdominal surgery, and can contain opiate and/or local analgesia. Much of the evidence for epidural use, however, comes from prior to the widespread adoption of ERAS protocols. Taqi *et al* (2007) found that thoracic epidural improves time to recovery of postoperative gut function and return to oral diet.[189] A meta-analysis of 16 colorectal surgery trials prior to 2005 showed that epidural reduced the duration of PPOI by a weighted mean difference of 1.55 days compared to parenteral opioids.[190] However, epidurals increased incidence of pruritus, urinary retention, postoperative hypotension, and did not reduce the length of stay.[190] A large retrospective series of 888,135 patients from 2002-2010 assessed the outcomes of epidural use after open colorectal surgery.[191] The authors found an increase in length of stay and PPOI rates with epidurals for colon resection, but there was no difference in length of stay or PPOI rates with epidurals in patients undergoing rectal resection.[191] Some trials have shown an improved time to first flatus and bowel motion with epidural analgesia compared to patient-controlled analgesia (PCA),[189, 192] whereas others found no improvement in return of gut function.[193] Furthermore, studies have failed to show an improvement in length of stay for patients who receive epidurals,[189, 192, 193] and evidence suggests that thoracic epidural are associated with increased hospitalization costs.[193] Adding local analgesia, such as bupivacaine, to epidurals leads to improved pain relief and faster return of postoperative gut function.[194] A Cochrane review found that epidural containing local anaesthetic, compared to opiate analgesia, improved time to return

of gut function by 17 hours, and a combination of both opiate and local anaesthetic in an epidural significantly reduces postoperative pain.[195] The review found a slight improvement in length of stay with local anaesthesia regimens but no difference in postoperative nausea or vomiting.[195]

Epidurals may work either by reducing the postoperative opiate burden for patients, or by reducing the severity of postoperative inflammation. As previously discussed, spinal afferents are involved in the initial phase of ileus and reducing the perception of the gut to insult may reduce the degree of intestinal dysmotility. Epidural use has been shown to increase postoperative IL-10 levels in one small series.[196] Conversely, an RCT by Fant *et al* (2013) showed that epidural reduced early postoperative cortisol levels compared to systemic opioids after prostatectomy, but had no impact on IL-6 or TNF-α levels.[197] Kuo *et al* (2006) found that thoracic epidural with lignocaine led to reduced postoperative IL-6 and IL-8 after colorectal surgery.[198] A further trial showed that the addition of clonidine to patient controlled epidural analgesia causes a reduction in IL-6 and IL-8 production in the early intraoperative and postoperative phase, and faster return of gut function.[199]

The role of epidural analgesia for patients who undergo laparoscopic surgery is much less clear. Some studies found no benefit from thoracic epidural analgesia after laparoscopic colon surgery,[200] and no improvement in time to postoperative oral intake, bowel function and length of stay within an ERAS setting.[201] A large retrospective series, of 191,576 patients, reviewed epidural use in laparoscopic surgery and found that it actually increased length of stay (by 0.6 days) and postoperative urinary infection.[202] Epidural use did not affect the incidence of PPOI for patients after laparoscopic surgery, and led to an increase in hospital costs.[202] Studies on epidural analgesia in particular are small and in the context of increased rates of laparoscopy, the beneficial role of epidurals within an ERAS framework is still unclear. Compared to patient-controlled opioid analgesia, postoperative pain levels are improved,[192, 193] but whether this translates into improved return of gut function is controversial. Epidurals also limit patient postoperative mobility, which is a key part of routine ERAS care, and early patient mobilization is protective for PPOI.[43]

1.6.7 NSAIDS

Non-steroidal anti-inflammatories (NSAIDs) inhibit cyclooxygenase (COX) activity. COX enzyme activity converts arachidonic acid into pro-inflammatory mediators such as prostaglandins, prostacyclins, and thromboxanes.[203] There are 2 forms of COX, COX-1 that is constitutively active, and COX-2 that is inducible.[203] Non-selective COX inhibitors

(diclofenac, ketorolac, flurbiprofen and ibuprofen) inhibit both COX-1 and COX-2, while selective inhibitors (parecoxib, celecoxib, valdecoxib) inhibit only COX-2. We know that COX activity, particularly inducible COX-2, plays an integral role in the development of ileus and PPOI.[141] Animal studies show that selective COX-2 inhibition reverses gut dysmotility induced by intestinal handing in rodents.[204] In fact, Venara *et al* (2016) found a direct correlation between levels of COX-2 expression and time to passage of flatus and stool after colorectal cancer surgery.[141] Elevated COX-2 mRNA expression is shown to correlate with delay in passage of first flatus.[140] NSAIDs, in particular COX-2 selective inhibitors, are promising targets for PPOI prevention.

Several trials have assessed the potentially beneficial role of NSAIDs after colorectal surgery on clinical markers of return of gut function,[205-210] including non-selective COX inhibitors,[205, 206, 209, 210] and COX-2 selective inhibitors.[207, 208] NSAID use reduces postoperative opiate consumption,[205-207, 210] improves time to postoperative mobilization,[205] and improves postoperative pain scores.[205, 206, 210] Most of these studies focused on open colorectal surgery,[205-209] and one assessed patients who underwent laparoscopic surgery.[210] The majority of studies showed that NSAIDs improved the mean time to passage of flatus and stool.[205-207, 209, 210] However, there was mixed evidence for whether perioperative NSAID use improved time to tolerate a diet.[205, 207, 210] An important limitation in these studies was that NSAID use was predominantly commenced postoperatively, and only 3 studies gave NSAIDs in the preoperative period.[207-209] A study by Xu *et al* (2008) gave NSAIDs 30 minutes preoperatively and found a significant reduction in postoperative inflammatory markers, IL-6 and IL-8.[209] This supports the idea that interventions for ileus prevention should commence prior to skin incision, so that they can reduce gut inflammation in response to surgery. However, all these patients also had a thoracic epidural, which makes it less generalizable to current laparoscopic-based ERAS protocols. The largest trial on NSAID use included 210 patients who underwent colorectal surgery, and compared placebo to both diclofenac or celecoxib.[208] They found that the incidence of PPOI was significantly lower in the celecoxib group compared to placebo or diclofenac, both did not improve the overall time to return of gut function or length of stay.[208] This trial comprised only patients undergoing laparotomy but did offer elements of an ERAS postoperative pathway.

There is evidence that NSAID use may be a risk factor for anastomotic leak after colorectal surgery. In particular, non-selective COX inhibitors, such as Diclofenac, are shown to increase the risk of anastomotic leak in large retrospective studies.[211, 212] A recent meta-analysis of NSAID use after gastrointestinal surgery found no difference in anastomotic leak

rates in patients who received COX-2 inhibitors.[213] An observational series by Raju *et al* found that 100mg celecoxib daily for up to 7 days was safe in patients who underwent bowel resection with anastomosis, and the rate of anastomotic leak was very low at 2/221 patients (0.9%).[214] NSAIDs may still be a useful tool in PPOI prevention. The current evidence for NSAID use after colorectal surgery relies on relatively few, small RCTs. There would be a significant benefit in a systematic review of NSAID use in colorectal surgery, therefore, to better determine the benefit of NSAIDs on markers of gut recovery and PPOI.

1.6.8 Chewing gum

Early enteral feeding is proven to be of benefit to patients after colorectal surgery. Chewing gum, also considered "sham feeding" may also provide a benefit for patients. Van den Heijkant *et al* (2015) conducted an RCT of 120 patients undergoing colorectal surgery, and allocated patients to chewing gum or a dermal patch, with a primary end point of PPOI (defined as lack of flatus of stool and diet on postoperative day 5) and length of stay.[41] Patients allocated to chewing gum were more likely to pass a bowel motion in the first 4 days after surgery, and had a significant reduction in rate of PPOI compared to controls (27% vs 48%).[41] Chewing gum also led to reduced levels of IL-8 in the surgical specimen and decreased gastric antral volumes seen on ultrasound.[41] There was no difference in length of stay with chewing gum, and patients had to chew 3 pieces of gum per hour as per the protocol.[41] The addition of nicotine to chewing gum did not provide any benefit in time to pass stool or tolerate oral intake in one small study of 40 patients.[19] There has been substantial interest in chewing gum for a range of abdominal surgical procedures, including colorectal and gynaecological surgery, with multiple trials and meta-analyses.

One meta-analysis of 17 studies and 1845 patients showed that gum chewing significantly reduces time to pass flatus after colorectal surgery, but the weighted mean difference was only -0.55 days.[215] There was only a small difference in time to first stool (-0.6 days), improvement in time to oral intake (-1.32 days), and reduction in length of stay (-0.88 days).[215] There was no difference in PPOI rates for gum chewing.[215] A further meta-analysis of showed faster time to pass flatus (by 8.81 hours), first stool (by 16.43 hours), and reduced length of stay (by 0.89 days).[216] They found that chewing gum reduced the odds ratio for PPOI to 0.41 (95% CI 0.23-0.73, p=0.003).[216] Only 6 studies mentioned POI in the 18 RCTs of gum chewing, colorectal surgery only. On subgroup analysis, patients who underwent open surgery benefitted more than those who had laparoscopic surgery.[216] The largest meta-analysis of gum chewing after colorectal surgery comprised 81 studies with 9072 patients, and found improved time to first flatus and bowel motion with gum chewing

after colorectal surgery (mean improvement of 10.4 hours and 18.1 hours respectively).[217] In conclusion, gum chewing is a simple, well tolerated and low cost, intervention that provides a mild to moderate improvement in time to flatus, stool and time to tolerate a diet.[217] Gum chewing may reduce PPOI, but PPOI was only considered an endpoint in 6 of the 18 RCTs assessed in the meta-analysis, and the definition varied considerably.[216] It is unclear whether gum chewing is beneficial in the context of an ERAS protocol, where it may only provide a minimal beneficial effect.[217, 218] While series show a statistically significant improvement in time to flatus or stool, it is important to recognize that the true clinical benefit of gum chewing is mild at best.

1.6.9 Intravenous lignocaine

Several studies have assessed the role of IV lignocaine in patients undergoing colorectal surgery. Early series suggests a benefit for IV lignocaine compared to placebo, with faster time to passage of stool after elective bowel surgery.[219, 220] Whether patients who undergo laparoscopic surgery will benefit from IV lignocaine is contentious.[221, 222] A meta-analysis of 8 trials that assessed intravenous lignocaine compared to controls showed a reduction in duration of ileus with a weighted mean difference of -8.36 hours and a reduction in overall length of stay of -0.84 days, in addition to reduced postoperative pain scores and postoperative nausea and vomiting.[223] More recently, a meta-analysis of 21 trials comparing IV lignocaine to placebo ,or blank control, for patients undergoing abdominal surgery showed faster time to first flatus, time to first bowel movement (6.92 hours) and shorter length of stay (-0.71 days).[224]

A Cochrane Review by Weibel *et al* (2018) assessed the benefit of IV lignocaine compared to placebo or no treatment in randomized trials.[225] A total of 68 trials were used, and 4525 patients, and both laparoscopic and open cases were included. They concluded that there was no convincing clinically meaningful difference in postoperative pain scores, risk of ileus, time to first bowel motion, risk of postoperative nausea and vomiting, or opioid consumption based on minimally clinically significant improvements and low quality of data.[225] The proposed mechanism of IV lignocaine is similar to thoracic epidural in that it reduces the amount of opiate required postoperatively,[222] and may attenuate the degree of systemic inflammation in the postoperative period. Some studies have shown reductions in postoperative inflammatory markers (IL-6 and IL-8) compared to controls,[220, 226] but whether this reduction in inflammatory response is important compared to a reduction in opiate usage is unclear.[222] Trials that directly compared thoracic epidural to IV lignocaine found either an improvement in recovery with thoracic epidural,[198] or no difference in

effect on markers of return of gut motility in both open,[227] and laparoscopic surgery.[228] IV lignocaine is therefore not a currently recommended treatment to reduce PPOI after colorectal surgery.

1.6.10 Coffee

Coffee may stimulate gut motility in healthy individuals,[229] and therefore has been investigated as a potential gastrointestinal prokinetic for patients who undergo abdominal surgery. After open or laparoscopic colectomy, coffee may improve time to passage of stool.[230, 231] Interestingly, Dulskas *et al* (2015) found that decaffeinated coffee led to significant improvements in time to first bowel motion and tolerance of diet compared to caffeinated coffee and water after laparoscopic colorectal surgery.[232] When postoperative coffee was compared to tea, coffee led to a faster time to first bowel motion.[233] The study notes, of course, that there were significant protocol violations and that the patients cannot be blinded to interventions in this case, and the majority of patients in this trial had open surgery.[233] Two systematic reviews of coffee use in abdominal surgery found that coffee improved mean time to first bowel motion by 10.4-14.8 hours,[234, 235] and improved time to tolerate a diet.[234] A recent meta-analysis of coffee use after abdominal surgery found that any coffee, both caffeinated and decaffeinated, had similar efficacy.[236] Coffee use is safe and mildly effective, and patients are commonly offered coffee during their inpatient stay.

1.6.11 Laxatives

There is uncertainty about whether laxatives can improve postoperative gut recovery after abdominal surgery. An international panel on postoperative ileus concluded that laxatives are not a recommended treatment or prevention modality for postoperative ileus.[11] Laxatives work either by stimulating gut activity or by causing osmotic distension of the bowel.[237] Early studies reported a mild improvement in time to passage of stool in patients who received postoperative laxatives such as bisacodyl, but there was no improvement in time to tolerate diet.[238] A small subsequent RCT that compared oral magnesium oxide to placebo found no difference in time to passage of flatus, stool or oral intake between groups, and no difference in postoperative length of stay.[239] This trial only included 49 patients and patients all underwent open colorectal surgery.[239] Another small single-center trial of 20 patients found that bisacodyl suppositories, commencing on postoperative day 3, improved time to passage of stool after elective colectomy.[240]

A recent systematic review and meta-analysis of 5 RCTs that assessed the benefit of laxatives (magnesium oxide or bisacodyl), for patients undergoing major abdominal surgery, found faster time to passage of stool for patients who received routine laxatives postoperatively.[237] Dosing was variable, with some studies starting laxatives on postoperative day 1 and some starting them postoperative day 3 and onwards. There was no difference in time to first flatus, time to tolerate a solid diet, and length of stay in the laxative group.[237] Laxative use was deemed safe, and there was no difference in postoperative complications.[237] When a subgroup analysis of only trials on colorectal resection was undertaken, there was no significant difference in time to passage of stool for those allocated to laxatives.[237] An international survey of laxative use after elective colorectal surgery showed that the majority of surgeons would not routinely prescribe postoperative laxatives, and the most common reason was perception of lack of benefit.[241] Recently, a single-center RCT by Dudi-Venkata *et al* (2021) tested the benefit of routine laxatives within a cohort of 170 patients who underwent elective colorectal surgery in an ERAS setting, with a primary endpoint of GI-2.[242] Patients who had a left sided resection received oral bowel prep preoperatively, right sided resections had an oral fleet preoperatively. This trial was not placebo-controlled, but patients were randomized to standard care compared to routine laxatives starting 6 hours postoperatively (oral coloxyl 1bd, oral macrogol 1bd, daily phosphate enema). Time to GI-2 was 1 day faster in the laxative group (median 2 days vs 3 days).[242] There was no difference in time to passage of flatus or to tolerance of oral diet. PPOI, defined as not achieving GI-2 by postop day 4, was reduced in the laxative group (22% vs. 38%, p=0.03), but there was no difference in NGT insertion rates.[242] There was a non-significant trend towards a 1 day faster time to discharge in the laxative group, and there was no difference in postoperative complications between groups.[242] Importantly, laxatives did not increase the risk of anastomotic leak in the STIMULAX trial.[242] Use of laxatives remains uncommon after colorectal surgery but would appear to be safe. The implications of a faster time to stool, but no faster time to oral intake or hospital discharge, suggests that the clinical benefit of laxatives is dubious, and further studies are warranted.

1.6.12 Prokinetics

Prokinetics would appear, on face value, to offer a benefit to postoperative patients. PPOI is a disorder characterized by intestinal hypomotility and dysmotility, and prokinetic drugs may therefore help improve time to resolution of postoperative gut function. The types of prokinetics, their mechanisms of action and the evidence for their benefit in the postoperative period is discussed below.

1.6.12.1 Metoclopramide

Metoclopramide is a dopamine D2 receptor antagonist, with serotonin-4 (5HT4) receptor agonistic and serotonin-3 (5HT3) receptor antagonistic activity.[243] Metoclopramide increases ACh release from gut neurons and increases gastric emptying, by inhibiting presynaptic and postsynaptic D2 receptors, and stimulating serotonin-4 receptors.[243] Small series have shown benefits in return to oral diet and reductions in postoperative nausea and vomiting with metoclopramide after abdominal surgery,[244, 245] but no significant improvement in the time to passage of stool,[246] or rate of postoperative ileus.[245, 247] Metoclopramide likely has minimal effect on colonic motility based on previous studies, and this makes it unlikely to be effective in reducing PPOI.[248] Only a single study has suggested that metoclopramide increases the time until passage of flatus.[249] Overall, metoclopramide has no beneficial role in postoperative ileus.[250]

1.6.12.2 Erythromycin

Erythromycin is a macrolide antibiotic that has prokinetic effects on the stomach by acting as a motilin receptor agonist.[251] Erythromycin induces migrating motor complexes in the gut, in particular in the stomach.[251] However, there is limited evidence for any beneficial effect of erythromycin in reducing postoperative ileus.[252] Several small trials using erythromycin in the postoperative period following abdominal surgery found no improvement in clinical markers of gut recovery.[252, 253] One trial found a slightly faster time to passage of flatus in patients allocated to erythromycin compared to placebo after elective colorectal surgery, but no difference in time to tolerate diet, passage of stool or requirement for NG insertion.[254] There is, therefore, no role for erythromycin as a postoperative prokinetic after abdominal surgery.[250]

1.6.12.3 Acetylcholinesterase inhibitors

Neostigmine is an acetylcholinesterase inhibitor, that increases gastrointestinal motility by increasing ACh levels at the neuromuscular junction in the myenteric plexus.[255] Neostigmine has a role in the management of acute colonic pseudo-obstruction, but also increases gastric and small bowel motor activity.[255] Two small series have assessed the role of neostigmine in recovery of postoperative gut function. They found only minor improvements in time to flatus and stool. One trial found a small benefit in time to passage of stool after cholecystectomy in patients who received neostigmine combined with propranolol the night of their operation.[256] Endonasal neostigmine led to a higher incidence of passage of stool on postoperative day 4 after abdominal surgery, which included procedures

such as cholecystectomy.[257] Due to small numbers and methodological concerns, neostigmine is not used in the management or prevention of PPOI.[250] Pyridostigmine is another acetylcholinesterase inhibitor that has been assessed as a preventative agent for PPOI in a recent small pilot study of 15 patients, where the drug was found to be safe but in this small study had no beneficial effect on postoperative gut recovery.[258] It is important to consider that acetylcholinesterase use is not without risk. Indeed, the regimen used by Neeley and Catchpole in 1971 to "treat" postoperative ileus used a combination of adrenergic blockade anticholinesterase medication, but lead to life-threatening complications.[259] Patients need to be monitored, often in an intensive care environment, for risk of bradycardia, hypotension and rarely cardiac arrest. This alone significantly limits its potential as a preventative measure for PPOI.

1.6.12.4 Cisapride

Cisapride is a prokinetic with properties similar to metoclopramide: it stimulates 5HT4 receptors and inhibiting 5HT3 receptors, except that it does not act on dopaminergic receptors.[260] In healthy adults, cisapride increases oesophageal motility, gastric emptying and improves small and large bowel transit time.[260] Early randomised control trials showed that cisapride significantly increased the rate of gastric emptying in patients with diabetic gastroparesis and functional dyspepsia as well as improving patient perceived symptoms.[261-263] One trial of 35 patients, who underwent elective colorectal surgery, found that cisapride given orally on postoperative day 1 improved time to first bowel motion, tolerance of diet and discharge by 24 hours.[264] However, in a small randomised double-blinded trial of rectal cisapride for patient undergoing upper or lower GI surgery, there was no difference in time to passage of stool.[265] In another study, cisapride induced motor activity after laparotomy based on small bowel manometry, but did not significantly improve time to flatus or bowel recovery.[266] Cisapride improved colonic motility based on radiopaque marker studies after cholecystectomy and improved time to passage of stool.[248] Cisapride increased the motility index on colonic manometry in patients who had a left sided colon resection, but did not clinically improve time to passage of stool.[267] On meta-analysis, cisapride improved time to first flatus but only in trials that continued its use for 72 hours or until discharge.[250] Cisapride had a non-significant trend towards faster time to oral intake and discharge from hospital.[264]

Cisapride's prokinetic effect is largely related to its agonism of enteric 5HT4 receptors,[260] but it also acts on a number of other receptors including the hERG-K voltage-gated potassium channel in cardiac cells.[268] This hERG-K stimulation can lead to prolonged QT

time, and ventricular arrhythmias, especially if the patient was already on anti-arrhythmic medication.[269] Cisapride was a potentially beneficial in reducing PPOI, but was later withdrawn from the market due to its cardiac side effects.[270] There remains a potential role for more selective serotonin agonists as pan-intestinal prokinetics, particularly those acting solely on the 5HT-4 receptor.

1.6.12.5 Cholecystokinin analogues

Cholecystokinin (CCK) is a peptide hormone that increases gastric emptying and increases gastric and pancreatic secretion.[271] Animal models also suggest that CCK stimulates ACh release from vagal neurons, which in turn reduces the intestinal response to inflammatory stimuli.[157] Early trials on the use of CCK-like substances, such as cerulein and ceruletide, showed mild improvements in time to stool and time to tolerance of oral intake.[272-274] Unfortunately, a meta-analysis suggests that these improvements are either mild or non-significant.[250] The current literature around CCK analogues comprises small studies of poor methodological quality. CCK analogues are therefore not recommended in the treatment or prevention of PPOI at this stage.

1.6.12.6 Ghrelin receptor agonists

Ghrelin is a gastrointestinal peptide hormone that stimulates migrating motor complexes in the gut and improves gastric emptying.[275, 276] Ghrelin receptor agonists (Ipramorelin, Ulimorelin, TZP-101) have been trialled as a possible preventative agent for postoperative ileus after abdominal surgery.[277] A small series of 24 patients, who underwent open colorectal surgery, found improved gastric emptying and time to pass stool compared to placebo if given as an infusion 3 hours preop and on postoperative day 2.[276] A phase 2 study of TZP-101 in patients undergoing open partial colectomy found an improvement in the number of patients who had recovered their gut function by 72 hours compared to placebo when it was given as a daily postoperative infusion.[278] However, more recently, a large RCT found no benefit of Ulimorelin on postoperative gut recovery.[279] Ghrelin is not considered a current target for further studies on POI prevention, but this may change based on future trials.

1.6.13 Mast Cell Stablilizers

As discussed previously, intestinal handling induces mast cell activation, which contributes to intestinal inflammation and postoperative ileus.[9, 65] However, the use of mast cell stabilizers to prevent postoperative ileus has not been well investigated in humans. One pilot study of 60 patients who underwent a laparotomy for gynaecological malignancy investigated the use of Ketotifen (a potent antihistamine agent). This study, in which patients were randomized to ketotifen (at doses of 4mg or 12mg) vs. placebo, found that patients had improved postoperative gastric emptying rates with ketotifen 12mg but similar colonic transit rates compared to placebo.[280] The majority of evidence for mast cell stabilizers relies on rodent models of ileus, and no further studies on the use of Ketotifen have been conducted. The use of mast cell stabilizers in postoperative ileus, particularly in the setting of colorectal surgery, is therefore speculative.

1.6.14 Opioid receptor antagonists (Alvimopan)

Alvimopan, known by its brand name Entereg, is a peripherally acting mu-opioid receptor antagonist that blocks the gastrointestinal effects of opiates. Alvimopan does not cross the blood brain barrier, so it has no effect on postoperative analgesia. Opioid activity in the gut leads to intestinal hypomotility. Animal models of ileus show that opiates, even at comparatively low doses, cause direct inhibition of gut motility.[204] Interestingly, pre-treatment of mice with alvimopan prior to intestinal manipulation ameliorates opioid-induced inhibition of gut motility.[204] In humans, retrospective series suggest that alvimopan is beneficial after colorectal surgery. Adam *et al* (2016) conducted a retrospective review of 660 colorectal patients at an ERAS institution, and found that alvimopan led to a reduced rate of PPOI (defined as NGT insertion) and a mild improvement in time to return of bowel function (0.6 days, p=0.0006).[281] Patients who received alvimopan had a rate of PPOI of 5% compared to 16%, and spent 1.6 days fewer days in hospital postoperatively (p=0.002).[281]

A large multi-centre RCT by Wolff *et al* (2004) randomised 510 patients undergoing bowel resection or hysterectomy to 6mg alvimopan, 12mg alvimopan or placebo.[282] Study medication started $\geq$2 hours preoperatively, and was continued for up to 7 days or until patient discharge.[282] The primary outcome was time to GI-3, but GI-2 was also considered, as well as length of stay and need for postoperative NGT insertion. An intention-to-treat analysis showed a dose-dependent improvement in time to GI-3 with alvimopan at

doses of 6mg and 12mg (mean 15 hours and 22 hours improvement respectively).[282] A similar improvement was seen in time to GI-2 with alvimopan compared to placebo (mean 20 hour and 28 hour improvement with 6mg and 12mg respectively).[282] Patient length of stay was significantly improved with both doses of alvimopan, and patients who received 12mg alvimopan had reduced rates of NGT insertion.[282]

Another RCT of 451 patients allocated to 6mg alvimopan, 12mg alvimopan or placebo who underwent open colectomy (excluding low anterior resection) or total abdominal hysterectomy found an improvement in mean time to GI-3 by 14.1 hours compared to placebo for patients allocated to 6mg alvimopan (p=0.003). The 12mg alvimopan group trended towards an improvement in GI-3 but this did not reach statistical significance.[283] Similar results were seen in time to GI-2, with a mean improvement in the 6mg alvimopan group of 15.2 hours compared to placebo (p=0.007).[283] The study found improvements in time until "discharge order written" but did not report actual patient length of stay. Ludwig *et al* (2008) conducted an RCT involving 654 patients who underwent open colorectal resections using an ERAS protocol, and allocated patients to either 12mg alvimopan or placebo.[22] They found a significant benefit in time to GI-2 and actual length of stay with alvimopan compared to placebo, using a modified intention-to-treat analysis, by a mean difference of 20 hours faster GI-2 (p<0.001) and 17 hours faster time to discharge (p<0.001).[22] Most studies use a dose of 12mg alvimopan, but the evidence doesn't suggest that 12mg is more effective than the lower dose of 6mg.[283] Conversely, one subsequent randomized control trial of 615 patients showed no benefit in time to GI-3 after open colonic resection or hysterectomy with either the 6mg or 12mg dose of alvimopan.[284]

There has been concern that alvimopan does not provide much additional benefit within an ERAS pathway that already minimises postoperative opioid anlagesia and favours laparoscopic surgery.[285, 286] Some studies have shown no benefit in PPOI rates for patients who receive alvimopan within an ERAS setting.[287] Alvimopan is expensive, and costs more than US $1000 for a 7-day course.[281] Some studies report a minimal economic benefit for alvimopan,[288] or no economic benefit with alvimopan use due to the expense of the medication.[287, 289] A retrospective series of patients undergoing colorectal resection or ostomy reversal looked at 636 patients prior to and after routine administration of postoperative alvimopan.[290] They found that routine alvimopan use, within an ERAS setting, reduced length of postoperative stay, and reduced hospitalisation costs by US $708.[290] PPOI was defined as absence of adequate bowel function by postoperative day 5 or NGT reinserstion, and was signficiantly reduced with alvimopan compared to controls (14.7% vs. 23.1% respectively, p=0.007).[290]

The majority of studies on alvimopan have been retrospective case-matched series and their conclusions should be interpreted with caution.[286] A 2021 systematic review of all available RCTs and non-randomized studies on alvimopan for patients who underwent abdominal surgery assessed the results of 9 RCTs and 35 non-randomized studies.[286] Only 2 RCTs assessed alvimopan in patients undergoing bowel resection (small bowel, colon or rectum) and 4 RCTs assessed patients undergoing bowel resection or total abdominal hysterectomy.[286] All of the RCTs identified were funded by the pharmaceutical industry, which may predispose them to bias. The study concluded that the best evidence for alvimopan use in bowel resection was for patients underoging open surgery, but when open surgery was combined with ERAS there was low quality evidence for a benefit with alvimopan.[286] Alvimopan reduced time to GI-2, GI-3 and reduced PPOI in patients underoging open surgery, in both ERAS and non-ERAS cohorts.[286] They found low quality or no evidence for a benefit with alvimopan for patients undergoing laparoscopic bowel resection.[286] Despite widespread use of alvimopan in some countries, there are relatively few convinving prospective double-blinded randomised trials demonstrating its benefit for patients underoing laparoscopic colorectal surgery within an ERAS framework. We know that endogenous opiates play an important role in PPOI pathophysiology, and there may still be a benefit for alvimopan in the recovery of patients underoging ERAS-based surgery. Further independent trials are required.

There is a clear beneficial effect of alvimopan in select patient cohorts, and perhaps it could be used as a targeted treatment for high-risk patients who are likely to develop PPOI rather than as a routine standard of care. For example, a recent trial demonstrated improvements in PPOI rates and time to first bowel motion for patients who underwent peritonectomy and intra-peritoneal chemotherapy.[291] Peritonectomy is a significant procedure associated with high postoperative morbidity, and carries a high risk of PPOI.[291] Such high risk groups may be the optimal targets for interventions such as alvimopan in the future.

1.7 Ileus treatment

Treatment options for PPOI are limited, and the current philosophy regarding ileus treatment is to reduce opioid analgesia and optimize patient fluid management.[11, 186] Treatment strategies for POI include pharmacological and non-pharmacological options.[187] Non-pharmacological interventions include minimizing NGT placement unless required, sham feeding, early oral enteral nutrition, preoperative counselling, and early ambulation.[186,

187] Adequate replacement of fluid losses with an appropriate balanced crystalloid solution (such as Plasmalyte 148, Hartmann's solution or Ringer's lactate), including replacing NG losses, and using isotonic dextrose-saline as maintenance at a rate of 1-1.25mL/kg/hr is advised. Patients are often managed nil by mouth, and an NGT placed to drain the stomach. NGT use for small bowel obstruction was first introduced in 1884 and has formed a cornerstone part of management of small bowel obstruction and of ileus ever since.[56] In 1990, NGT use was the "only proven effective therapy" for ileus.[56]
While NGT use in PPOI is not always seen as mandatory,[11] there have been few recent breakthroughs in ileus management.

Parenteral nutrition (PN) is recommended from postoperative day 7 in patients who are still unable to tolerate an oral diet.[11] PN can be started earlier if the patient was malnourished preoperatively.[186] A parenteral formulation consisting of 20% protein, 30% fat and 50% carbohydrate at 25-30kcal/kg/day has been recommended.[186] Weaning of PN is not required, and PN can be ceased upon resumption of oral feeding.[186] Postoperative enteral feeding offers significant advantages to regular parenteral feeding and should be commenced as soon as feasible.[186] In the treatment of PPOI, it is important to consider other surgical complications that may be exacerbating the PPOI. PPOI resolves without surgical intervention, but similar symptoms occur in patients with missed surgical complications such as anastomotic leak, early postoperative small bowel obstruction or intra-abdominal abscess.[11] These so called causes "secondary" PPOI should be excluded.[186] There are no current algorithms or guidelines on when to remove NGT for ileus. The evidence for treatment of PPOI is poor and is considered "supportive".[11]

1.7.1 Water-soluble contrast media

Gastrografin is an oral water-soluble contrast media that is often used for patients with adhesional small bowel obstruction. In small bowel obstruction, gastrografin can be used as a diagnostic tool to predict patients who should resolve with conservative management, and those who wont. Gastrografin may have a therapeutic effect in small bowel obstruction by drawing oedema out of the obstructed bowel wall via an osmotic effect.[39] As discussed previously, the enteric inflammatory response to surgery leads to bowel oedema and reduced gut motility, and it has been hypothesised that gastrografin may improve gut hypomotility in PPOI by a similar mecahnism. If gastrografin is effective in PPOI, it would be one of the only effective agents to actually treat an established PPOI.

In 1985, a retrospective series of 40 patients showed that gastrogtafin may improve time to resolution of ileus.[292] A subsequent case-control study looked at patients who underwent gynaecoligical surgery and received gastrografin if their bowel function had not return by postoperative day 3.[293] They found that gastrografin did not improve time to passage of flatus or stool in this series, although it was well tolerated.[293] Importantly, the definition of ileus used in this study (lack of "bowel function" defined as passage of flatus or stool by postoperative day 3) does not fit with the current idea of ileus as a pan-intestinal disease, meaning it is unclear whether patients in this study truly had PPOI or not. In a randomized control trial by Chen *et al* (2005), 25 patients who underwent elective colorectal surgery were allocated to oral gastrografin on postoperative day 3 compared to patients allocated to 200mL oral dextrose solution.[294] Patients who received gastrografin had a significantly faster time to oral diet and a shorter hospital stay.[294] These results are signifciantly prone to bias as the study was unblinded. In addition, the study was conducted prior to adoption of ERAS techniques, which limits its generalizability. Gastrografin is not without risks, and while complications between groups were similar in the above series, aspiration of gastrografin carries a significant mortality risk.[294]

Two recent trials have assessed the role of gastrografin as a treatment for PPOI. Vather *et al* (2015) conducted a single-institution double-blind single-centre RCT using a predefined and comprehensive definition of PPOI.[39] PPOI resolution was defined as resolution of nausea and vomiting over 12 hours with NGT removed or spigotted, tolerance of a solid or semi-solid diet, absence of abdominal distension, passage of flatus or stool over the preceding day.[39] On postoperative day 4, patients who met the diagnostic criteria for PPOI were enrolled and given either 100mL undiluted gastrografin or a placebo solution, which was designed to mimic the smell, consistency and taste of gastrografin.[295] All patients underwent elective colorectal surgery, using an ERAS framework, and a total of 80 patients, (40 per arm) were recruited.[39] A total of 71 patients were analysed (35 gastrografin, 36 placebo) and the primary outcome was duration of PPOI. There was a trend towards faster resolution of PPOI in the gastrografin group compared to placebo (mean 83.7 hours vs 101.3 hours), but this did not reach statistical significance (p=0.191).[295] Gastrografin did significantly improve time to passage of flatus and stool compared to placebo, and improved time to resolution of abdominal distension.[295] Gastrografin did not improve time to discharge but was safe to use, without an increase in postoperative morbidity or mortality.[295]

Biondo *et al* (2016) conducted a multi-centre randomized double-blinded control trial of gastrografin compared to placebo to treat PPOI, using the same prospective PPOI definition

as Vather *et al* (2015).[296] They assessed the duration of PPOI from NG tube insertion until tolerance of diet maintained until discharge. The study recruited 29 patients per arm, and found a trend towards faster resolution of PPOI, tolerance of diet, passage of flatus or stool and length of stay, but none of these reached statistical significance.[296] Both of these trials had relatively small numbers, and one key limitation is whether this resulted in a type 2 error (the chance of a false negative result). Clinical trends in improvement of PPOI symptoms may have reached statistical significance if assessed in a larger cohort, or by combining the data of these trials. There may still be a role for gastrografin as a "rescue medication" in the context of PPOI, which warrants further assessment.

1.8 Prucalopride, a promising new target for PPOI prevention

This chapter has discussed what we currently know about PPOI prediction, prevention, and treatment. There are few definitive management strategies and proven preventative agents for PPOI outside of current ERAS-based care. There are, however, new targets emerging for PPOI prevention that warrant further interest. One promising target for PPOI prevention is the selective 5HT-4R agonist, Prucalopride. The role of serotonin signaling in the gut, it's implications for PPOI prevention, and the therapeutic safety of prucalopride will be examined in the following section.

1.8.1 Serotonin signalling in the gut as a target for PPOI

Serotonin (5HT) is a neurotransmitter well known for its role in the central nervous system. However, 95% of serotonin production and utilisation occurs in the gut, and this has become a major target for modern research into gut motility and dysmotility.[297] Current evidence suggests that serotonin plays a critical role in modulating peristalsis of the gut and in visceral perception, by acting on specific serotonin receptors. For example, the 5HT3 receptor is involved in visceral perception and can cause nausea when activated; Ondansetron is a 5HT3 receptor antagonist, which explains its antiemetic properties.[297, 298] The 5HT4 receptor is primarily involved in enhancing the release of acetylcholine from cholinergic motor neurons in the gut and has shown promise as a therapeutic agent for gastroparesis, constipation and constipation-predominant irritable bowel syndrome.[299] The physiology of serotonin signalling in the gut is complex, but understanding it opens up numerous pharmaceutical targets for intestinal dysmotility and disease.

Several agents that target serotonin signalling in the gut have been developed and investigated. Cisapride, as discussed previously, and tegaserod are agonists of the 5HT4 receptor and had a role in the treatment of gastroparesis.[300] Cisapride also had a high affinity for cardiac voltage gated potassium channels (hERG-K), leading to cardiac arrhythmias.[269, 299] Prucalopride, or “Resotrans”, has recently been developed as a therapeutic agent for constipation. Prucalopride acts pre-synaptically on 5HT4 receptors on enteric neurons, with high affinity and selectivity,[301, 302] stimulating ACh release and promoting coordinated intestinal contraction.[303] Prucalopride could be a promising medication for PPOI prevention, and the evidence for its effects is summarised in the following section.

1.8.2 Colonic prokinetic

Prucalopride has strong prokinetic effects. Prucalopride increases the frequency of high amplitude propagating complexes detected on manometry in healthy adults.[304] Prucalopride is believed to lower the threshold for smooth muscle contraction when stimulated by the vagus, thus increasing the frequency of colonic motor complexes, and it has synergistic effects on intestinal contractility when combined with acetyl cholinesterase inhibitors neostigmine and donepezil.[303, 305-307] Initial use of prucalopride in healthy volunteers showed a predominant increase in colonic motility associated with prucalopride.[308] In patients with chronic constipation, prucalopride significantly increases the number of high-amplitude propagating complexes detected with colonic manometry, after only a single 2mg tablet of prucalopride,[307] and long term use is associated with a persistent clinical benefit in constipation-related symptoms.[309] For chronic constipation, increasing the dose of prucalopride from 2mg to 4mg does not result in an improved number of weekly bowel motions or patient-based quality of life scores.[310] Prucalopride is now registered for use in Europe, America and Australia for the treatment of chronic constipation in patients where laxatives have failed, and is supported by series showing significant improvements in soft bowel motions, regular bowel opening and quality of life scores in patients with chronic constipation, including those with opioid-induced constipation.[302, 311-313]

1.8.3 Gastric and small intestinal prokinetic

The ability of prucalopride to stimulate colonic transit is well established, but there is a growing body of evidence for its efficacy as a gastric and small bowel prokinetic agent. Early studies showed contradictory results; Emmanuel *et al* (1998) showed an increase in oro-caecal transit time, using the hydrogen breath testing method, in 18 healthy patients who

received 1mg or 2mg of prucalopride, or control.[314] Conversely, a study from the Mayo Clinic showed no difference in gastric emptying rates using scintigraphy in 53 healthy subjects receiving varying doses of prucalopride (up to 4mg) daily or placebo.[308] Since these initial reports, research into prucalopride's effect on gastric emptying has largely involved in vitro studies using animal and human tissue. De Maeyer *et al* (2006) showed that prucalopride increased electrically stimulated smooth muscle contraction in pig stomach, and this effect was directly attributed to stimulation of the 5HT4 receptor.[315] Recent evidence in human in vitro gastric tissue suggests that prucalopride does increase the sensitivity of gastric fundus and antrum to electrically-stimulated contraction.[306, 316] An interesting study by Kessing *et al* (2014) looked at gastric emptying rates, determined using scintigraphy, high-resolution manometry and ambulatory pH measurement, in 21 healthy patients receiving 6 days of 4mg prucalopride.[317] The results showed that prucalopride significantly increased gastric emptying times and reduced residual stomach volumes after a meal.[317] Prucalopride has been shown to improve gastric emptying times and small bowel transit in patients who undergo video capsule endoscopy.[318] In patients with gastroparesis, 4mg of prucalopride led to faster gastric emptying and an increase in frequency of bowel motions.[319] Similar results were seen in a trial of 2mg prucalopride daily for patients with gastroparesis: prucalopride led to improved gastric emptying times and patient-reported symptoms of gastroparesis using the GCSI (gastrointestinal cardinal symptom index).[320] The potential role of prucalopride as a stimulator for gastric emptying demands further research, and may make it a promising target for conditions of pan-intestinal hypomotility, such as PPOI.

1.8.4 5HT4 receptor and PPOI

There is evidence that 5HT4 receptor agonists may have a beneficial role in PPOI prevention. Similar to prucalopride, mosapride is a drug that acts as an agonist for 5HT4R, but it also strongly antagonises the 5HT3 receptor. Mosapride has been shown to benefit patient outcomes after colectomy in 2 small RCTs.[321, 322] Narita *et al* (2008) studied the effect of mosapride, compared to placebo, commenced from day 1 postoperatively in 40 patients undergoing laparoscopic colectomy.[321] They found a significantly shorter time to first flatus (48.5 hours compared to 69.3 hours, p=0.015) as well as a shorter time to discharge (by 1.7 days).[321] In addition, gastric emptying using the 13C- acetate breath test showed faster gastric emptying on postoperative day 2 in the mosapride group compared to control.[321] The effect of mosapride on postoperative gastrointestinal motility was further analysed in a small RCT by Tomoyasu *et al* (2011), where 30 patients undergoing colectomy were randomised to mosapride or placebo from day 1

postoperatively.[322] Mosapride conferred a significant decrease in time to first flatus and defecation.[322] Interestingly upper intestinal pressure waves were measured using manometry in these same patients on day 8 postoperatively, showing an increase in antral and duodenal contractions in the mosapride group compared to placebo in both fed and fasted states.[322] These trials are of small numbers and only used mosapride in the postoperative period, but have introduced the idea of 5HT4 receptor agonists as promising targets for further PPOI research.

More recently, interest has turned to prucalopride as a potential therapeutic target for PPOI. Animal models show a strong benefit for prucalopride in ameliorating postoperative gut dysmotility. Studies in guinea pigs using intestinal manipulation as a model for ileus have shown that prucalopride stimulates both upper and lower bowel transit postoperatively.[323] Interestingly, later studies suggest that prucalopride may act as an anti-inflammatory agent in addition to its role as a prokinetic. The hypothesis for this action is that prucalopride mimics, or potentiates, the vagal cholinergic anti-inflammatory pathway. 5HT4 receptors are highly expressed on enteric neurons, and these neurons play an integral role in reducing activation of resident intestinal macrophages in response to surgical trauma.[99] In a mouse model of ileus induced by intestinal manipulation, preoperative prucalopride reduced intestinal inflammation, reduced IL6 and IL1β expression and significantly increased intestinal motility.[301] Postoperative administration alone did not lead to a reduction in ileus after intestinal manipulation and did not reduce intestinal inflammation in animal models.[301] The anti-inflammatory effect of prucalopride was negated in a7AChR knockout mice, which is the ACh receptor expressed by enteric resident macrophages.[99, 301] A similar study found that mosapride significantly reduced macrophage infiltration in rats following intestinal manipulation, and that direct inhibition of the 5HT4 receptor prevented this benefit.[324] Further animal studies in mice confirm that treatment with prucalopride prior to intestinal manipulation results in reduced cytokine expression, reduced influx of inflammatory cells and faster intestinal transit times postoperatively.[99] Vagotomy does not ameliorate the anti-inflammatory effects of prucalopride in mouse models, which means prucalopride acts directly on enteric neurons as part of its mechanism.[99] Conversely, postoperative prucalopride administration does not reduce intestinal inflammation, and does not improve intestinal transit times in animal models.[99]

1.8.5 Recent human trials

Prucalopride has been investigated in a large scale phase 2b randomised double-blind dose-finding control trial in 317 patients undergoing elective partial colectomy.[325] The primary

outcome of this study was time to first flatus. In the group who received 4mg of prucalopride there was a significant decrease in time to first flatus and stool.[325] Prucalopride at lower doses had a similar effect, but the difference was not statistically significant.[325] Prucalopride was administered subcutaneously to patients within 2 hours of finishing surgery and continued for only 3 days postoperatively. The incidence of overall and serious adverse events were reported as not significantly different between treatment groups.[325] Unfortunately this data was presented in abstract and has not been published.

Gong *et al* (2016) conducted an RCT to assess the role of postoperative oral prucalopride after abdominal surgery.[326] They recruited 110 patients, aged 18-75, and included patients who underwent segmental gastric, small bowel or colonic resection, either by laparoscopic or open surgery.[326] Patients were excluded if they had ASA grade of 4 or higher, had a planned stoma formation, had an epidural, or who had a total or subtotal colectomy. Patients with inflammatory bowel disease were included. Early postoperative oral nutrition was allowed, but there was no description of whether a formal ERAS pathway was used. NSAIDs were given as part of their standard analgesia protocol, unless contraindicated. Randomisation occurred postoperatively, and participants received either 2mg oral prucalopride on postoperative day 1 or placebo, for a maximum of 7 days or until they had passed a bowel motion.[326] The primary outcome was time to first bowel motion, incidence of PPOI (using Vather's definition),[2] time to oral intake, and complications. The study was powered to detect a 24 hour improvement in time to first bowel motion, with 90% power and a 10% dropout rate, and used an intention-to-treat analysis.[326] Patients were excluded from the per protocol analysis if they had an NGT insertion, withdrew consent or developed an adverse event. There was a significant improvement in time to passage of flatus (mean improvement 20 hours, $p<0.001$) and stool (mean improvement 29.5 hours, $p=0.001$) in the prucalopride group on intention-to-treat analysis.[326] There was a reduced incidence of PPOI (16.4% in the prucalopride group, 34.5% in the placebo group, $p=0.026$), but no difference in time to tolerance of diet.[326] There was a 24 hour median improvement in length of stay (median 7 days vs 8 days) for patients who received prucalopride, and no difference in major complications (Clavien-Dindo grade 3+).[326] They found no changes in postoperative CRP levels between groups on postoperative days 1 or 3, and a slight reduction in CRP on postoperative day 5 with prucalopride.

The key limitations to this study are that it was powered to an endpoint of time to stool, which may leave it significantly underpowered to detect a change in GI-2. GI-2 is a much more reliable measure of return of postoperative gut function. Prucalopride had no meaningful improvement on postoperative inflammatory markers, but was only given postoperatively,

meaning that it's potential anti-inflammatory effect would have been minimised or missed intraoperatively. Animal studies suggest that preoperative administration of prucalopride is essential. The study also included a significant number of patients with inflammatory bowel disease, small bowel and gastric resection, and only 34.5% underwent laparoscopic surgery.[326] There was no mention of a standardised ERAS pathway, meaning that we cannot draw conclusions about the beneficial role of prucalopride in a contemporary cohort of colorectal patients. Despite these limitations, Gong *et al* (2016) have highlighted a promising role for prucalopride to improve time to first bowel motion and reduce PPOI when it is given after abdominal surgery.

A recent trial of preoperative prucalopride by Stakenborg *et al* (2019) has shown promising results to support the theory that prucalopride reduces intraoperative inflammation and results in improved gut recovery after pancreaticoduodenectomy.[99] This trial recruited 30 patients who were randomised to either prucalopride, vagal nerve stimulation or placebo/sham treatment (10 per arm). Patients in the prucalopride group received 2mg prucalopride at 16 hours and 2 hours preoperatively. Vagal nerve stimulation occurred for 2 minutes at the start and end of the surgical procedure. The results of this trial show significant improvements in markers of intestinal inflammation, and in return of gut function with preoperative prucalopride administration.[99] Prucalopride reduced the time until removal of NG tube after pancreaticoduodenectomy, led to a significantly faster time to tolerate an oral diet, and reduced length of postoperative stay.[99] Prucalopride also reduced pro-inflammatory gene expression (IL6 and IL8) in intestinal muscularis tissue samples taken.[99] There was no improvement in time to first defecation in the prucalopride group compared to placebo.[99]

Preoperative prucalopride administration improves intraoperative and postoperative intestinal inflammation and time to tolerate an oral diet, but does not improve time to first defecation in patients undergoing pancreaticoduodenectomy. Postoperative prucalopride improves time to first defecation for patients who undergo open or laparoscopic abdominal surgery, but does not improve postoperative inflammatory markers and does not improve time to tolerate a diet. Therefore, the optimal administration of prucalopride should include both pre and postoperative dosing, allowing both its anti-inflammatory and prokinetic effects to improve pan-intestinal gut recovery. This makes prucalopride one of the most promising agents to improve postoperative gut recovery and to prevent PPOI.

1.8.6 Prucalopride safety

The risk profile of prucalopride has also been well investigated. A meta-analysis of 4 randomised control trials showed that prucalopride use over 12 weeks for chronic constipation was well tolerated in 1821 patients, with only mild-moderate adverse events (Aes) reported.[327] Common Aes included nausea, headache and diarrhoea and occurred in around 40% of patients on prucalopride compared to 15-30% in the placebo arm.[327] The majority of these complications occur early in treatment, usually within a few hours of first medication dosing, last a short duration, and are reported as mild to moderate in severity.[308, 314, 317] The only significant AE for prucalopride that persisted past day 1 of use on meta-analysis was diarrhoea.[269, 308, 327] A review by Tack *et al* (2011) found that the rate of discontinuation of prucalopride was as low as 3% due to nausea and diarrhoea.[269] Importantly, prucalopride has no effect on the QT interval on serial electrocardiograms (ECGs) in doses up to 20mg,[269, 328] and has no effect on in vitro cardiac tissue.[329] A study in a nursing home population where 88% of patients had a history of cardiovascular disease showed no change in ECG parameters or vital signs.[330] Prucalopride is largely excreted by the kidneys with little metabolism by the liver, and a standard dose is 2mg orally per day, with a dose reduction to 1mg where creatinine clearance is less than 50mL/min.[331] Studies have shown that plasma concentration rises rapidly to achieve a peak plasma concentration in 2-3 hours after ingestion and a steady state is reached in 4-7 days.[330, 331]

The current guidelines for patients aged >65 years old receiving long-term (up to 24 weeks) prucalopride for constipation suggest starting at 1mg prucalopride daily and then increasing to 2mg daily based on efficacy. One study assessed the safety of prucalopride in doses ranging from 0.5-2mg daily for 4 weeks in patients over 65 years old.[330] No differences in vital signs, overall adverse events or withdrawals from medication were noted between the different dosing regimens.[330]

In conclusion, the serotonin signalling pathways of the gut remain complex but a growing body of evidence suggests that stimulating the 5HT4 receptor may help prevent PPOI. Prucalopride has proven efficacy in chronic constipation, however research in vitro, and in recent human data, suggests that prucalopride could be used as a therapeutic agent for PPOI. The effect of prucalopride, orally, must be better quantified in patients undergoing colorectal surgery, who bear the highest incidence and burden of PPOI. Finally, the real benefit of prucalopride may not be an increase in stimulation of bowel motility

postoperatively, but instead the prevention of intestinal inflammation at time of surgery that confers patients the most significant improvement in postoperative recovery.

1.9 Summary

In this chapter, we have defined PPOI and demonstrated the burden PPOI places on all aspects of the healthcare system. We have discussed current management and prevention of PPOI and highlighted possible future areas for intervention. There are significant gaps in the literature that we aim to address as part of this PhD. Firstly, we plan to quantify the true economic burden of PPOI within an ERAS cohort, using a strict and valid definition of PPOI. We plan to prospectively validate the I-Score in a multicenter cohort study, to better predict patients at high-risk for PPOI, thereby identifying those who would benefit most from preventative measures. By understanding the pathophysiology of PPOI, we have identified the potential role of COX inhibitors in PPOI prevention, however, current evidence relies on relatively few and small RCTs. We plan to systematically review the role of NSAIDs in PPOI prevention and in improving postoperative gastrointestinal function. Gastrografin may be the sole therapeutic agent for PPOI, but the two trials that assessed it may have been underpowered. We plan to perform a pooled analysis of these trials to better determine if gastrografin is an effective treatment for PPOI. Finally, we have identified a promising target to prevent PPOI and improve postoperative gut dysmotility after abdominal surgery: prucalopride, a selective 5HT4 receptor agonist. We will design and carry out a double-blind randomized control trial of prucalopride, given both preoperatively and postoperatively, to see if it is effective in improving postoperative gut motility and in preventing PPOI.

Chapter 2 Thesis Objectives and Overview

The goal of this PhD is to better understand the burden of PPOI and to identify options for PPOI treatment and prevention.

Our understanding of the economic burden of PPOI is based upon clinical coding data collected retrospectively, with varying definitions of PPOI. This makes it difficult to interpret within our healthcare system model, and within a modern ERAS patient cohort. Chapter 3 will assess the economic burden of PPOI within a NZ-based cohort of patients, using prospectively collected data and the strict definition of PPOI proposed by Vather *et al* (2013).[2]

As explained in the introduction, if clinicians could accurately predict patients at risk of PPOI, those patients could be targeted with a bundle of preventative measures to reduce their risk. To date, clinicians still lack an accurate prediction score for PPOI development, and those scores currently available have not used a comprehensive definition of PPOI. Chapter 4 will present the results of a large multi-center cohort study, including sites in New Zealand and Spain, to test the ability of the I-Score to prospectively predict PPOI development after elective colorectal surgery.

There are a variety of proposed prevention strategies for PPOI, but few are proven effective other than ERAS. There is evidence for interventions such as alvimopan in select patient groups, however, alvimopan is not available in NZ and the cost of the medication is prohibitive. The pathophysiology of ileus clearly involves COX activity; however, we lack a systematic review to summarize and collate the data on whether COX inhibitors are effective in restoring postoperative gut motility, and in preventing PPOI. Therefore, we will conduct a systematic review of all available RCTs to determine whether NSAIDs are effective after colorectal surgery. Chapter 5 describes the methodology and findings of this systematic review.

There are few effective treatments for an established PPOI, as explained in chapter 1. One possible intervention is gastrografin, which may improve return of gut function for patients with PPOI after colorectal surgery. The results of the 2 trials on gastrografin use for PPOI

were inconclusive. Both trials cited concern that they may have been underpowered. We therefore plan to conduct a pooled analysis of both trials using their raw data, to see if increasing patient numbers leads to a different outcome. Chapter 6 will present the results of our pooled analysis to determine whether gastrografin is an effective treatment for PPOI.

Finally, Chapter 7 will present a randomized double-blind placebo-controlled trial to test whether prucalopride is an effective medication in improving postoperative bowel function and reducing the rate of PPOI. This trial will be a multicenter trial using independently sourced prucalopride and placebo, to avoid bias. This trial will form the cornerstone of this PhD thesis, and hopefully demonstrate a new effective intervention that improves outcomes for patients after colorectal surgery

Chapter 3

Prolonged postoperative ileus significantly increases the cost of inpatient stay for patients undergoing elective colorectal surgery: results of a multivariate analysis of prospective data at a single institution.

3.1 Introduction

Postoperative ileus (POI) refers to a period of postoperative gut dysmotility and is especially common in patients undergoing abdominal surgery. The pathophysiology of POI involves complex neural and inflammatory pathways triggered at the time of surgery that reduce gut motility, usually lasting up to 2-4 days postoperatively.[1, 4] Some patients suffer prolonged postoperative gut dysmotility, lasting 4 or more days after surgery or requiring insertion of a nasogastric tube, which leads to a significant increase in postoperative complication rates and length of stay.[6, 44] Recent international series estimate the rate of prolonged POI (PPOI) to be between 10-27% after colorectal surgery.[16, 43]

The high incidence of PPOI after colorectal surgery, and its associated morbidity, places a substantial economic burden on the healthcare system.[6] Goldstein *et al* estimated that the total annual cost of PPOI to the US healthcare system was around $1.5 billion.[6] Several large retrospective studies have shown that the healthcare system spends around 50-100% more on patients who develop PPOI compared to those who do not,[6, 37, 48] and that 91% of those increased costs are directly related to the patient's immediate postoperative stay.[6]

The limitations of previous studies assessing the economic burden of PPOI in patients after abdominal surgery are that these studies have typically been retrospective and have relied on clinical coding data, therefore lacking a precise definition for what constitutes a "normal" POI compared to a PPOI. Reliance on clinical coding likely leads to an underestimate in rates of PPOI, which may in turn lead to underestimation of associated total costs.[332, 333] Therefore, clinicians and decision makers lack robust data on the economic impact of PPOI based on prospective evidence.

This study aims to evaluate the cost of PPOI, using a strict and prospective definition,[2] in patients undergoing elective colorectal surgery at a single institution within an Enhanced Recovery After Surgery (ERAS) setting.

3.2 Materials and Methods

This study included prospectively assessed patients that were part of a previous observational study looking at risk factors for PPOI at Auckland City Hospital between September 2012 and June 2014.[43] After ethical approval, economic data on cost of inpatient stay were audited from Auckland District Health Board for all patients.

The inclusion criteria were all patients aged 18 or older undergoing elective colorectal surgery within the recruitment period at Auckland City Hospital. All patients were managed post-operatively according to a protocolled and carefully monitored colorectal care pathway that included preoperative counseling, minimal oral restriction preoperatively, restrictive fluids, subcutaneous thromboprophylaxis (enoxaparin 40mg), stepwise analgesia progression, avoidance of nasogastric tube, early post-operative feeding, and structured mobilisation regimens in conjunction with physiotherapy. The use of opioids are restricted but opioid antagonists, such as alvimopan, are not used. Patients were diagnosed with PPOI using a strict prospective definition, based on an international survey.[2] PPOI was defined as the presence of two or more of the following criteria on or after postoperative day 4: moderate to severe nausea/vomiting, inability to tolerate a solid or semi solid diet, moderate to severe abdominal distension, absence of flatus and stool, radiological evidence of ileus on x-ray or CT scan. Patients were excluded if they were unable to participate in postoperative assessments due to language difficulty, postoperative confusion, or cognitive impairment. Patients were also excluded if they required TPN preoperatively, or if they required a re-operation before they could be formally assessed for PPOI.

Economic data were audited from Auckland District Health Board Information Management Service for all enrolled patients, including total cost of stay as well as departmental costs (laboratory services, pharmacy and medication, ward costs, theatre costs, medical costs, and allied health costs). Demographic data for patients with or without PPOI were compared using the chi-squared or Fischer's exact test for dichotomous data. The distribution of continuous data was assessed using a histogram and the Shapiro-Wilk test. Data that were normally distributed were expressed as mean $\pm$ 1 standard deviation (SD) and analyzed using an independent samples t-test. Non-parametric continuous data were expressed as median, interquartile range (IQR) and compared using the Mann-Whitney U test.

A multivariate linear regression analysis was performed on log-normal transformed total cost of inpatient stay. A multivariate analysis allows an estimate of PPOI-attributable cost to control for other factors increasing the cost of inpatient stays, whilst the transformation of costs allows the regression to account for left skewness in the data. These covariates include the length of stay and whether the patient developed other major complications based on the Clavien-Dindo system.[334] All statistics were performed in SPSS version 24.0 for Mac (SPSS Inc., Chicago, IL). A p-value of <0.05 was deemed to be significant on both univariate and multivariate analysis, and all p-values were 2-sided.

3.3 Results

Resource utilisation data were obtained from 325 patients undergoing elective colorectal surgery between September 2012 and June 2014. In total, 88 (27%) patients in the cohort were diagnosed with PPOI. Table 3-1 describes the differences in demographic data, type and indication of operation, operative technique and outcomes for patients with and without PPOI. As described previously in this cohort of patients,[2] PPOI was more common in patients who were male ($p=0.021$), patients undergoing total colectomy ($p=0.013$), patients who required an open or converted-to-open operation ($p<0.005$), and patients with a higher ASA grade ($p=0.025$). Patients undergoing ileostomy reversal were less likely to develop a PPOI compared to other operations ($p=0.038$).

Table 3-1. Comparison of demographic data between PPOI and non-PPOI patients (325 patients)

	PPOI (88 patients)	No PPOI (237 patients)	P-value
Age (Mean, SD)	65.4 (14.9) years	62.2 (16.9) years	0.117
Gender			0.021
Male	59 (67%)	125 (53%)	
Female	29	112	
Procedure			
Reversal ileostomy	15 (18.3%)	67 (81.7%)	0.038
Reversal colostomy	11 (39.3%)	17 (60.7%)	0.128
Right Hemi	19 (25.8%)	34 (64.2%)	0.116
Anterior resection	28 (25.2%)	83 (74.8%)	0.588
APR	4 (28.6%)	10 (71.4%)	0.898
Total colectomy	7 (58.3%)	5 (41.7%)	0.013
Formation stoma	1 (9.1%)	10 (90.9%)	0.172
Small bowel resection	0 (0%)	4 (100%)	0.220
Other	3 (30%)	7 (70%)	0.833
Indication			
Cancer	69	175	0.397
IBD	7	23	0.628
Diverticular disease	3	19	0.142
Volvulus	2	2	0.297
Other	7	18	0.914
Open/converted technique*			<0.005
Yes	68 (77%)	128 (54%)	
No	20	109	
ASA			0.025
1 or 2	48 (54.5%)	161 (67.9%)	
3+	40 (45.5%)	76 (32.1%)	
Major complication (CD≥3)			0.001
Yes	19 (21.6%)	20 (8.4%)	
No	69	217	
Length of stay (Median, IQR)	12.5 (7-18) days	5 (3-7) days	<0.005

Dichotomised data using Chi-squared test
Continuous data, parametric using independent samples t-test, non-parametric using Mann-Whitney U test
* Includes stoma reversal

Table 3-2 demonstrates the economic burden of PPOI in this cohort. The total median cost of inpatient stay for patients with PPOI, which includes length of stay and incidence of major complications, was $27,981 (IQR = $20,198-$42,174) compared to $16,317 (IQR = $10,620-$23,722) for patients without PPOI (p<0.005). This represents a 71% increase in median cost for patients with PPOI compared to those without. The median cost of medical care (medical staff time managing the patient) and ward care (the cost of nursing care) was increased in ileus patients by 74% and 122% respectively (p<0.005). Median radiology,

laboratory, medication/pharmacy, and allied health costs were also all significantly increased (p<0.005). The median cost of laboratory tests and medication were doubled for patients with PPOI (107% increase and 111% respectively, p<0.005).

Table 3-2. Summary of cost of inpatient stay (NZD)

	PPOI	No PPOI	
	Median (interquartile range)	Median (interquartile range)	P-value
Total cost of inpatient stay	$27,981 ($20,198, $42,174)	$16,317 ($10,620, $23,722)	<0.005
Medical cost	$4,484 ($3,498, $6,641)	$2,583 ($1,870, $3,943)	<0.005
Laboratory cost	$2,688 ($1,319, $3,666)	$1,287 ($401, $2,266)	<0.005
Radiology cost	$687 ($109, $1,534)	$0 ($0, $247)	<0.005
Medication cost	$735 ($416, $1,745)	$348 ($216, $496)	<0.005
Ward and nursing cost	$8,457 ($5,742, $13,381)	$3816 ($2,598, $6,573)	<0.005
Allied health cost	$349 ($184, $438)	$229 ($138, $367)	<0.005

Mann-Whitney U test for non-parametric data

The incidence of postoperative complications was higher in patients who met the criteria for PPOI, in particular Clavien-Dindo grade 3 or higher complications (21.6% vs. 8.4%, p=0.001). Patients with PPOI also had a significantly longer median length of stay compared to those with normal postoperative recovery of gut function: 12.5 days (IQR = 7-18 days) vs. 5 days (IQR = 3-7 days) respectively (p<0.005). A multivariate analysis was performed on log-costs of total inpatient cost of stay. Table 3 displays the results of univariate and multivariate factors that were included in the model. On multivariate analysis, patient ASA grade ≥3, preoperative albumin <34g/L, operation duration ≥3 hours, formation of stoma (ileostomy or colostomy), opioid use higher than the median (p=0.049), and development of a PPOI or a Clavien-Dindo complication of grade 3 or higher, were all significant (p<0.05) predictors of increased cost of stay. PPOI related to a major complication (3 with anastomotic leak and 4 early postoperative bowel obstructions) was more than twice as expensive as “primary” PPOI, without an obvious secondary cause (median $57,871, IQR $48,687-$61,231 vs. $25,889, IQR $20,156-$37,960, p=0.001). However, “primary” PPOI was still more expensive than patients with normal postoperative recovery (P<0.001). Age, gender, previous abdominal surgery, BMI, surgery for cancer, were not independently associated with hospitalisation costs (P>0.05). TPN was required in 30 patients with PPOI

(34%), and the median cost of inpatient stay for patients who required TPN was $31,120 (IQR $30,250, $58,522).

Table 3-3: Results of multivariate linear-regression analysis on total cost of inpatient stay (NZD)

Variable	Proportion of patients	Median cost (IQR)	Univariate P-value*	Multivariate P-value
Age > 70			0.044	0.191
Yes	125 (38%)	$20,518 ($11,200, $29,836)		
No	200 (62%)	$17,458 ($9,158, $25,758)		
Gender			0.221	0.848
Male	184 (57%)	$19,268 ($10,206, $28,330)		
Female	141 (43%)	$17,733 ($9,411, $26,025)		
Previous abdominal surgery			<0.001	0.391
Yes	194 (60%)	$17,038 ($9,615, $24,461)		
No	131 (40%)	$21,546 ($12,444, $30,648)		
Comorbidity				
ASA > 3				
Yes	116 (36%)	$24,557 ($14,783, $31,320)	<0.001	0.001
No	209 (64%)	$16,259 ($9,367, $23,151)		
BMI ≥30				
Yes	85 (26%)	$22,282 ($12,417, $32,147)	0.017	0.906
No	240 (74%)	$17,334 ($9,201, $25,467)		
Preop Haemoglobin ≤109g/L				
Yes	53 (16%)	$24,549 ($12,953, $36,145)	0.001	0.073
No	272 (84%)	$18,159 ($6,563, $29,755)		
Preop albumin <34g/L				
Yes	14 (5%)	$36,238 ($22,192, $50,284)	<0.001	0.006
No	297 (95%)	$18,248 ($10,655, $25,841)		
Operative factors				
Surgical technique				
Laparoscopic/assisted	129 (40%)	$18,409 ($11,636, $25,182)	0.557	0.186
Open/converted	196 (60%)	$19,456 ($9,303, $29,609)		
Duration of operation				
≥3 hours	161 (50%)	$24,565 ($16,532, $32,598)	<0.001	<0.001
<3 hours	164 (50%)	$12,580 ($8,191, $16,969)		
Indication				
Cancer	244 (75%)	$19,992 ($10,646, $29,338)	0.007	0.271
Other	81 (25%)	$16,124 ($9,600, $22,648)		
Stoma formation				
Yes	108 (33%)	$26,611 ($17,181, $36,038)	<0.001	<0.001
No	217 (67%)	$15,360 ($9,063, $21,657)		
Postoperative factors				
Periop blood transfusion				
Yes	46 (14%)	$33,178 ($18,724, $47,632)	<0.001	0.078
No	279 (86%)	$17,046 ($10,106, $23,986)		
Postop opioid use > median				
Yes	161 (50%)	$20,474 ($12,946, $28,002)	0.003	0.049
No	163 (50%)	$16,317 ($7,461, $25,173)		
Day of first mobilization				
Day 0/1	213 (66%)	$15,500 ($8,746, $22,254)	<0.001	0.095
Day 2 or later	112 (34%)	$24,892 ($15,688, $34,096)		
PPOI				
Yes	88 (27%)	$27,981 ($16,992, $38,970)	<0.001	<0.001
No	237 (73%)	$16,317 ($9,766, $22,868)		

Clavien-Dindo Grade					
	≥3	39 (12%)	$43,843 ($28,701, $58,985)	<0.001	<0.001
	<3	286 (78%)	$17,131 ($10,480, $23,782)		

Laparoscopic surgery did not reduce the cost of inpatient stay compared to open/converted surgery (median $18409, IQR = $11636-$25082 vs. $19456, IQR = $9322-$29560 respectively, p=0.557), despite a significant reduction in length of stay for patients the laparoscopic cohort compared to the open/converted cohort (median 5 days, IQR = 1-9 days vs. 7.5 days, IQR = 4-11 days, p=0.01). Laparoscopic resection significantly increased surgery duration (median 210 mins, IQR = 140-280 mins vs. 142 mins, IQR = 77-207 mins, p<0.001) and cost of operation (median $5278, IQR = $3817-$6379 vs. $4413, IQR = $2567-$6259, p=0.018) versus open/converted surgery respectively.

A sensitivity analysis was performed to assess the impact of length of stay on the economic burden of PPOI. When length of stay was included in the statistical model, PPOI remained a significant cause of increased health spending (p=0.012). Taking into account all variables, PPOI had a Beta coefficient of 0.141, which equates to a 15% (95% CI: 3-29%) or $2,875 increased cost for patients who develop PPOI when considering other significant associated factors related to their care, including major complications and prolonged length of stay.

3.4 Discussion

This study is the first to determine the economic impact of PPOI using a strict definition, based on systematic review and global survey.[2] All patients in this study were prospectively diagnosed with PPOI, which avoids the inaccuracies of clinical coding and the limitations of similar previous studies.[6, 37, 332] The results showed that PPOI is a significant burden for the healthcare system, increasing median cost of inpatient stay by 71%. When adjusting for other associated sources of increased health cost in these patients, PPOI remains a significant economic burden for the hospital. All departments experienced increased costs for patients who developed PPOI, due to an increased need for nursing care, blood tests and laboratory work, radiology and allied health input.

The economic burden of ileus has previously been assessed in several large retrospective studies, and the results of our present work validates and expands upon those studies with a higher quality of evidence.[6, 48, 333] Despite the healthcare systems in the United States and New Zealand utilising different models of funding, our results closely match those in the US, where ileus has been shown to increase the cost of inpatient stay by up to 100%.[6, 48,

333] A study by Iyer *et al* similarly found that patients with ileus also had a 15% increase in health cost on multivariate analysis when adjusting for patient age, gender, incidence of complications and type of admission (elective, emergency).[37] Our study provides substantially greater confidence than previous literature by using prospectively collected and detailed demographic, operative and postoperative data.

To date, there are few effective interventions to prevent or treat PPOI.[250, 335] One of the challenges facing clinicians is developing effective and cost-efficient means to prevent or reduce the burden of PPOI. The use of an ERAS protocol has been the mainstay of modern day PPOI prevention for patients undergoing colorectal surgery.[336] However, recent studies suggest that the true cost benefit of the ERAS program is poorly defined, ranging from Euro 153-6537 per patient.[337] Furthermore, a patient developing a PPOI is one of the strongest predictors for inability to adhere to the ERAS protocol in the postoperative period.[338] The results of our multivariate analysis showed that patients who develop PPOI are inherently more expensive than similar patients, when adjusting for the incidence of major complications and length of stay. Our results suggest that there is still a significant economic benefit for interventions that reduce PPOI, even if they do not reduce overall length of stay. These results should further motivate efforts to develop improved preventative strategies because, despite advances in ERAS care, the rate of PPOI remains high for at-risk patients.[2] Interestingly, laparoscopic surgery did not reduce overall cost of stay, despite reducing rates of PPOI and length of stay. This may be explained by the increased duration and equipment cost associated with laparoscopic surgery. Current literature is unclear regarding the cost effectiveness of laparoscopic surgery for colorectal surgery.[339, 340]

We have previously shown low preoperative albumin (<34g/L) to be a risk factor for the development of PPOI.[43] Here we show that low albumin is also an independent risk factor for increased cost of inpatient stay. Pre-operative low albumin may suggest poor preoperative nutritional status, and albumin is often used as a tool to assess frailty in patients undergoing surgery.[341, 342] Interventions to improve preoperative nutritional status may reduce postoperative morbidity and mortality.[343] It is unclear whether preoperative albumin can be meaningfully corrected before surgery,[344, 345] or is just a marker of patient frailty.

An increased use of opioids led to an increased cost of stay, which agrees with the current literature.[333] To reduce healthcare spending, it is important to consider alternative pharmaceutical means to reduce opiate consumption. Alvimopan is a peripheral μ-opioid

receptor antagonist that blocks the action of opioids in the gut. While studies show that alvimopan does not reduce opiate consumption,[346] it does reduce the rate of PPOI for patients undergoing colorectal surgery.[281, 332] Importantly, alvimopan only offers a modest reduction (4-7.5%) in associated healthcare spending.[281, 332] There is some controversy about the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in colorectal surgery and their potential to increase anastomotic leak.[347] We await further studies on their safety and efficacy in patients undergoing colorectal surgery.

Stoma formation (ileostomy or colostomy) is known to be a significant cause of increased cost of inpatient stay. Stoma formation may increase the length of stay for patients treated under an ERAS framework,[348, 349] and there is clear evidence to suggest that post-discharge costs and morbidity associated with stoma reversal are significant issues for both the patient and healthcare system.[161, 350] We show that stoma formation is a significant expense for the hospital irrespective of increased complication rates and length of stay. Further studies looking at the economic benefit of early stoma closure or avoidance of stoma formation, in conjunction with accurate and early prediction of anastomotic leak, are required.

This study is the first to assess the economic cost of ileus using a multivariate model of demographic, operative and postoperative factors in patients prospectively assessed for PPOI. However, there are some limitations to consider. This study was performed at a single centre. Ideally, future studies would use prospective economic data in patients who meet strict criteria for PPOI diagnosis, across multiple centres and countries to improve the generalisability of the results. Our findings correlate well with previous studies in the USA, which means that the percentage increase in cost of ileus in our study is likely translatable to the healthcare models of other countries.[37, 48] The number of patients included in this trial was relatively low compared to the previously published large retrospective series.[6, 333] Despite these limitations, we believe this study balances lower patient numbers with a reliable incidence of PPOI in our patient cohort based on the definition we have used. This research offers important insights into the cost of PPOI and highlights potential areas for increasing the efficiency of healthcare for patients undergoing elective colorectal surgery.

3.5 Conclusion

PPOI is a major source of increased cost of inpatient stay for patients undergoing elective colorectal surgery. Even when correcting for patient comorbidity, postoperative morbidity and length of stay, PPOI imparted a significant fiscal burden. The targets for future PPOI research include developing accurate risk-prediction models for PPOI development, and

testing new and effective medications to prevent and treat PPOI. Chapter 4 will present the results of a validation study for a risk prediction tool for PPOI, the I-Score. Chapters 5 and 6 will then assess the preventative role of NSAIDs in postoperative gut dysmotility, and the role of gastrografin as a treatment for PPOI, respectively. The healthcare system needs to continue to develop new and cost-effective interventions to reduce PPOI in addition to ERAS, in order to improve patient outcomes and reduce healthcare spending.

Chapter 4

Can the I-Score predict prolonged postoperative ileus after elective colorectal surgery: results of a multi-center cohort study.

4.1 Introduction

Chapter 3 described the economic burden of PPOI within a contemporary patient cohort. The significant financial impacts of PPOI on our healthcare system demand advances in PPOI prediction and prevention. Despite being such a major, and well recognised, complication after abdominal surgery, clinicians lack a validated tool to predict PPOI development. It is important to understand that some degree of gastrointestinal dysfunction after abdominal surgery is likely to be normal. Therefore, the most effective use of a pharmacological agent to prevent PPOI would be targeted towards high-risk patients. As we have described, there are also significant costs associated with treating all patients ubiquitously with medications such as Alvimopan.[287-289] Selective use of pharmacological agents would prevent unnecessary treatment related adverse events in patients, who would otherwise have an uncomplicated post-operative stay, and would reduce healthcare spending. Therefore, a clinical tool that could stratify patients into high and low risk for developing PPOI would improve the effectiveness of preventative strategies, improve patient care, and reduce healthcare spending. Conversely, identifying low-risk patients may facilitate earlier discharge home.

Many studies have looked at factors predictive of developing PPOI.[15, 20, 35, 102] However, these studies were retrospective in nature, had varying definitions of PPOI, and lacked validation in an external study population. Vather *et al* (2013) published the results of a prospective risk-stratification tool for PPOI development, the "I-Score".[43] This scoring system triaged patients into high, moderate and low risk to develop PPOI. The I-Score can be applied either immediately postoperatively or on day 1 after surgery, making it a clinically relevant tool to predict PPOI early in the patient's post-operative course. Importantly, this was a prospective study, and used a rigorous definition of PPOI based on global survey and systematic review. Our current study aims to validate the "I-score" as a predictive tool for

PPOI in a prospective multi-center and international cohort study of patients undergoing elective colorectal surgery.

4.2 Materials and Methods

Ethical approval was attained through the NZ Health and Disability Ethics Committee, and locality ethical approval was gained for all involved study sites. The study commenced recruitment in January 2017 and was completed in December 2018.

All patients who underwent elective colorectal surgery for any indication at Auckland DHB, Mercy Hospital, North Shore Hospital in New Zealand, and Bellvitge University Hospital in Barcelona, were screened for eligibility. The inclusion criteria were: Age ≥18 years old, able to understand risks and benefits of the study, able to give informed consent. Eligible procedures included: right/left hemicolectomy, sigmoid colectomy, anterior resection, Hartmann's procedure, proctectomy, abdominoperineal resection, total or subtotal colectomy, formation of ileostomy/colostomy, reversal ileostomy/colostomy. Patients were excluded if they were pregnant, had an ASA grade 4 or greater, were on pre-operative parenteral nutrition, had pre-existing gut dysmotility including endocrine, metabolic or neurological causes, or were unable to participate in the consent or postoperative assessment process due to dementia, cognitive impairment, language difficulties, delirium

Patients were consented preoperatively, and written consent obtained. Patient demographic and healthcare data, preoperative and postoperative blood test results on days 1 and 3, operative and anaesthetic details were recorded prospectively. All patients were assessed daily by a study investigator between 8am-10am from postoperative day 1 until discharge. Markers of clinical recovery, such as time to flatus, stool, and tolerance of oral diet, were assessed. If patients had not achieved any of these criteria prior to discharge they were telephoned by a study investigator after discharge. Preoperative, intraoperative and postoperative medications, analgesia and IV fluid and blood product administration data were recorded. Medications and fluid administration were recorded up to midnight of postoperative day 3, prior to patients being diagnosed with or without PPOI. Opiate usage was calculated based on a morphine equivalent daily dose.[351, 352] NSAID use intraoperatively and postoperatively was recorded, postoperative NSAID dose was converted into units of NSAID: 1 unit of NSAID was equivalent to 1200mg ibuprofen, 100mg diclofenac, 750mg naproxen, 800mg celecoxib, 80mg parecoxib, 50mg rofecoxib, 1200mg aspirin.[353, 354]

Surgeons completed a questionnaire postoperatively to assess the degree of operative difficulty and bowel handling (assessed on a 10-point Likert scale), the degree of contamination (nil, minimal, moderate or major), and the estimated intraoperative blood loss. Anaesthetic charts were assessed for the volume of intraoperative IV fluid given, and medications such as opiate and NSAIDs.

All patients followed a semi-structured ERAS protocol. This includes stepwise analgesia progression, restrictive use of IV fluids and narcotic analgesia, early removal of catheters, nasogastric tubes and IV lines, early post-operative feeding and mobilisation. In the event that a patient was unable to adhere to the ERAS protocol, they were still monitored as part of the study. Decisions regarding patient analgesia and peri-operative care (including epidural analgesia) were left to the treating team.

The primary outcome was development of PPOI, defined according to the definition by Vather el al (2013), as described below in figure 4-1.[2] Patients who developed 2 or more of these criteria on or after postoperative day 4 were defined as having PPOI.

Diagnostic criteria for PPOI **2+/5 on postoperative day 4 or later**	
Nausea or vomiting over preceding 24 hours	Patient reported moderate nausea >4/10
Inability to tolerate solid or semi-solid diet over 2 preceding meal times	Inability to eat ≥ 25% preoperative meal volume
Abdominal distension	Clinician defined moderate or severe distension with abdominal tympany
Absence of flatus and stool over preceding 24 hours	Patient reported. Absence of gas or bowel content in stoma bag
Radiological evidence of ileus over preceding 24 hours	Based on abdominal Xray or CT scan, requiring 2 or more of: gastric distension, air-fluid levels, dilated small or large bowel loops without a transition point

Figure 4-1 Diagnostic criteria for PPOI

Prior to diagnosis of PPOI, all patients were assessed using the I-Score risk prediction tool. The aim of the study was to assess and validate the I-Score in an external cohort of patients, and to identify other risk factors for PPOI development that could be used to predict patients

at high risk of PPOI. The I-Score comprised 6 criteria and each patient was given a score from 0-6 based on this scale, as seen in figure 4-2.[43]

The I-Score
Male
Pre-operative albumin <34g/L
Operative difficulty ≥8 reported by surgeon
Open or converted to open technique
Wound size >10cm (sum of all abdominal wounds)
Red blood cell transfusion

Figure 4-2 The I-Score risk prediction tool

All statistics were conducted using SPSS for Mac (Version 25; SPSS, Chicago, IL). Data were analysed in relation to development of PPOI as the primary endpoint. Dichotomous variables were described as numbers and percentages, and were analysed using the Chi-squared test or Fischer's exact test where appropriate. Continuous variables were assessed for their distribution using histograms and the Shapiro-Wilk test. Continuous data with a normal distribution were analysed using an independent-samples student t-test. Continuous data that did not follow a normal distribution were analysed using the Mann-Whitney U test. All variables that were significantly associated with PPOI or nearly significant ($p<0.10$) were assessed using a multivariate binary logistic regression model. Each patient was given an I-Score value, and the ability of the I-Score to predict PPOI was assessed using a ROC curve. The resulting area under the curve (AUC) was compared to the original study's I-Score AUC of 0.742, to see if the model maintained its "fair" predictive capability in an external cohort.[43] A clinically meaningful change in AUC >0.05 would suggest a significant difference between the 2 models.[355] Vergouwe *et al* (2005) recommended at least 100 events (in this case the development of a PPOI) and 100 non-events for external validation sets, in order to reach a predictive power of 80%.[356] Therefore, we planned to recruit 370 patients, with an estimated PPOI rate of 27%.[39] Assuming a 10% dropout rate during this study, we planned to enrol 410 patients.

4.3 Results

This study assessed 435 patients that were eligible for enrolment, 14 patients did not consent, 3 patients had cognitive or intellectual impairment, 1 patient had severe

constipation, 6 patients had language difficulties, and 1 patient was deemed ASA 4 prior to surgery. In total, 410 patients consented to the study. After enrolment, 1 patient withdrew consent, 1 patient was withdrawn for severe postoperative delirium, and 4 patients were excluded as they did not have a primary outcome (PPOI) recorded. 404 patients were recruited for analysis, 121 from Auckland City Hospital, 168 from Mercy Hospital, 43 from Northshore Hospital, 72 from Bellvitge University Hospital Barcelona. PPOI occurred in 98 patients (24.3%). An analysis of risk factors for PPOI was separated into preoperative, intraoperative and postoperative variables.

4.3.1 Preoperative variables

The results of preoperative variables related to PPOI is described in Table 4-1. Univariate analysis showed that a history of peripheral vascular disease (p=0.010) and previous PPOI (p<0.001) were significant risk factors for PPOI development. Use of a preoperative beta-blocker was associated with PPOI (p=0.005). There was a trend towards a higher rate of PPOI in patients with ASA 3, but this did not reach statistical significance (p=0.060). There was no difference in risk of PPOI based on patient age, BMI, ethnicity or preoperative blood tests. In particular preoperative albumin was no different between patients who did and didn't develop PPOI (mean 36.7 ± 3.9 vs. 36.7 ± 3.8 respectively, p=0.978). The rate of PPOI was slightly higher in males (26.5%) compared to females (21.7%) but this did not reach statistical significance (p=0.260). The indication for surgery did not impact the risk of PPOI, and PPOI was not significantly different for patients who had inflammatory bowel disease (p=0.147).

Table 4-1 Analysis of preoperative variables

	Total (n=404)	PPOI (n=98)	No PPOI (n=306)	P-value
Age, years (Median, IQR)	64 (54, 74)	65 (57, 74)	62 (52, 73)	0.106
Sex				0.260
Male	215 (53.2%)	57 (26.5%)	158	
Female	189 (46.8%)	41 (21.7%)	148	
Ethnicity				0.771
European	348 (86.1%)	87 (25%)	261	
Maori	13 (3.2%)	2 (15.4%)	11	
Pacifika	10 (2.5%)	1 (10%)	9	
Asian	17 (4.2%)	5 (4.1%)	12	
Indian	12 (3%)	3 (25%)	9	
Other	4 (1%)	0 (0%)	4	

Medical Comorbidity				
Cardiac	72 (17.8%)	23 (31.9%)	49	0.099
Hypertension	140 (34.7%)	40 (34.1%)	100	0.152
Peripheral vascular disease	18 (4.5%)	9 (50%)	9	0.010
Respiratory	57 (14.1%)	17 (29.8%)	40	0.301
Renal	26 (6.4%)	8 (30.8%)	18	0.433
Diabetes	45 (11.1%)	11 (24.4%)	34	0.991
Neurological	22 (5.4%)	6 (27.3%)	16	0.745
Psychiatric	43 (10.6%)	9 (20.9%)	34	0.577
ASA Grade				0.060^
1	70 (17.3%)	15 (21.4%)	55	
2	216 (53.5%)	47 (21.8%)	169	
3	118 (29.2%)	36 (31%)	82	
BMI	26.5 (23.3, 29.7)	27.1 (24.6, 30.4)	26.5 (23.1, 29.4)	0.602
Previous abdominal surgery	214 (53%)	59 (27.6%)	155	0.112
Previous PPOI	47 (11.6%)	22 (46.8%)	25	<0.001
Preoperative medications				
Opioids	18 (4.5%)	3 (16.7%)	15	0.436
Steroids	28 (6.9%)	8 (28.6%)	20	0.592
NSAIDs	62 (15.3%)	16 (25.8%)	46	0.776
Calcium channel blocker	56 (13.9%)	14 (25%)	42	0.177
ACE inhibitor	87 (21.5%)	26 (29.9%)	61	0.177
Beta-blocker	56 (13.9%)	22 (39.3%)	34	0.005
Antibiotics	13 (3.2%)	3 (23.1%)	10	0.912
Antidepressant	38 (9.4%)	6 (15.8%)	32	0.195
Statin	98 (24.3%)	24 (24.5%)	74	0.976
Smoking status				0.550
Current	30 (7.4%)	5 (16.7%)	25	
Ex-smoker	122 (30.2%)	29 (23.8%)	93	
Never smoked	252 (62.4%)	64 (25.6%)	186	
Preoperative blood tests*				
Haemoglobin	133 ± 17	133 ± 17	133 ± 17	0.361
White cell count	7.3 ± 4.3	6.8 ± 2.2	7.1 ± 3.0	0.227
Creatinine	79 ± 21	79 ± 19	79 ± 21	0.127
Albumin	36.7 ± 3.9	36.7 ± 3.8	36.7 ± 4.0	0.978
Sodium	140 ± 3	140 ± 2	139 ± 3	0.747
Potassium	4.2 ± 0.4	4.3 ± 0.4	4.2 ± 0.4	0.069
Calcium	2.37 ± 0.10	2.37 ± 0.09	2.37 ± 0.10	0.482
Magnesium	0.83 ± 0.08	0.85 ± 0.08	0.84 ± 0.08	0.379
Indication for surgery				0.353
Cancer	321 (79.5%)	73 (22.7%)	248	
Inflammatory bowel	42 (10.4%)	14 (33.3%)	28	0.147
disease	25 (6.2%)	5 (20%)	20	
Diverticular disease	16 (3.9%)	6 (37.5%)	10	
Other				

Percentages given denote the rate of PPOI in each demographic category
*Parametric continuous data analyzed using a student's t-test and described as mean ± standard deviation, all other continuous variables analyzed with Mann-Whitney U test and described as median (interquartile range)

4.3.2 Intraoperative variables

The type of procedure significantly correlated with PPOI risk. PPOI occurred in 35.3% after APR and in 60% after subtotal colectomy. PPOI was more common in patients after open

(29.9%) or converted to open (33.3%) surgery compared to laparoscopic or laparoscopic-assisted surgery (p=0.016). Wound size, surgeon perceived operative difficulty and the reported degree of bowel handling all increased the risk of PPOI, as did estimated blood loss and the degree of operative contamination. The mean volume of IV crystalloid was significantly higher in patients who developed PPOI (1630mL ± 1123mL) compared to those who didn't (1388mL ± 940mL), p=0.013. Interestingly, of the 87 patients who received intraoperative NSAID, only 14.9% developed PPOI, compared to 27.1% in those who didn't receive intraoperative NSAID (p=0.02). There was a trend towards higher intraoperative opiate doses in patients who developed PPOI, but this did not reach statistical significance (p=0.057). Patients who received an epidural were more likely to develop PPOI (40%) compared to patients without an epidural or with a spinal (p=0.037). The full analysis of intraoperative variables is displayed in Table 4-2.

Table 4-2. Analysis of intraoperative variables

	Total (n=404)	PPOI (n=98)	No PPOI (n=306)	P-value
Procedure				0.019
Reversal ileostomy	78 (19.3%)	19 (24.4%)	59	
Reversal Hartmann's	13 (3.2%)	3 (23.1%)	10	
Right hemicolectomy	120 (29.7%)	33 (27.5%)	87	
Anterior resection	138 (34.2%)	23 (16.7%)	115	
Abdominoperineal resection	17 (4.2%)	6 (35.3%)	11	
Subtotal colectomy	10 (2.5%)	6 (60%)	4	
Other	28 (6.9%)	8 (28.6%)	20	
Technique				0.016
Laparoscopic	81 (20%)	30 (18.9%)	129	
Lap-assisted	159 (39.4%)	18 (22.2%)	63	
Open	137 (33.9%)	41 (29.9%)	96	
Converted to open	27 (6.7%)	9 (33.3%)	18	
Stoma formation				
Ileostomy	96 (23.8%)	29 (30.2%)	67	0.119
Colostomy	20 (5%)	7 (35%)	13	0.250
None	288 (71.3%)	62 (21.5%)	226	
Regional anaesthesia				
None	331 (82%)	77 (23.3%)	254	
Epidural	30 (7.4%)	12 (40%)	18	0.037
Spinal	43 (10.6%)	9 (20.9%)	34	0.590
Duration of surgery (mins)	170 (117, 263)	182 (120, 281)	168 (112, 255)	0.117
Wound size	10 (6.4, 15)	13 (8, 19)	9 (6, 15)	<0.001
Operative difficulty	5 (3, 7)	6 (4, 8)	5 (3, 7)	<0.001
Operative bowel handling	4 (3, 6)	6 (4, 7)	4 (3, 5)	<0.001
Estimated blood loss, mL	75 (50, 200)	100 (50, 250)	50 (36, 150)	0.001
Operative contamination				0.001
Nil	291 (72%)	56 (19.2%)	235	
Minimal	64 (15.8%)	20 (31.3%)	44	
Moderate	35 (8.7%)	16 (45.7%)	19	
Major	3 (0.7%)	1 (33.3%)	2	

Intraoperative fluid*				
Crystalloid, mL	1450 ± 990	1630 ± 1123	1388 ± 940	0.013
Colloid, mL	64 ± 218	45 ± 142	70 ± 238	0.160
Intraoperative blood transfusion	10 (2.5%)	2 (20%)	8	0.750
Intraoperative analgesia				
Morphine MEDD	37 (23, 50)	40 (30, 51)	35 (21, 50)	0.057
NSAID	87 (21.5%)	13 (14.9%)	74	0.020
No NSAID	317 (78.5%)	85 (27.1%)	229	

*Parametric continuous data analyzed using a student's t-test and described as mean ± standard deviation, all other continuous variables analyzed with Mann-Whitney U test and described as median (interquartile range)

4.3.3 Postoperative variables

Postoperative IV crystalloid administration was the most significant variable related to PPOI development. Patient who developed PPOI received more than double the average amount of IV crystalloid than other patients (4913mL ± 3403mL vs. 2070mL ± 2072mL respectively, $p<0.001$). Adherence to an ERAS protocol trended towards reduced PPOI (22.1% vs. 32.2%) but did not reach significance ($p=0.052$). Patients who did not mobilize by the end of postoperative day 1 were much more likely to develop PPOI. Postoperative opioid, NSAID use and NSAID dosage were not predictors of PPOI. There were some variations in the postoperative blood results between PPOI patients and patients who recovered normally. Postoperative day 1 creatinine, potassium, calcium, and magnesium were statistically different between groups, but the differences were not clinically significant. Furthermore, postoperative day 3 differences in creatinine, albumin, sodium, calcium, and magnesium were found but were also not of clinical significance. The analysis of postoperative variables is described below in Table 4-3.

Table 4-3 Analysis of postoperative variables

	Total (n=404)	PPOI (n=98)	No PPOI (n=306)	P-value
Postoperative day 1 bloods*				
Haemoglobin	119 ± 17	116 ± 18	120 ± 17	0.190
White cell count	10.9 ± 3.4	10.5 ± 2.8	11.1 ± 3.6	0.599
Creatinine	76 ± 22	79 ± 25	75 ± 22	0.032
Albumin	30.5 ± 3.8	29.7 ± 3.7	30.7 ± 3.8	0.126
Sodium	138 ± 3	138 ± 3	138 ± 3	0.602
Potassium	4.3 ± 0.4	4.3 ± 0.4	4.2 ± 0.4	0.013
Calcium	2.21 ± 0.12	2.19 ± 0.12	2.23 ± 0.13	0.035
Magnesium	0.88 ± 0.09	0.90 ± 0.11	0.87 ± 0.08	0.004
Postoperative day 3 bloods*				
Haemoglobin	119 ± 19	120 ± 19	119 ± 19	0.815
White cell count	8.3 ± 3.0	8.6 ± 3.9	8.2 ± 2.6	0.678
Creatinine	71 ± 18	74 ± 20	71 ± 17	0.022
Albumin	30 ± 4	28.9 ± 3.9	30.3 ± 3.9	0.002
Sodium	139 ± 3	137 ± 3	139 ± 3	<0.001
Potassium	4.1 ± 0.4	4.1 ± 0.6	4.1 ± 0.4	0.268
Calcium	2.32 ± 0.11	2.30 ± 0.12	2.32 ± 0.14	0.172
Magnesium	0.81 ± 0.08	0.83 ± 0.09	0.81 ± 0.08	0.046
Change from preop to postop*				
Haemoglobin	15 ± 12	18 ± 14	14 ± 11	0.714
Creatinine	8 ± 16	6 ± 20	8 ± 14	0.410
Albumin	7.3 ± 3.4	7.6 ± 3.7	7.2 ± 3.4	0.344
ERAS protocol				0.052
Yes	317 (78.5%)	70 (22.1%)	247	
No	87 (21.5%)	28 (32.2%)	59	
Postop IV fluid (day 0-4)*				
Crystalloid, mL	2760 ± 2744	4913 ± 3403	2070 ± 2072	<0.001
Colloid, mL	54 ± 214	87 ± 271	44 ± 191	0.087
Postoperative analgesia				
Morphine MEDD, units	34 (18, 63)	42 (20, 72)	33 (17, 63)	0.114
NSAID	176 (43.6%)	44 (25%)	132	0.756
No NSAID	224 (56.4%)	53 (23.7%)	171	
NSAID units	0 (0, 0.25)	0 (0, 0.13)	0 (0, 0.3)	0.350
Postop blood transfusion	19 (4.7%)	8 (42.1%)	11	0.062^
Mobilized on day 1	358 (88.6%)	81 (82.7%)	277 (90.5%)	0.033

*Parametric continuous data analyzed using a student's t-test and described as mean ± standard deviation, all other continuous variables analyzed with Mann-Whitney U test and described as median (interquartile range)
^Fisher's exact test used

A linear regression analysis showed that postoperative IV crystalloid volume was the only significant multivariate risk factor for PPOI (p<0.001).

4.3.4 Clinical recovery of patients with PPOI

Table 4-4 shows the outcomes of clinical recovery for patients with and without PPOI. PPOI leads to double the median time to achieve GI-2, nearly double the length of postoperative stay and significantly delays time to passage of flatus, stool, and tolerance of diet.

Table 4-4 Impact of PPOI on postoperative recovery

	Total (n=404)	PPOI (n=98)	No PPOI (n=306)	P-value
Day first flatus	2 (1, 2)	2 (1, 3)	1 (1, 2)	<0.001
Day first stool	3 (2, 4)	3 (2, 5)	2.5 (2, 4)	<0.001
Day tolerated diet	2 (1, 4)	6 (5, 11)	2 (1, 3)	<0.001
Time to GI-2	4 (2, 5)	6 (5, 11)	3 (2, 4)	<0.001
Length of stay	5 (4, 7)	9 (7, 13)	5 (4, 6)	<0.001

All data analyzed with Mann-Whitney U test and described as median (interquartile range)

4.3.5 Assessment of the I-Score model

Table 4-5 shows the incidence of PPOI when the I-Score is applied to this cohort. Patients with moderate to high risk were more than more likely to develop PPOI (33.7% and 39.8% respectively) compared to low risk (14.9%), p<0.001.

Table 4-5 Impact of I-Score on PPOI risk

I-Score	PPOI	Total	Incidence of PPOI
Low risk (0-1)	26	175	14.9%
Moderate risk (2)	33	124	33.7%
High risk (≥3)	39	105	39.8%

The I-Score was applied to our cohort, and a ROC curve was generated to determine an AUC. Figure 4-3 demonstrates the AUC for the I-Score model in this cohort. We found that the AUC was 0.644, which means that the accuracy of the I-Score to predict PPOI in this cohort was poor. These results show that a high I-Score is associated with PPOI development, but this study was unable to validate the I-Score as an accurate predictive tool for PPOI after elective colorectal surgery.

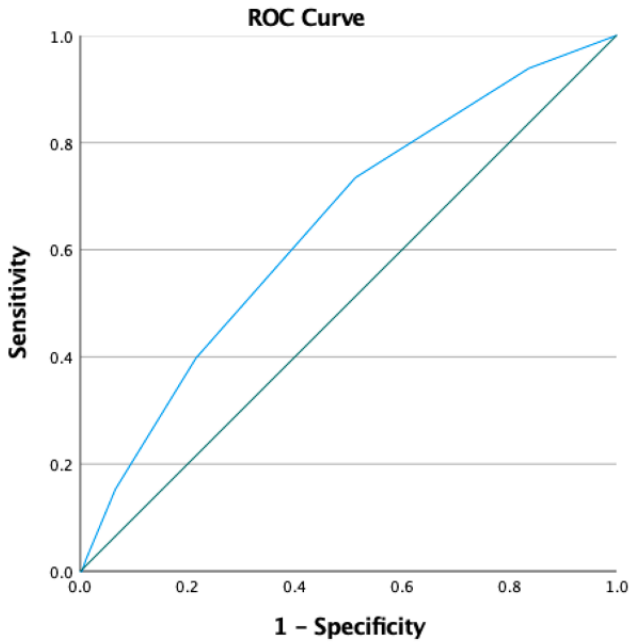

Figure 4-3. Receiver operating characteristic (ROC) curve of the I-Score to predict PPOI

4.4 Discussion

This study presents the results of a large multi-center international study of the risk factors for PPOI development after elective colorectal surgery. The majority of patients adhered to a standardized ERAS protocol and importantly, PPOI was predefined and assessed prospectively in all patients. The aim of this study was to validate a risk-prediction tool for PPOI development, the I-Score. While this study found a significant association between I-Score and PPOI, the I-Score was not able to accurately predict PPOI development in this cohort.

There were a number of significant risk factors for PPOI development identified in this study. The most important predictor of PPOI development on multivariate analysis was the volume of postoperative IV crystalloid, and patients who developed PPOI received more than twice the amount of IV fluid postoperatively. These data also support the idea that the magnitude of the surgical insult impacts the degree of POI. Open surgery with larger abdominal wounds, larger operations (APR and subtotal colectomy) that are more difficult and involve a greater degree of bowel handling, a greater intraoperative blood loss and contamination, all significantly increased the risk of PPOI. In many cases, these risk factors are inevitable, and are related to each individual patient's pathology. Aside from adhering to laparoscopic surgery where technically possible, risk factors related to technical aspects of a patient's

operation are likely to serve solely as prognostic factors and cannot be modified. Interestingly, we found that intraoperative NSAID was associated with a significant reduction in PPOI rate (14.9% vs. 27.1%, p=0.020) on univariate analysis. There was also a trend towards higher doses of intraoperative morphine units in patients who developed PPOI, but no significant difference in morphine or NSAID use in the postoperative period. One possible conclusion is that the most impactful use of a pharmacological agent to reduce PPOI would be in the preoperative or intraoperative period, rather than postoperatively alone.

The strengths of this study are that it was conducted across multiple sites, and within an international cohort, which increases its generalizability. This study also shows that Vather's definition of PPOI is easy to apply prospectively.[2] While this study was not able to validate the I-Score as a prospective prediction tool, it provides information that could be used to generate new ileus prediction scores in the future. This study was unable to define any key modifiable preoperative risk factors for PPOI. However, the results do highlight the importance of intraoperative analgesia dosage compared to postoperative analgesia on PPOI development, which has not been reported before in the literature. This is a promising target for future research.

There were statistical differences in postoperative serum electrolytes levels between patients who developed PPOI and those who did not. The clinical implications of these small variations are unclear. In addition, if the perioperative period is the most important time to initiate preventative measures for PPOI, the most clinically relevant prediction model for PPOI should involve preoperative variables alone. One possibility is that our current statistical methodology is unable to adequately identify important correlations in individual patient parameters, that could predispose to PPOI. Recent series have employed "machine learning", or artificial intelligence, techniques to develop comprehensive and powerful models to predict postoperative complications in large patient cohorts.[357-359] These methods have yet to be applied to a study with PPOI as the primary endpoint but could be invaluable in future research.

4.5 Conclusion

Chapter 4 has demonstrated the difficulties clinicians face in predicting PPOI. This study was unable to validate the I-Score as an accurate prediction tool for PPOI but has described several new risk factors for PPOI that are clinically relevant and warrant further research. Importantly, this study supports the idea that NSAID use may reduce PPOI. This thesis will further assess the role of NSAIDs in postoperative gut recovery and ileus in Chapter 5. The

pursuit of an accurate predictive score for PPOI is ongoing but would provide significant benefit to both patients and the healthcare system.

Chapter 5

Non-steroidal anti-inflammatory drugs reduce the time to recovery of gut function after elective colorectal surgery: a systematic review and meta-analysis.

5.1 Introduction

Chapter 3 has outlined the significant impact of PPOI on the cost of elective colorectal surgery. It is likely that any intervention that either reduces the time to return of gut function, or the incidence of PPOI, will be of benefit to both the patient and the healthcare system. The role of COX enzymes in POI development is clear. However, the evidence for NSAID use to reduce postoperative gut dysmotility, and to prevent PPOI, has not been fully investigated in a meta-analysis. Intraoperative NSAID use was a protective measure for PPOI development in the previous study. Chapter 5 will assess the quality of evidence for NSAID use after elective colorectal surgery, and their efficacy to reduce postoperative gut dysmotility.

There remain few effective medications available to treat or prevent POI. Prokinetic agents, such as erythromycin and metoclopramide, have shown no benefit in POI on meta-analysis.[250] Alvimopan, a peripheral mu-opioid receptor antagonist, has been shown to reduce the duration of POI after colorectal and urological surgery.[360, 361] However, the cost effectiveness of alvimopan under a modern Enhanced Recovery After Surgery (ERAS) framework is still unclear.[281, 288, 362] Novel agents, such as prucalopride, have shown benefit in POI,[326] but clinicians await further studies and cost-analyses of their efficacy. Inflammation is a key component in POI pathogenesis,[1, 4] and non-steroidal anti-inflammatory drugs (NSAIDs) may play a role in POI prevention.[214, 363] However, a systematic evaluation is lacking regarding the efficacy of NSAIDs to improve post-operative time to return of normal bowel function and reduce POI.

The aim of this study was to assess the evidence for NSAIDs in reducing the time to return of normal bowel function by systematic literature review and meta-analysis. The outcomes of interest were time to first flatus, time to passage of stool and time to tolerance of solid diet, from randomized controlled trials (RCTs) comparing use of NSAIDs to placebo after elective colorectal surgery.

5.2 Materials and Methods

5.2.1 Systematic literature search

Two independent reviewers (TM, RJ) performed a systematic search of all relevant literature in OVID MEDLINE, EMBASE and CENTRAL until April 2017. The Cochrane Collaboration sensitivity maximizing search strategy was used for selecting RCTs. In addition, reference lists of identified papers and conference proceedings were searched. The strategy used for OVID MEDLINE is shown in Appendix 2. No date or language restrictions were applied. This review followed the standard reporting guidelines as detailed in the PRISMA statement.[364] Where there was disagreement between the reviewers, a third reviewer (IB) determined whether a paper would be included or not.

The inclusion criteria for this study were: RCTs, adult patients undergoing elective colorectal surgery, use of NSAID compared to placebo (preoperatively, post-operatively or both), reported outcomes on time to tolerate oral diet, time to passage of flatus or stool. Excluded studies included: no clinical endpoint related to gut recovery or ileus, non-randomized trials, observational or retrospective studies, non-major abdominal operations, did not compare NSAID use to placebo, used NSAIDs as part of multimodal analgesia.

5.2.2 Data extraction

Data were extracted from included studies on study design, number of patients, type/dose/time of administration of NSAID or placebo. Outcomes of interest were median or mean time to tolerate an oral diet, time to passage of flatus, time to passage of stool, and use of opioid analgesia.

5.2.3 Risk of bias assessment

Studies that were included in the meta-analysis were assessed for risk of bias using the Cochrane Risk of Bias Tool.[365] Each study was assessed with a “yes”, “no” or “unclear” for compliance with the following 7 criteria: presence of random sequence generation, adequate allocation concealment, blinding of study participants and personnel, blinding of outcome assessment, completeness of outcome data, absence of selective reporting, absence of other sources of bias.

5.2.4 Statistical analysis

Continuous data were analyzed for relevant outcomes of time (in hours) to pass flatus and stool and to tolerate a solid diet. Due the expectation of significant heterogeneity between study methods and results, the inverse-variance method was used with a random-effects model to calculate a mean difference (in hours) between groups. The I^2 statistic was used to estimate the level of heterogeneity between study results.

For studies that reported median and range, the Hozo *et al* method was used to estimate a mean and standard deviation for analysis.[366] Where median and interquartile range were reported, the method of Wan *et al* was used to determine mean and standard deviation.[367] If studies reported multiple intervention arms, the intervention data were combined using the calculator in RevMan 5.3. Subgroup analyses were planned for all primary outcomes of studies that focused on colorectal surgery and for studies that used COX2 selective NSAIDs. In the event of significant heterogeneity in our results, a sensitivity analysis was planned, by removing studies where estimation of the mean and standard deviation was required.

All data were stored and analyzed using Review Manager (RevMan) [Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

5.3 Results

This study identified 930 articles, including ten RCTs on patients receiving NSAIDs compared to placebo before or after major abdominal surgery. Figure 5-1 presents the PRISMA flowchart of the systematic review search outcome process.

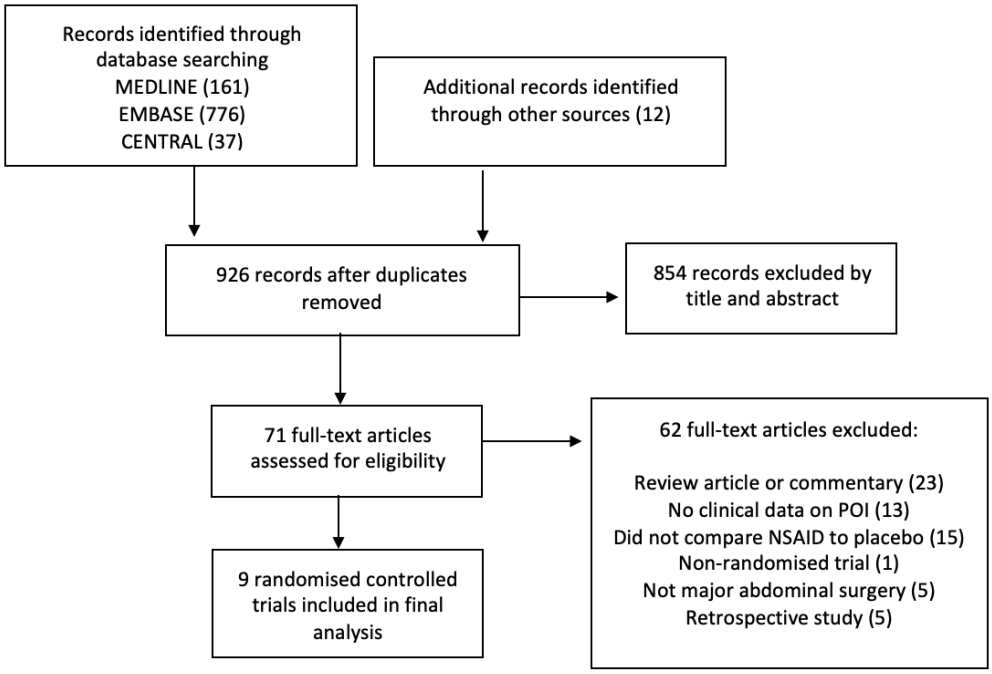

Figure 5-1. PRISMA flowchart of search strategy

Of the identified RCTs, six were on patients undergoing elective colorectal surgery.[205-210] Mean and standard deviation data for return to gut motility were able to be attained or estimated (using the methods explained above) for five RCTs.[205-209] The characteristics of the RCTs included in the meta-analysis are displayed in Table 5-1. Full data were not available for one RCT in elective colorectal surgery, and this RCT was not included in the meta-analysis.[210]

Table 5-1. Characteristics of studies included in meta-analysis

Study	Operations included	Intervention	No. of patient	Control	No. of patients	Time when study medication given	Primary outcome	Relevant outcomes for meta-analysis
Chen *et al* 2005	Elective colorectal surgery	PCA ketorolac 1.2mg/mL + Morphine 1mg/mL	39	PCA morphine 1mg/mL	45	Postoperatively until VAS on movement <3	Cumulative morphine consumption until passage of first stool	Time to first stool
Chen *et al* 2009	Elective colorectal surgery	PCA ketorolac 1.2mg/mL + morphine 1mg/mL	52	PCA morphine 1mg/mL	50	Postoperatively until VAS on movement <3	Cumulative morphine consumption until passage of first flatus	Time to first flatus Time to first stool
Sim *et al* 2007	Elective colorectal surgery	PO valdecoxib 40mg	40	PO placebo	39	First dose 1-3 hours preoperatively then daily	Time to first bowel movement	Time to first flatus Time to first stool Time to first oral diet
Wattchow *et al* 2009	Elective colorectal surgery	PO celecoxib 100mg PO diclofenac 50mg	74 69	PO placebo	67	1-2 hours preoperatively then BD for 7 days postoperatively	Composite outcome of tolerance of food, passage or flatus, passage of stool	Time to first flatus Time to first stool Time to first oral diet
Xu *et al* 2008	Elective colorectal surgery	IV flurbiprofen 1mg/kg	20	IV placebo	20	30 min prior to skin incision then 6 hours after skin incision	Time to first bowel movement	Time to first flatus Time to first stool

In total, the five included RCTs comprised 515 patients (294 NSAID vs. 221 placebo). The time and regimen of drug administration differed between studies: three studies gave study medication prior to skin incision whereas two studies gave study medication postoperatively. Only three of the included RCTs used time to return of gut motility (flatus, stool, diet, or a combined endpoint) as the study's primary outcome.[207-209] Patient numbers in the included studies ranged from 40 to 210 patients. The type of NSAIDs used varied between studies: three studies used non-selective COX inhibitors (ketorolac, flurbiprofen),[205, 206, 209, 368] one study used a COX-2 selective NSAID (valdecoxib),[207] and a further study used a 3-arm trial with a non-selective COX inhibitor (diclofenac) and a COX-2 selective NSAID (celecoxib).[208] Only one of the included studies adhered to an ERAS protocol of perioperative management.[208] Because only two studies used COX-2 selective NSAIDs, a subgroup analysis based on NSAID type was not undertaken.

5.3.1 Risk of bias

Table 5-2 demonstrates an assessment of bias for all studies included in the meta-analysis using the Cochrane Risk of Bias Tool. All included trials used appropriate random sequence generation. In the studies by Chen *et al* 2005 and Chen *et al* 2009,[205, 206] allocation concealment was not described and one of the study authors prepared the study medication and was, therefore, unblinded to treatment allocation. Furthermore, Chen *et al* (2005) did not report data on non-significant outcomes in the study relating to passage of flatus and tolerance of oral diet.[205] Only three studies had recent use of NSAID as an exclusion criterion,[206, 207, 209] and of the remaining studies none reported on pre-existing NSAID use prior to surgery.

Table 5-2. Risk of bias assessment of studies included in meta-analysis

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Completeness of outcome data	Free from selective reporting	Free from other sources of bias
Chen *et al* 2005	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes
Chen *et al* 2009	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Sim *et al* 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wattchow *et al* 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xu *et al* 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes

5.3.2 Time to pass flatus

Time to first flatus was reported as an outcome in four studies, with a total of 431 patients (255 NSAID, 176 placebo). The time to first flatus was significantly faster for patients receiving NSAID (Figure 5-2), the mean difference was -9.44 hours (95% CI: -17.22, -1.65) in patients who received NSAIDs compared to control (p=0.02).

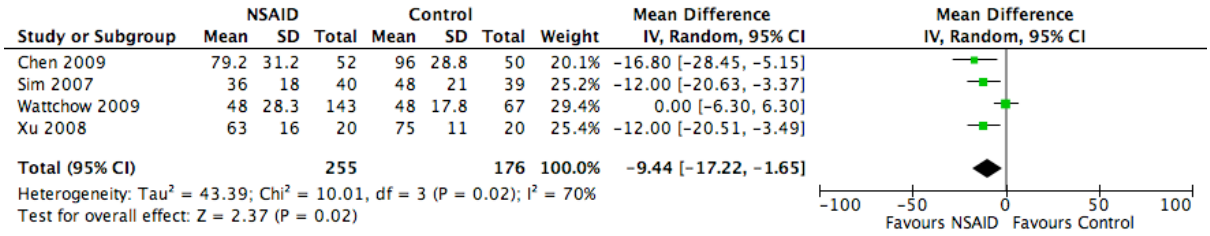

Figure 5-2. Meta-analysis of time to first flatus for patients undergoing elective colorectal surgery

There was moderate heterogeneity in the primary analysis of time to flatus (Chi^2 = 0.02 and I^2 = 70%). This heterogeneity may have been due to combining both intervention arms in the study by Wattchow *et al*,[208] providing outlying data. A sensitivity analysis that excluded the studies by Sim and Wattchow (studies that required estimation of mean and standard deviation) continued to show a significant mean difference of -13.67 hours (95% CI: -20.54, -6.80) and an I^2 of 0% (p<0.001).

In addition, Schlachta *et al* found a significant reduction in time to pass flatus for patients receiving NSAID compared to placebo (median 2 vs. 3 days respectively, p<0.001).[210]

5.3.3 Time to pass stool

Time to first stool was reported in five studies and occurred significantly earlier in patients receiving NSAIDs (Figure 5-3). A total of 515 patients were included in this analysis (294 NSAID, 221 placebo). The mean difference was -12.09 hours (95% CI: -17.16, -7.02) favoring NSAIDs (p<0.001). There was little heterogeneity between studies included for time to first stool (Chi^2 =0.64 and I^2 =0%).

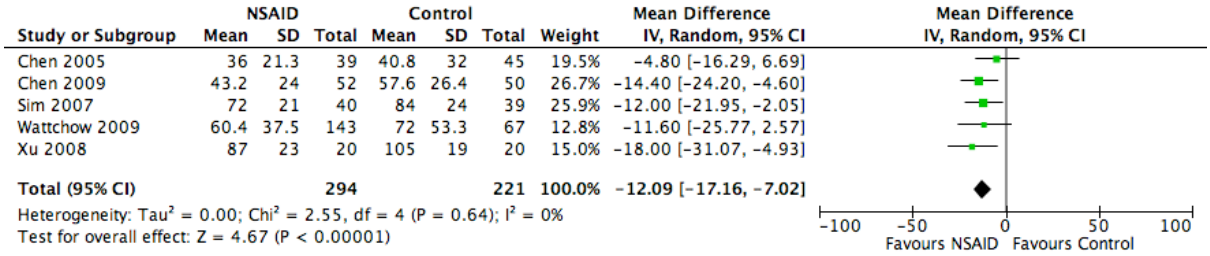

Figure 5-3. Meta-analysis of time to first bowel motion for patients undergoing elective colorectal surgery

5.3.4 Time to tolerate a solid diet

Only two studies (289 total: 183 NSAID, 106 placebo) reported on time to first tolerate a solid diet (Figure 5-4). The time to tolerate an oral diet was again significantly faster for patients receiving NSAIDs compared to placebo: mean difference -11.93 hours (95% CI -18.64, -5.22) favoring NSAIDs (p<0.001). Heterogeneity was minimal between the results of the 2 included studies (Chi^2 =0.98 and I^2 =0%). The RCT by Schlachta *et al* found a significant reduction (p=0.033) in time to tolerate a solid diet in the NSAID group (median 2.5 days) compared to placebo (median 3.0 days).[210]

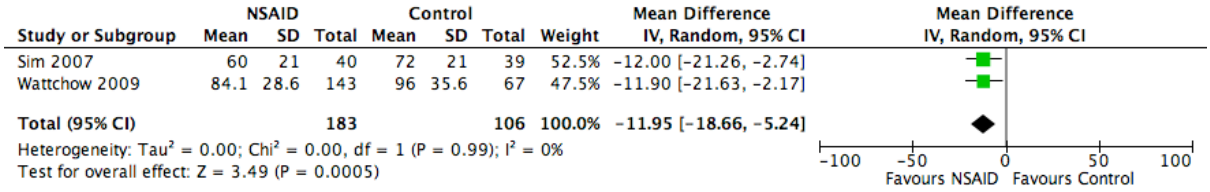

Figure 5-4. Meta-analysis of time to tolerate solid diet for patients undergoing elective colorectal surgery

5.3.5 Postoperative opioid use

Three of the included studies showed that use of opioids in the postoperative period was significantly reduced in the NSAID group compared to placebo.[205-207] Patients who were allocated to NSAID compared to placebo respectively had reduced total morphine consumption (median 71.4mg vs. 93.3mg, p<0.05),[205] reduced morphine consumption over the first 72 hours (mean 66.0mg vs. 80.8mg, p<0.05),[206] and reduced PCA dose per 12-hour period (median 635mg vs. 1303mg, p=0.001).[207] The study by Wattchow *et al* found no difference in opioid use between the NSAID and placebo group, and importantly this study was the only trial included to adhere to an ERAS framework of perioperative care.[208] One study did not report on use of opioids.[209]

5.4 Discussion

The results of this systematic review and meta-analysis show that NSAIDs significantly improve the time to passage of flatus (9 hours faster), stool (12 hours faster) and tolerance of solid diet (12 hours faster) in patients undergoing elective major colorectal surgery. In

addition, NSAIDs led to significant reductions in time to flatus and stool for patients undergoing non-colorectal major abdominal surgery. Tolerance of diet and passage of stool are the most important clinical markers of return to gut recovery after abdominal surgery,[23] and a mean reduction in 12 hours for these outcomes is clinically significant. The findings of this study should fuel interest in conducting future trials focusing on POI prevention, a common and difficult to manage complication that currently has few effective treatments.

The results of this paper are consistent with outcomes from recently published observational studies focusing on post-operative recovery in patients undergoing abdominal surgery. In a retrospective review of prospectively collected patient data, Raju *et al* showed that short course celecoxib 100mg for up to 7 days, or until discharge, led to a reduction in postoperative ileus in patients undergoing major abdominal surgery for those who received celecoxib compared to controls (7.23% vs. 13.4% respectively, $p<0.05$), and an anastomotic leak rate of only 0.9%.[214] In addition, multicenter retrospective studies have shown reduction in postoperative length of stay in patients who received early postoperative NSAIDs compared to those who did not receive NSAIDs during their post-operative recovery.[369, 370] The key strength of our current study is that it provides clear evidence that NSAIDs improve return to normal gut recovery after abdominal surgery.

The majority of studies included in this review found a significant reduction in opioid use for patients receiving NSAID, ranging from an 18-51% reduction.[205, 206, 210] However, the role of COX isoforms in the pathogenesis of POI means that NSAIDs may also provide other benefits that are independent of opioid reduction.[1, 4] COX-derived prostaglandins play an important role in the way the bowel responds to surgery, and are expressed in lymphocytes, macrophages and neurons in the gut.[363] While the role of COX-1 derived prostaglandins in POI development is unclear, COX-2 activity seems to play an important role in the early inflammatory response to gut handling that is characterized by POI.[1, 363] In rodent models of POI, jejunal manipulation causes pan-intestinal upregulation of COX-2 and leads to a reduction in circular muscle contractility,[47] but not in mice with COX-2 knockout.[80] In normal humans, COX-2 inhibitors do not affect gastric emptying or small intestinal transit,[371] yet intraoperative COX-2 blockade increases small intestinal contractility in patients undergoing laparotomy.[76] Colonic manipulation, in particular, strongly increases upregulation of pro-inflammatory mediators such as COX-2, with levels increasing from 3-6 hours postoperatively.[1] Manipulation of the inflammatory response of the gut to surgery is becoming a key target for randomized trials looking at reducing the burden of POI on patients and the healthcare system.

To date, the use of NSAIDs in patients undergoing abdominal surgery remains contentious. Despite evidence of benefit for the recovery of gut motility postoperatively, use of NSAIDs is still not widely accepted due to their link with anastomotic leak. There have not been any new clinical trials published on NSAIDs in patients undergoing colorectal surgery since 2009. To evaluate the potential role of NSAIDs after abdominal surgery it is helpful to consider the status of evidence regarding their causative effect on anastomotic dehiscence. Several large observational studies have aimed to assess the impact of NSAIDs on anastomotic leak. Kotagal *et al* compared leak rates in 398,752 patients retrospectively assessed for ketorolac use after abdominal surgery, and found significant increases in leak, need for re-intervention and readmission postoperatively.[372] Hakkarainen *et al* showed that use of NSAIDs increased the risk of leak by 24% in 13,082 patients, but only in non-elective colorectal surgery.[212] NSAID use carries other risks, in particular long term use can be associated with renal impairment, and Valdecoxib has been discontinued due to an increased risk of myocardial infarction and stroke.

It appears that the type of NSAID used (COX-2 selective or non-selective) is important to their putative contribution to the risk of leak. A significant increase in leak rate has been reported in studies using non-selective NSAIDs (ibuprofen, diclofenac, ketorolac),[211, 369, 372] but not in patients receiving COX-2 selective inhibitors.[373] A recent meta-analysis, by Smith *et al*, of both randomized controlled trials and observational studies looking at use of NSAIDs after abdominal surgery found that clinical trial data did not support a significant increase in anastomotic leak with NSAIDs (RR 1.96, 95% CI 0.74-5.16, I^2=0%).[347] The authors comment that despite meta-analyzing available clinical trials the statistical power of their results likely remains low.[347] Observational study data did show a significant increase in leak rate in patients receiving NSAIDs (OR 1.46, 95% CI 1.14-1.86, I^2=54%), but on sensitivity analysis only non-selective COX inhibitors significantly increased the risk of leak.[347] Therefore, the current evidence does not support a clear increase in anastomotic leak with COX-2 selective NSAIDs.

Complications were not a focus of the current meta-analysis, and they were not consistently reported in the included trials. NSAIDs appear well tolerated after abdominal surgery and did not increase the overall rate of complications in several large observational studies.[370, 373, 374] Long-term use of COX-2 selective medications has been linked to an increased risk of cardiovascular death relating to an imbalance in prostacyclin formation and platelet-derived thromboxane A_2.[375] However, a recent series of 24081 patients receiving NSAIDs over a mean of 20 months by Nissen *et al* showed no increase in cardiovascular risk in patients receiving celecoxib compared to ibuprofen or naproxen.[376] NSAID use has also

been linked to an increase in acute kidney injury, hypertension, skin hypersensitivity reactions, and bleeding complications, particularly in at-risk patients.[376, 377] Recent studies on short-term use for postoperative pain have found no significant increase in renal adverse events, postoperative bleeding or rates of major complications.[377, 378]

The main limitation of this study is that the number of included trials is small, and the included studies were of low numbers of patients. Two out of the five included studies were unclear in their adherence to allocation concealment and blinding. Only 2 studies reported time to tolerance of diet, which is one of the most important outcomes regarding return of gut function and readiness for patient discharge. The included studies were all in patients undergoing laparotomy, and few of the included studies adhered to an ERAS protocol. In addition, it is important to view POI as a pan-intestinal disease. Future trials should use an outcome such as GI-2, (tolerance of diet and passage of stool),[23] or a focused definition of prolonged POI such as the definition presented by Vather *et al*.[2]

Our current research shows that NSAIDs do reduce the burden of POI in patients undergoing elective colorectal surgery. Further high-quality randomized controlled trials are now recommended to determine whether NSAIDs, specifically COX-2 inhibitors, should be part of routine care in colorectal patients. A key consideration for this research is whether these results are clinically relevant within a modern ERAS framework of perioperative care. Current evidence suggests that, despite use of ERAS, POI still occurs in up to 25-30% after elective colorectal surgery.[107, 140, 379] Venara *et al* recently looked at expression of COX-2 mRNA in pathology specimens from patients who underwent elective colorectal surgery and found that ERAS patients had significant reductions in COX-2 mRNA expression than patients who did not follow an ERAS pathway.[140] Of particular interest was that laparoscopic surgery, compared to laparotomy, did not significantly reduce levels of COX-2 mRNA.[140] This suggests that there may be additional benefits of short term COX-2 selective NSAID use in additional to core ERAS principles. Finally, this research strengthens the hypothesis for using other potentially anti-inflammatory agents (such as prucalopride, ghrelin or intra-peritoneal lignocaine) in future clinical trials to reduce POI.[1, 4]

5.5 Conclusion

NSAIDs significantly reduce the time to tolerate an oral diet, pass flatus and pass stool in this meta-analysis of five trials on patients undergoing elective colorectal surgery. NSAIDs, specifically COX-2 inhibitors, are an important target for future research into reducing the

duration of POI after colorectal and non-colorectal major abdominal surgery. As previously described, there is no definitive preventative measure for PPOI. For patients who do develop PPOI, despite best care, the options for treatment are relatively few. Gastrografin has been recently studied as a potential means to reduce the duration of PPOI. Chapter 6 will therefore assess the available evidence for gastrografin in the treatment of PPOI, using a pooled analysis of raw data.

Chapter 6

Gastrografin may reduce time to oral diet in prolonged postoperative ileus: a pooled analysis of two randomised trials.

6.1 Introduction

A number of preventative strategies, both pharmacological and non-pharmacological, exist for PPOI. However, as discussed in the introduction chapter, there are relatively few options for PPOI treatment. The previous chapters have outlined the burden of PPOI, and assessed the role of NSAIDs as a potential preventative measure for PPOI. Despite all available preventative measures PPOI remains common problem, even within a modern ERAS-based cohort of patients, as described in chapter 4.

A “rescue medication” for those who develop PPOI would significantly benefit surgical patients and the healthcare system. Gastrografin (Diatrizoate Meglumine and Sodium Diatrizoate) is a widely used hypertonic, water-soluble, contrast agent that has been shown on meta-analysis to significantly improve conservative management of adhesive small bowel obstruction.[380] The proposed mechanism of gastrografin in adhesive small bowel obstruction is that it draws oedema from the bowel wall into the lumen,[381, 382] and research suggests that the mechanism of PPOI also involves gut inflammation and oedema causing gut dysmotility.[1, 4]

Two recent randomised control trials, by Vather *et al* and Biondo *et al*,[39, 296] assessed the benefit of gastrografin as a treatment for patients who develop PPOI after elective colorectal surgery. Gastrografin has previously been used in patients after abdominal surgery but these studies were retrospective,[292] utilised historical controls,[293] or gave gastrografin prior to a diagnosis of PPOI.[294]

The aim of this study is to assess the pooled results of these two randomised controlled trials, to increase their statistical power, and therefore to clarify whether gastrografin deserves consideration for clinical use in PPOI, or whether further research is required to define its role.

6.2 Materials and Methods

6.2.1 Study comparability

The methods used by the two included trials were highly comparable and are described in Table 6-1.

Table 6-1. Comparison of included randomised controlled trials

	Vather *et al* 2015	Biondo *et al* 2015
Patients	18yo+ Elective colorectal surgery Neoplasia, IBD, diverticular Single centre	18yo+ Elective colorectal surgery Neoplasia, IBD, diverticular Multi-centre (3)
Intervention	100mL gastrografin orally or via NGT	100mL gastrografin via NGT
Comparator	100mL placebo	100mL placebo
Primary outcome	Time to PPOI resolution from diagnosis	Time to resolution of PPOI after administration of gastrografin (from beginning of NGT insertion)
PPOI definition	2+ criteria on/after day 4: 1. Nausea or vomiting 2. Absence of flatus and stool 3. Moderate-severe abdominal distension 4. Inability to tolerate semi-solid oral diet 5. Radiological evidence of ileus	2+ criteria on/after day 4: 1. Nausea or vomiting 2. Absence of flatus or stool 3. Abdominal distension 4. Persistent/non-specific abdominal pain 5. Oral intolerance 6. Radiological evidence of ileus
PPOI resolution	Resolution of all the following: 1. Nausea or vomiting 2. Absence of flatus and stool 3. Moderate-severe distension 4. Inability to tolerate semi-solid oral diet	Tolerance of semi-solid oral diet maintained until discharge
Jadad Score	5/5	5/5

Both trials included all adult patients who underwent elective bowel resection and used the same criteria for PPOI diagnosis. Operations included right hemicolectomy, left hemicolectomy/anterior resection, total/subtotal colectomy, abdominoperineal resection, Hartmann's procedure/colostomy formation in both trials. In addition, Vather *et al* included colostomy and ileostomy reversal.[39] For the sake of comparability, stoma closures were excluded from our study analysis. After the diagnosis of PPOI, patients in both trials were given gastrografin 100mL, or an equal volume of identical placebo, orally or by nasogastric tube. The primary outcome in both studies was duration of PPOI from diagnosis to

resolution, and secondary outcomes included time to tolerance of diet, time to passage of flatus/stool, rate of postoperative complications and length of postoperative stay. The Jadad score was used to assess the methodological quality of the included trials.

6.2.2 Study outcomes

Anonymised individual data from both trials were collected with author consent and pooled into a single database for analysis. Data on patient demographics, operative management and indications for surgery were compared. Detailed consideration was given to definitions of PPOI diagnosis and resolution, as well as secondary outcomes such as passage of stool or flatus, tolerance of a semi-solid diet. Where definitions used were sufficiently similar, the data were merged and directly compared. If definitions varied, individual outcome measures that were identical between the two studies were used to create combined outcomes.

The primary outcome of interest in this study was the time (in hours) from PPOI diagnosis to resolution in patients receiving gastrografin compared to placebo. Although both studies used the same definition for PPOI diagnosis, the definition of PPOI resolution was different between the two studies, as described in Table 1. To make these outcomes comparable, duration of PPOI was defined as time until a patient had both tolerated a semi-solid diet and passed stool or flatus after PPOI diagnosis.

Secondary outcomes of interest included time to tolerate a semi-solid diet after PPOI diagnosis, time to passage of stool or flatus, overall patient length of stay and differences in complication rates between the intervention and placebo groups. Other outcomes assessed in this study included the length of stay from PPOI diagnosis to discharge, requirement for and duration of NGT insertion and parenteral nutrition (TPN).

6.2.3 Analysis

All relevant data were merged into a single database for analysis. Both studies used an intention-to-treat analysis and this was continued in our present study. Dichotomous variables were compared using the chi-squared test and Fischer's exact test where appropriate. Continuous variables were first assessed for parametricity using the Shapiro-Wilk test, and then an independent samples t-test or Mann Whitney U test where appropriate. All p-values used were 2-sided and a p-value of <0.05 was deemed to be significant. All statistics were conducted using SPSS 20.0 for Mac (SPSS Inc., Chicago, IL).

6.3 Results

The combined data of both RCTs yielded 108 patients in total, with 53 patients in the gastrografin group and 55 patients in the placebo group. Table 6-2 compares demographic information between the 2 studies, and identifies no significant differences in patient characteristics, indication for surgery and operative technique. Both included trials received a Jadad Score of 5/5 for methodology.

Table 6-2. Comparison of study demographic information

	Vather et al	Biondo et al	p-value
Age (years)	68.4 (13.6)	68.5 (11.8)	0.96
Number of patients (total)	50	58	
Gastrografin	24	29	
Placebo	26	29	
Gender			0.96
Male	36	42	
Female	14	16	
ASA Grade			0.40
1	1	0	
2	27	32	
3	22	24	
BMI (Kg/m^2)	28.3 (4.1)	27.0 (4.0)	0.10
Indication			0.47
Cancer	45	55	
Inflammatory/Diverticular	5	3	
Procedure			0.34
Right hemicolectomy	15	18	
Left hemicolectomy/Anterior resection	22	28	
Abdominoperineal resection	4	3	
Sub-total or total colectomy	6	4	
Ileostomy/Colostomy formation	1	5	
Other	2	0	
Technique			0.30
Laparoscopic	15	23	
Open/Converted	35	35	

Continuous data is normally distributed and expressed as mean (SD)

Analysis of the key primary and secondary outcomes of the two combined trials is shown in Table 6-3. The results show that the median duration of PPOI trended towards being shorter in patients who received gastrografin (96 hours) compared to placebo (120 hours), but this difference was not statistically significant (p=0.11).

Table 6-3. Primary and secondary outcomes of pooled data

	Gastrografin		Placebo		P-value
	Patients	Median (IQR)	Patients	Median (IQR)	
Duration of PPOI (hours)	53	96 (39, 135)	55	120 (78, 162)	0.11
Time to tolerate oral diet (hours)	51	84 (46, 122)	54	107 (59, 155)	0.04*
Time to passage of stool or flatus (hours)	49	24 (0, 64)	52	42 (0, 86)	0.36
Total length of stay (days)	53	14 (8, 19)	55	15 (11, 19)	0.35

Statistical significance determined using Mann-Whitney U test for non-parametric data

Pooled analysis demonstrated that gastrografin did confer a significantly faster time to tolerate a semi-solid diet compared to placebo: the median time to tolerate a semi-solid diet was 23 hours faster in the gastrografin group compared to placebo (p=0.04). Gastrografin did not, however, shorten time to passage of flatus or stool (p=0.36) and did not reduce the overall length of stay in hospital (p=0.35).

No difference was found in the mean length of stay from PPOI diagnosis to discharge between the gastrografin and placebo group (12.1 $\pm$ 8.0 days vs. 13.8 $\pm$ 11.8 days respectively, p=0.6). No significant difference was determined between the gastrografin and placebo groups respectively with respect to requirement for NGT insertion (67% vs. 82%, p=0.15), mean duration of NGT insertion (5.3 $\pm$ 4.0 days vs. 5.5 $\pm$ 4.8 days, p=0.91), requirement for TPN (49% vs. 64%, p=0.13) and mean duration of TPN (8.9 $\pm$ 3.6 days vs. 8.7 $\pm$ 6.6 days, p=0.15).

Importantly, there was no significant difference between the number and severity of complications between the gastrografin and placebo group (Table 6-4).

Table 6-4. Comparison of complications between gastrografin and placebo group

Clavien-Dindo Grade	Gastrografin	Placebo	P-value
1	10	8	0.59
2	40	41	0.95
3	5	9	0.27
4	0	2	0.50
5	2	0	0.24

Two deaths occurred in the gastrografin group: one patient died from pneumonia acquired prior to gastrografin administration, another patient had carcinomatosis at time of operation and eventually developed multiple organ failure after PPOI diagnosis.

6.4 Discussion

The pooled results of these two randomised controlled trials show that gastrografin significantly reduced the time to tolerate an oral diet compared to placebo after PPOI diagnosis (median of 23 hours faster). A non-significant reduction in overall duration of PPOI was also observed. Gastrografin did not significantly reduce patient length of stay after administration. The main strength of this study is that raw data were able to be amalgamated, because both studies adhered to strict diagnostic criteria for PPOI diagnosis. This helps improve the power of the combined results to better evaluate the effectiveness of gastrografin in PPOI.

The results of this pooled analysis show some differences compared to the results of the original trials. Vather *et al* found a significantly reduced time to passage of flatus or stool (18.9 hours vs. 32.7 hours, p=0.047), and time to resolution of abdominal distension (52.8 hours vs. 77.7 hours, p=0.013), after gastrografin administration compared to placebo respectively.[39] There was a non-significant trend towards a reduction in time to tolerate oral diet, resolution of nausea and vomiting, and PPOI duration.[39] Biondo *et al* found trends towards a reduction in PPOI duration (9.1 days vs. 10.3 days), time to tolerate an oral diet (5.9 days vs. 8.1 days) and time to passage of flatus or stool (4.0 days vs. 5.2 days) for patients receiving gastrografin over placebo respectively, but these trends were not statistically significant.[296] Neither trial found a benefit in total length of stay for the gastrografin group.[39, 296]

Gastrografin is an important therapy for patients with adhesive small bowel obstruction,[380, 383] and it confers a statistically and clinically significant reduction in time to resolution of adhesive small bowel obstruction and length of stay compared to placebo.[384-386] The mechanism of gastrografin in adhesive small bowel obstruction potentially relates to its high osmolarity, meaning that ingested gastrografin may draw oedema from the bowel wall and increase the pressure gradient across a partial obstruction, leading to resolution of the obstruction.[39, 294, 387] The current hypothesis for PPOI onset relates to bowel inflammation induced by surgical manipulation of the gut, involving activation of resident macrophages and peritoneal mast cells, production of cytokines and chemokines, inducing pan-intestinal hypomotility.[1, 4] As a therapeutic agent, gastrografin may act in PPOI by reducing bowel wall oedema and improving gut motility.

The use of gastrografin in patients with impaired or obstructed gut motility is not without risk. Aspiration of both concentrated and dilute gastrografin can lead to aspiration pneumonitis and pulmonary oedema, likely due to the hypertonicity of gastrografin (osmolarity of 1900mOsm/L), with significant morbidity and mortality.[388-390] There have also been reported cases of intravasation of gastrografin if given via a nasogastric tube that is incorrectly placed, leading to renal failure or anaphylaxis.[380] Fortunately, these complications are rare and are reported to occur in <1/1000 patients.[391] A recent meta-analysis by Abbas *et al* found that patients given gastrografin for adhesive small bowel obstruction did not have a significantly increased risk of morbidity or mortality compared to placebo.[380] The pooled results of our included trials also found no significant difference in complication rates, severity of complications and mortality between gastrografin and placebo.

Given the trends towards faster clinical recovery from PPOI with gastrografin on pooled analysis, it is possible that the combined data remains underpowered to detect a significant difference in some outcomes. In future, we would recommend trials continue to use the same rigorous definition of PPOI diagnosis as Vather *et al* to allow direct comparison between studies on meta-analysis.[2] In addition, a combined endpoint for resolution of gut dysmotility should be used, such as the time to passage of stool and tolerate a solid diet, which provides an accurate definition of return to bowel transit and correlates directly with scintigraphy.[23]

One of the weaknesses of this study is that the number of patients was still comparatively low despite combining the two trials, and that there were differences between their definitions of PPOI resolution (Table 1). This meant that a primary outcome of PPOI

resolution had to be defined using raw data to determine the time to both tolerate a semi solid diet and passage of flatus or stool.

6.5 Conclusion

In conclusion, our results provide evidence that gastrografin significantly reduces the time to tolerate an oral diet in patients with PPOI, and could be used as a rescue medication in this setting. In order to effectively reduce the duration of PPOI, however, an agent must improve time to tolerate a diet and pass stool. Gastrografin did not meet these criteria compared to placebo in our current study, and did not reduce patients' length of stay. More research is still required to fully clarify the clinical role of gastrografin in ileus. Without an effective treatment for PPOI, the goals of further PPOI research should focus on prevention. Chapter 7 will now outline the results of a randomised control trial of prucalopride to improve postoperative gut dysmotility and reduce PPOI.

Chapter 7

Randomized double-blind controlled trial on the effect of prucalopride to improve time to gut function recovery following elective colorectal surgery

7.1 Introduction

Chapter 3 has demonstrated the burden of PPOI after elective colorectal surgery within a modern patient cohort. In chapter 4, we identified the influence of perioperative medication on PPOI risk. Subsequently, chapter 5 showed a benefit for NSAID use on postoperative gut recovery, although the efficacy was mild, and it was unclear whether this translated into a reduction in PPOI incidence. Chapter 6 showed that gastrografin was, overall, not an effective medication to treat PPOI and reduce its duration. A new and effective preventative strategy or medication is desperately required for PPOI, and it would have a substantial benefit for patients and healthcare systems internationally.

One of the key problems with delayed return to normal gut motility, and PPOI, is that there are few effective treatments for it, or preventative measures to reduce its burden.[5] Postoperative ileus affects the entire gastrointestinal tract,[59, 392] which means that prokinetics that only selectively target the colon or stomach, for example, are unlikely to be effective. As previously discussed, recent evidence suggests that the pathophysiology of postoperative ileus is mediated by an initial neurologically mediated phase and then a delayed inflammatory response to surgery in the gut, and that this inflammatory response can be diminished by drugs that potentiate vagal nerve activity.[50, 59, 392] The inflammatory phase is thought to contribute to the development and duration of PPOI.[1]

Prucalopride is a serotonin-4-receptor agonist that increases pre-synaptic acetylcholine release from vagal neurons, improves colonic motility and is a gastric prokinetic.[99, 307, 318, 319] A recent trial by Gong *et al* (2016) showed that prucalopride given after elective colorectal surgery improved time to passage of flatus and stool.[326] In addition, recent studies show that prucalopride, when given preoperatively and continued in the post-operative period, reduces the inflammatory response associated with surgery,[301] and improves time to tolerate diet.[393]

The aim of this study was therefore to conduct a double-blinded placebo-controlled randomized trial to investigate whether prucalopride given preoperatively and continued postoperatively improves time to return of postoperative gut motility, by improving time to tolerate diet and passage of stool, in patients undergoing elective colorectal resections. The secondary aim of this study was to determine whether prucalopride reduces the incidence of PPOI after elective colorectal surgery.

7.2 Methods

This study was approved by the New Zealand Health and Disability Ethics Committee, as well as by the Auckland District Health Board and Southern District Health Board's Research Review Committees. The trial was prospectively registered with clinicaltrials.gov (identifier: NCT02947269).

7.2.1 Study design

This study is a multicenter, double-blind, parallel, placebo-controlled randomized trial to investigate whether prucalopride improves time to recovery of postoperative gut function compared to placebo. Eligible patients were aged 18 or older, who had elective colorectal surgery at 2 tertiary New Zealand hospitals (Auckland City Hospital and Dunedin City Hospital) between October 2017 and May 2020. Patients and the public were not involved in the design or conduct of this study. There was no change to the trial methods after commencement.

7.2.2 Inclusion criteria

Patients who underwent a right hemicolectomy, sigmoid colectomy/anterior resection, subtotal colectomy, Hartmann's procedure, or abdominoperineal resection (APR) for colon cancer, diverticular disease, or volvulus, with or without a colostomy formation, were included. All patients had to be able to give informed consent and understand the risks and benefits of the study. All patients were seen pre-operatively in clinic and given verbal and written information on the study's design, purpose, risks, and benefits. Written consent was attained for all study participants, and patients could withdraw themselves from the study at any stage.

7.2.3 Exclusion criteria

Patients were excluded if they had an ASA score of 4 or higher, any allergy to serotonin-based medication, active inflammatory bowel disease, moderate to severe renal impairment (eGFR<50mL/min), severe hepatic impairment, pregnancy or were on pre-operative intravenous nutrition (IVN). Patients with a planned ileostomy formation were excluded. Patients were also excluded if they had pre-existing gut dysmotility due to endocrine, metabolic, or neurological causes. Patients unable to consent due to dementia, cognitive impairment, language difficulties or delirium were not included.

7.2.4 Demographics and data collection

Demographic data were collected on patient factors including age, sex, procedure, indication, comorbidities, and ASA score. Patients were assessed twice daily (0800 and 2000) by a blinded study investigator until their achieved GI-2 and then daily after that. Information on primary and secondary outcomes, bloods, and complications were recorded on pre-made data collection sheets. Patients were phoned to determine time to passage of stool, if not achieved at time of discharge. The primary outcome of this study was time to GI-2 (passage of stool and tolerance of oral diet).[23] Tolerance of oral diet was defined as the ability to eat a solid or semi-solid diet of 25% or more of their pre-operative meal intake without significant nausea or vomiting over 2 or more consecutive meals. Secondary outcomes included: time until passage of flatus, stool and tolerance of diet, preoperative and postoperative bloods from days 1-3 including Hb, CRP, white cell count (WCC) and differential, renal function, and electrolytes. Length of stay, need for re-operation and 30-day readmission rates were also recorded. Volumes or quantities of perioperative and postoperative IV fluid, analgesia, antiemetic, and anti-inflammatory were recorded. Adverse events were graded by system and severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4 guidelines, and complications were graded using the Clavien-Dindo classification system.[51] Patients were also assessed for PPOI using the definition by Vather *et al* (2013) as a secondary endpoint, as well as need for NGT or IVN.[2] Specifically, patients were diagnosed with PPOI if they met 2 or more of the following criteria on or after postoperative day 4: nausea or vomiting, inability to tolerate an oral diet over the last 24 hours, absence of flatus over the last 24 hours, abdominal distension, radiological evidence of ileus.[2] All patients also completed a Gastroparesis Cardinal Symptom Index (GCSI) questionnaire prior to surgery and daily until discharge.[394] The GCSI comprises 9 patient-reported components, each rated in severity from 0-5, with a total score of 45. The

questions involve 3 sub-scales (postprandial fullness/early satiety, nausea/vomiting, and bloating). Higher scores correlate with worse symptoms of gastroparesis.

7.2.5 Randomization and methods

Patients were randomized by study investigators on the morning of their operation to receive either 2mg prucalopride or 2mg identical placebo capsule, using a computer-generated randomization list made by an external pharmacy. Study medication was prepared by an external pharmacy, block randomized into groups of 10 in a 1:1 allocation and numbered sequentially. Participants, study investigators and clinical staff were all blinded to medication allocation. Only the external pharmacy had access to the unblinded study medication allocation data. Study medication was given 2 hours pre-operatively, so that prucalopride reached its peak plasma concentration at time of surgery,[302] and continued daily in the morning for up to 6 days, or until the patient had achieved the primary endpoint or was discharged. All patients undergoing elective colorectal surgery at Auckland City and Dunedin hospitals follow a structured Enhanced Recovery After Surgery (ERAS) protocol. The ERAS protocol included pre-operative oral carbohydrate drinks, early introduction of post-operative diet, stepwise analgesia progression, minimization of intravenous fluids, bowel preparation and opiate use, early patient mobilization, subcutaneous thromboprophylaxis and omission or early removal of drains, lines, nasogastric tubes, and catheters.

7.2.6 Power calculation

An *a priori* power calculation was performed using retrospective data from a previous prospective trial on postoperative ileus at Auckland City Hospital.[43] Pilot data were extracted from 76 patients undergoing elective bowel resection without ileostomy formation, which showed a mean time to GI-2 of 4.9 days (± 2.6 days). An alpha value (chance of false positive) of 0.05 was used, and a beta of 0.2 (chance of a false negative) with a study power of 80%. The hypothesis was that prucalopride would reduce the time to GI-2 by a clinically meaningful 25%. Using the computer-simulated bootstrapping technique, and in consultation with a biostatistician, for power calculation as described by Walters *et al* (2004),[395] and a two-tailed test in a 1:1 allocation ratio, 65 patients per study arm were required. An expected 15% drop-out rate was used, for a total recruitment of 150 patients across both study sites.

7.2.7 Statistical analysis

All statistical analyses were conducted as intention-to-treat and no interim analysis was performed. Statistical tests were run on SPSS for Mac (Version 24; SPSS, Chicago, IL). Data were assessed for normal distribution using a histogram plot and the Shapiro-Wilk test. Normally distributed data were analyzed with an independent samples student's *t*-test, and data that had an asymmetrical distribution were analyzed with the Mann-Whitney U test. The chi-squared test was used for categorical univariate analyses. All tests were 2-sided and a p-value of <0.05 was deemed to be significant. The datasets generated during and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

7.3 Results

A CONSORT diagram is provided in Figure 7-1. 330 patients were assessed for eligibility, of which 180 were excluded. 150 patients were randomized, 75 per arm, and one patient in each group was excluded after randomization. One patient in the prucalopride group was withdrawn preoperatively by the surgeon due to patient comorbidity, one patient in the placebo group was withdrawn as their operation was cancelled on the day. Therefore, 148 patients were analyzed, 74 patients per study arm. No patients were lost to follow up. Eight patients in the prucalopride group and nine patients in the placebo group discontinued treatment early (11% and 12% respectively), due mainly to development of postoperative ileus. None of the patients who discontinued medication early were excluded from analysis. Patients received preoperative medication on average 138mins ($\pm$ 60 mins) before surgery, and 2 patients (one per arm) did not receive their preoperative dose of study.

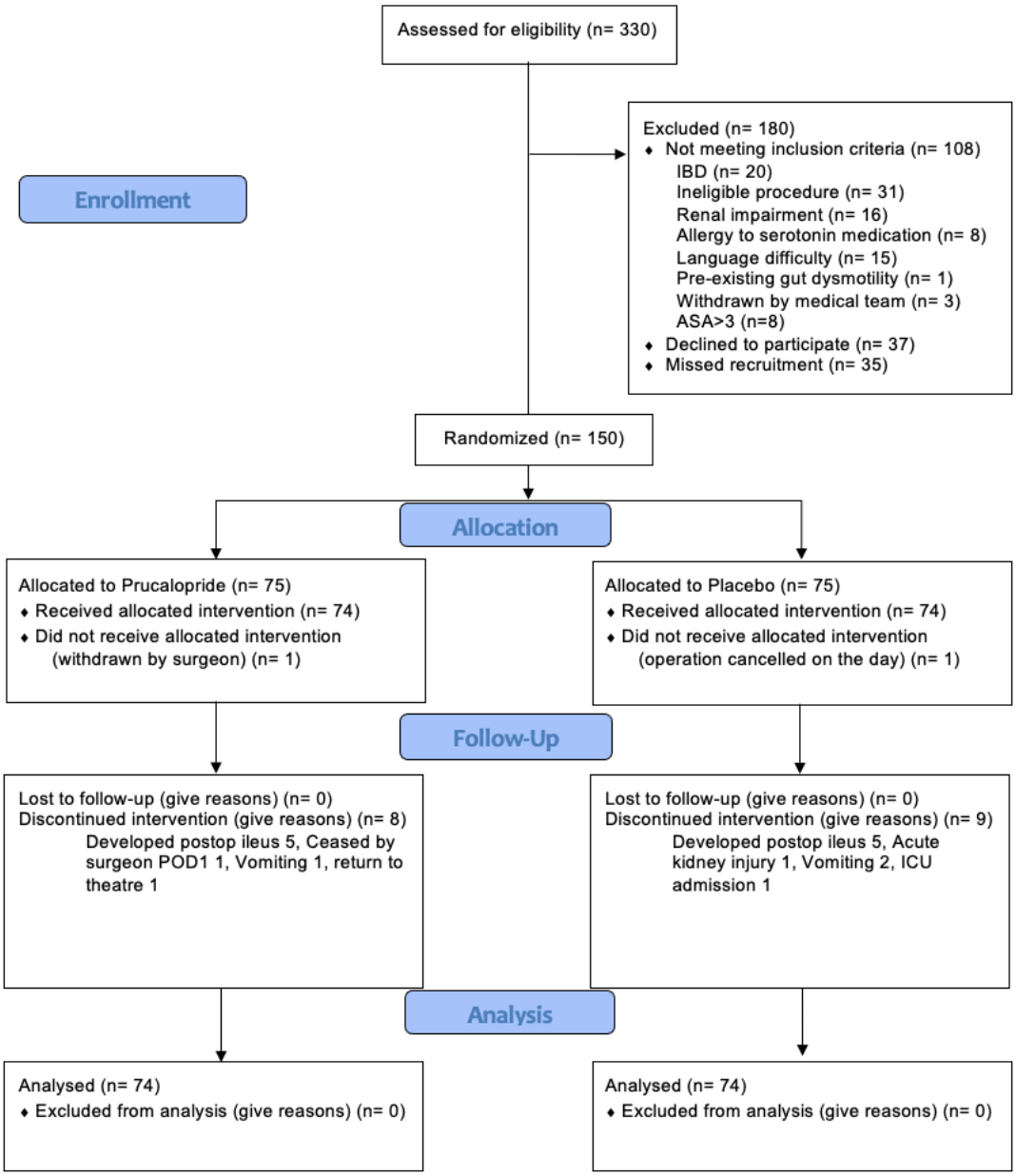

Figure 7-1. CONSORT Diagram

7.3.1 Demographic data

The demographics of this study's patient cohort are described in Table 7-1. Dunedin hospital recruited 91 patients (62%) and Auckland Hospital recruited 57 patients (38%). Demographic data, including age, sex, ethnicity, BMI, ASA grade and indication for surgery were not statistically different between groups. The technique (laparoscopic, lap-assisted, open, or converted) used was also the same for both groups. All APRs occurred in the Prucalopride group (5 patients); the groups were otherwise similar in terms of type of colon resection. There was a difference between groups in the number of patients who had an unplanned

ileostomy formation (4.1% of the prucalopride group vs. 9.5% of the placebo group) but the statistical significance of this was uncertain (p=0.128). Perioperative management was similar between the prucalopride and placebo patients. There was no difference in the use of a spinal or epidural block (p=0.870): 45.9% of patients in the prucalopride group had a spinal and 8.1% had an epidural, 43.2% of placebo patients had a spinal and 6.8% had an epidural. Of the patients who underwent laparoscopic surgery, 2 had an epidural (1 in each group). There was no difference in the volume of perioperative crystalloid (p=0.716), units of non-steroidal anti-inflammatory drugs (NSAIDs) (p=0.882) or opiate units (p=0.598) between groups.

Table 7-1. Demographic data

	Total (n=148)	Prucalopride (n=74)	Placebo (n=74)	P-value
Age, years (Median, IQR)	70.5 (64.5, 76.5)	71 (64, 78)	69.5 (64, 75)	0.698
Gender				
Male	83 (56%)	45 (61%)	38 (51%)	0.246
Female	65 (44%)	29 (39%)	36 (49%)	
Ethnicity				
NZ European	138 (93.2%)	68 (91.9%)	70 (94.6%)	0.669
Maori	3 (2%)	1 (1.4%)	2 (2.7%)	
Asian	2 (1.4%)	1 (1.4%)	1 (1.4%)	
Indian	4 (2.7%)	3 (4.1%)	1 (1.4%)	
Other	1 (0.7%)	1 (1.4%)	0 (0%)	
BMI (Median, IQR)	27 (24.3, 31.5)	27.6 (23.7, 31.5)	26.8 (23.8, 29.8)	0.129
ASA Grade				0.410
1	16 (10.8%)	8 (10.8%)	8 (10.8%)	
2	93 (62.8%)	43 (58.1%)	50 (67.6%)	
3	39 (26.4%)	23 (31.1%)	16 (21.6%)	
Operation				0.128
Right hemicolectomy	54 (36.5%)	24 (32.4%)	30 (40.5%)	
Anterior resection	81 (54.7%)	41 (55.4%)	40 (54.1%)	
APR	5 (3.4%)	5 (6.8%)	0 (0%)	
Subtotal colectomy	8 (5.4%)	4 (5.4%)	4 (5.4%)	
Technique				0.828
Laparoscopic	112 (75.7%)	54 (73%)	58 (78.4%)	
Lap-assisted	13 (8.8%)	8 (10.8%)	5 (6.8%)	
Open	19 (12.8%)	10 (13.5%)	9 (12.2%)	
Converted to open	4 (2.7%)	2 (2.7%)	2 (1.4%)	
Stoma				
None	133 (89.9%)	66 (89.2%)	67 (90.5%)	0.785
Ileostomy	10 (6.8%)	3 (4.1%)	7 (9.5%)	0.190
Colostomy	5 (3.4%)	5 (6.8%)	0 (0%)	0.023*
Indication				0.249
Cancer	137 (92.6%)	71 (95.9%)	66 (89.2%)	
Diverticular disease	10 (6.8%0	3 (4.1%)	7 (9.5%)	
Volvulus	1 (0.7%)	0 (0%)	1 (1.4%)	
Operation duration, mins (Median, IQR)	188 (142, 240)	199 (144, 255)	180 (135, 226)	0.55

7.3.2 Primary outcomes

There were no clinically, or statistically, meaningful difference in time to GI-2 (passage of stool and tolerance of diet) between the prucalopride and placebo groups, median (IQR) of 3.5 days (2, 5) vs. 4 days (3, 5) respectively (p=0.124). The time to tolerate oral diet was the similar between groups: 2 days (0.5, 3.5) vs. 2 days (0.5, 3.5), p=0.669. Patients who received prucalopride had a faster time to pass stool (median 3 days (2, 4)) vs. placebo (median 4 days (2.7, 5.3)), p=0.027. Time to flatus occurred at the same time in both groups (median 2 days). There was a statistical (p=0.029) difference in time to flatus between groups, but this is not clinically significant. Table 7-2 shows the full statistical analysis of primary and secondary outcomes. The rate of PPOI (p=1.0), NGT insertion (p=0.082) and requirement for IVN (p=0.785) was similar between groups. Length of stay was equivalent between the prucalopride (median 4 days (2, 6)) and placebo group (median 4 days (2, 6)), p=0.929.

Table 7-2. Results of intention-to-treat analysis

	Total (n=148)	Prucalopride (n=74)	Placebo (n=74)	P-value
Time to GI-2, days (Median, IQR)	4 (3, 5)	3.5 (2, 5)	4.0 (3, 5)	0.124
Time to Diet, days (Median, IQR)	2 (1, 4)	2 (0.5, 3.5)	2 (0.5, 3.5)	0.669
Time to Flatus, days (Median, IQR)	2 (1, 2)	2 (1.5, 2.5)	2 (1.5, 2.6)	0.029*
Time to Stool, days (Median, IQR)	3 (2, 4)	3 (2, 4)	4 (2.7, 5.3)	0.027*
Length of stay, days (Median, IQR)	4 (3, 7)	4 (2, 6)	4 (2, 6)	0.929
Incidence of PPOI	32 (21.6%)	16 (21.6%)	16 (21.6%)	1.000
NGT required	23 (15.5%)	10 (13.5%)	13 (17.6%)	0.082
IVN required	9 (6.1%)	4 (5.4%)	5 (6.8%)	0.785

There was no difference in terms of patients' symptoms reported using the Gastroparesis Cardinal Symptom Index (GCSI) questionnaire from postoperative days 1-4 between groups either (see Figure 7-2).

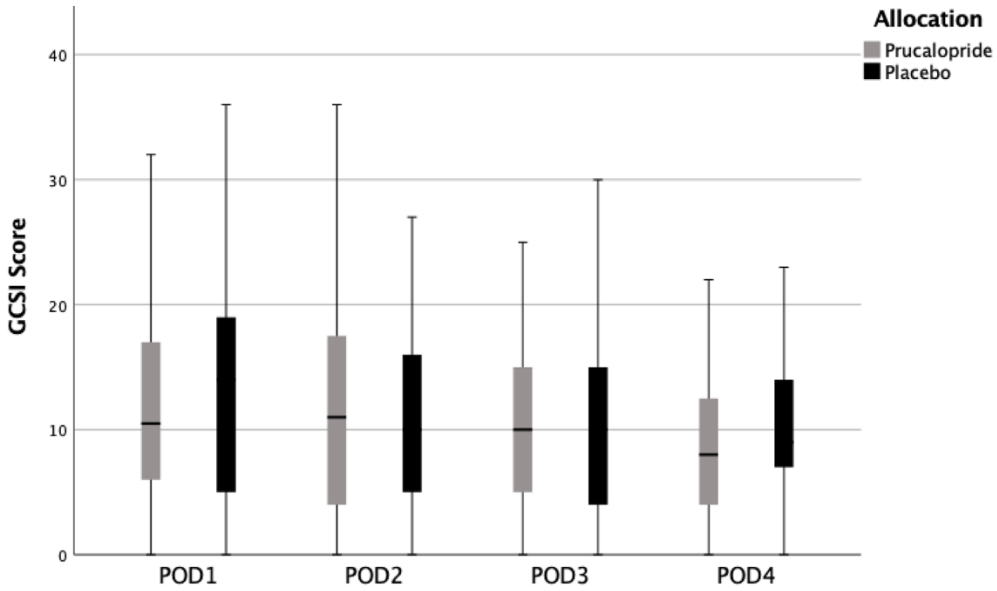

Figure 7-2. Box plot of results of Gastroparesis Cardinal Symptom Index (GCSI) questionnaire

7.3.3 Complications and adverse events

Table 7-3 describes the rate of complications and adverse events between the prucalopride and placebo group. The rates of postoperative complications and adverse events were similar between groups. The rate of anastomotic leak (2.7% vs. 1%, p=0.560) and reoperation (4.1% vs. 4.1%, p=1.0) were no different between the prucalopride and placebo group respectively, and there was no difference in readmission rates within 30 days (p=0.597). The rate of cardiac complications was similar for prucalopride patients (12.2%) and placebo patients (8.1%), p=0.414. Patients in the prucalopride group suffered fewer renal related complications (2.7% vs. 10.8%, p=0.049).

Table 7-3. Description of complications and adverse events

	Total (n=148)	Prucalopride (n=74)	Placebo (n=74)	P-value
Clavien-Dindo Grade				
1	19 (12.8%)	9 (12.2%)	10 (13.5%)	0.806
2	31 (20.9%)	19 (25.7%)	12 (16.2%)	0.157
3	11 (7.4%)	7 (9.5%)	4 (5.4%)	0.347
4	6 (4.1%)	3 (4.1%)	3 (4.1%)	1.000
5	0 (0%)	0 (0%)	0 (0%)	-
Readmission 30 days	16 (10.8%)	9 (12.2%)	7 (9.5%)	0.597
Reoperation	6 (4.1%)	3 (4.1%)	3 (4.1%)	1.000
Anastomotic leak	3 (2%)	2 (2.7%)	1 (1.4%)	0.560
CTCAE Grade				
1	39 (26.4%)	18 (24.3%)	21 (28.4%)	0.576
2	44 (29.7%)	20 (27%)	24 (32.4%)	0.472
3	39 (26.4%)	22 (29.7%)	17 (23%)	0.351
4	7 (4.7%)	4 (5.4%)	3 (4.1%)	0.699
5	0 (0%)	0 (0%)	0 (0%)	-
CTCAE System				
General	7 (4.7%)	6 (8.1%)	1 (1.4%)	0.116
*Cardiac**	15 (10.1%)	9 (12.2%)	6 (8.1%)	0.414
Gastro	49 (33.1%)	24 (32.4%)	25 (33.8%)	0.861
Infection	18 (12.2%)	10 (13.5%)	8 (10.8%)	0.615
Neurological	10 (6.8%)	4 (5.4%)	6 (8.1%)	0.512
*Renal^*	10 (6.8%)	2 (2.7%)	8 (10.8%)	0.049*
Respiratory	3 (2%)	2 (2.7%)	1 (1.4%)	0.560
Vascular	14 (9.5%)	7 (9.5%)	7 (9.5%)	1.000
Blood and lymphatic	8 (5.4%)	3 (4.1%)	5 (6.8%)	0.467
Injury, poisoning, procedural	4 (2.7%)	3 (4.1%)	1 (2.7%)	0.311
Metabolism/Nutrition	6 (4.1%)	4 (5.4%)	2 (2.7%)	0.405

*Description of cardiac complications:

Prucalopride: atrial flutter (1), sinus arrhythmia (1), AF (5), chest pain (1), sinus tachycardia (1)

Placebo: bradycardia (3), AF (1) sinus tachycardia (2)

^Description of renal complications:

Prucalopride: urinary retention (2)

Placebo: Acute kidney injury (5), urinary retention (3)

7.3.4 Laboratory results

There was no difference in WCC on postop days 1 (p=0.465), 2 (p=0.529), or 3 (0.860) for patients who received prucalopride vs placebo respectively. Levels of postop CRP on postoperative days 1 (p=0.544), 2 (p=0.860) or 3 (p=0.725) were also no different.

7.3.5 Per-protocol analysis

A sub-group, per-protocol, analysis was performed that excluded patients who did not receive preoperative medication (2) and those who had an unplanned ileostomy formation (10). The results were consistent with the intention-to-treat analysis. Patients in the prucalopride group passed flatus (p=0.041) and stool (p=0.006) faster than placebo patients

but did not have faster time to diet (p=0.446), GI-2 (p=0.177) or shorter length of stay (p=0.850). Because all the APRs occurred in the prucalopride group, a further analysis was performed to determine if this had skewed the results. There was no difference in GI-2 (p=0.244), time to diet (p=0.419), time to flatus (p=0.062), or length of stay (p=0.691), however patients in the prucalopride group had faster time to passage of stool (p=0.014).

7.3.6 Laparoscopic vs. open surgery analysis

A *post-hoc* analysis was performed of patients who only underwent laparoscopic or laparoscopic-assisted surgery. When these patients were analyzed separately, patients in the prucalopride group (n=62) achieved GI-2 a median of 1 day faster than placebo patients (n=63). Median time to GI-2 for prucalopride patients who underwent laparoscopic surgery was 3 days (2, 4) vs. placebo's 4 day (3, 5), p=0.012. However, there was no difference in median length of stay between the prucalopride (4 days (3, 5)) and placebo groups (4 days (2.5, 5.5)) in this sub-group analysis, p=0.469. The incidence of PPOI (p=0.478), NGT insertion (p=0.375), and IVN (p=0.833) were similar between groups. There was no difference in postoperative inflammatory markers (WCC or CRP) on days 1-3 between groups. The rate of complications and adverse events were similar in both groups who underwent laparoscopic surgery.

Interestingly, an analysis of patients who had open surgery or surgery converted to open (12 prucalopride, 11 placebo) showed no difference in time to passage of flatus (p=0.177) or stool (p=0.687), but there was a trend towards slower time to tolerate diet in the prucalopride group. Median time to tolerate diet in patients who underwent open surgery in the prucalopride group was 6.3 days (1.5, 8.7) compared to 3 days (1.5, 4.5) in the placebo group, p=0.054. Median time to GI-2 in the prucalopride group was 6.3 days (5.1, 7.5) versus 5 days (3, 7) in the placebo group, p=0.204. There was no difference between prucalopride and placebo in the length of stay for patients who underwent open surgery (p=0.147) and no difference in complications or adverse events.

7.4 Discussion

This randomized placebo-controlled double-blind trial found that, overall, prucalopride did not improve time to GI-2 or reduce the rate of PPOI compared to placebo in patients undergoing elective colorectal surgery. While prucalopride significantly improved time to passage of flatus and stool, there was no improvement in time to tolerate diet or symptoms of gastroparesis with prucalopride. Prucalopride did not shorten the length of postoperative

stay. Prucalopride was safe in this cohort, there were no differences in postoperative complications rates, severity, or adverse events between groups. Prucalopride did not reduce levels of postoperative WCC or CRP from postoperative days 1-3. Importantly, there was no difference in cardiac complications or anastomotic leak rates between groups.

One potential advantage of prucalopride was seen in the laparoscopic surgery cohort. In patients who underwent laparoscopic or laparoscopic-assisted surgery, prucalopride significantly improved time to GI-2 by 1 day. This is a clinically meaningful reduction in time to recovery of gut function, but this did not translate to a difference in length of stay for patients who had laparoscopic procedures in the prucalopride group in this trial. It is important to note that this was a *post-hoc* analysis and was not a part of the original statistical analysis plan. However, most patients in this study underwent laparoscopic surgery (84.5%), in adequate numbers to suggest that these results may be meaningful. Inflammation plays a key role in the development and prolongation of postoperative ileus.[1, 392] The inflammatory response after laparoscopic surgery is significantly less than that after open surgery.[185, 396] It is, therefore, possible that prucalopride was ineffective in patients who underwent open surgery due to the marked increase in inflammatory response to laparotomy. Further studies assessing the differences in postoperative inflammatory markers are planned for follow up on this finding.

The strength of this study is that it represents the largest randomized control trial comparing prucalopride to placebo for patients undergoing elective colorectal surgery. It is also the first study to assess to efficacy of prucalopride, when given both pre and postoperatively, in improving time to return of pan-intestinal gut motility. Preoperative administration is important so that prucalopride is active at time of surgery, which is when the neurally and inflammatory-mediated mechanisms of ileus commence.[1] This study provides the results of a double-blinded, multicenter RCT with an intention-to-treat analysis that is adequately powered.

There are some limitations to this study. Based on the study's inclusion criteria, 33% of patients were excluded, and this included exclusion due to language barriers, renal impairment, and inflammatory bowel disease. This may reduce the study's generalizability. While some differences in ileostomy and APR rates occurred between groups, the authors do not believe this would have impacted the primary outcomes, as these differences were accounted for in sub-group analysis. All APRs occurred in the prucalopride group, but the number of APRs in this cohort was low (only 5). The number of patients with an unplanned ileostomy was also low in both groups and fell below the study's drop-out rate of 15%. The

results of the per-protocol analysis (with ileostomy excluded) were consistent with the primary analysis.

One consideration is whether an adequate dose of preoperative prucalopride was provided. Stakenborg *et al* (2019) found a reduction in postoperative IL6, IL8 and TNF-α in intestinal samples of patients who received 4mg preoperative prucalopride, but no difference in serum samples.[99] However, increasing the prucalopride dose from 2mg to 4mg did not significantly improve outcomes for patients with chronic constipation,[310, 326] and both 2mg and 4mg of prucalopride were sufficient to improve gastric emptying times in patients with gastroparesis in recent series.[319, 320] It is unclear whether patients would benefit from additional preoperative dosing to fully benefit from the anti-inflammatory properties of prucalopride, or to achieve a steadier state of the drug preoperatively.

7.5 Conclusion

Postoperative ileus remains a significant problem for patients and healthcare professionals after colorectal surgery. Although prucalopride was ineffective in improving time to GI-2 and reducing the rate of PPOI in the overall cohort, it had an apparent advantage in time to passage of stool for all patients, and significantly improved time to GI-2 in patients undergoing laparoscopic surgery. Prucalopride may therefore be effective in improving time to return of postoperative gut function in selected patients undergoing elective minimally invasive colorectal surgery.

Summary of Results

The aims of this thesis were to better quantify the economic burden of PPOI and to critically assess currently available methods for PPOI prevention and treatment. The overall goal of this body of work was to assess whether prucalopride was effective in reducing postoperative gut dysmotility and preventing PPOI after elective colorectal surgery.

The introduction chapter provided a comprehensive analysis of the definitions, incidence and burden of PPOI. Importantly, it describes the currently used definition for PPOI on which to base further research. The first chapter also highlights the pathophysiological mechanisms of PPOI, and how our understanding of PPOI physiology has developed in modern times. The complicated inter-play between inflammatory mediators that occurs secondary to abdominal surgery is impacted by aspects of inpatient management, and a detailed description of the risk factors of PPOI has been provided. The prevention and treatment of PPOI is complicated, and we lack a definitive way to prevent it. The first chapter summarises the evidence for interventions to prevent and treat PPOI, including the aspects of ERAS and pharmaceutical management. Finally, we provide evidence for a potential benefit of prucalopride in PPOI and critically appraise its safety in patients.

The first study aimed to determine the economic burden of PPOI for patients undergoing elective colorectal surgery. Economic data were audited from a prospective database of patients who underwent surgery at Auckland City Hospital, a large tertiary referral centre utilising an Enhanced Recovery After Surgery protocol, between September 2012 and June 2014. Patients were prospectively diagnosed with PPOI using a standardized definition. The cost of inpatient stay was analysed with regards to patient demographics, operative and post-operative factors. A multivariate analysis was performed to determine the cost of PPOI when accounting for other significant covariates. Economic data were attained from 325 patients, and 88 patients (27%) developed PPOI. The median inpatient cost (NZ Dollars) for patients with PPOI, including complication rates and length of stay, was $27,981 (IQR = $20,198-$42,174) compared to $16,317 (IQR = $10,620-$23,722) for other patients, a 71% increase in cost ($p<0.005$). PPOI increased all associated healthcare costs: medical/nursing care, radiology, medication, laboratory costs and allied health ($p<0.05$). Multivariate analysis showed that PPOI remained a significant financial burden ($p<0.005$) when considering rates of major complications and length of stay. We concluded that PPOI causes a substantial financial burden on the healthcare system, in addition to greater complication rates and

length of stay in these patients. This was the first study to assess the financial impact of PPOI, diagnosed prospectively using a standardized definition.

The second study aimed to validate the I-Score within an external cohort of patients from multiple centres including New Zealand and Spain. The study recruited 404 patients across 4 different sites, and found a rate of PPOI of 24.3%. PPOI therefore remains a signficiant problem even when using a strict and prospective definition within an ERAS setting. The data showed that the I-Score was significantly associated with increased PPOI risk, but was unable to accurately predict patients prior to PPOI development. The most significant risk factor for PPOI development on multivariate analysis was the volume of postoperative iV crystalloid given. This strengthens the argument for adherence to ERAS protocols, and restrictive perioperative fluid administration, for patients undergoing elective colroectal surgery. Additionally, this study highlighted the importance of several new risk factors for PPOI. In particular, patients who had a previous PPOI had a higher risk of developing PPOI again, and patients who received intraoperative NSAID specifically, had a reduced rate of PPOI development. These results may lay the ground work for further prospective risk-prediction studies, working towards an individualised risk-profile for PPOI that could be applied to patients preoperatively.

The third study sought to determine the benefit of NSAIDs in patients undergoing elective colorectal surgery on recovery of post-operative gut function by conducting a systematic review and meta-analysis. The databases MEDLINE, EMBASE, CENTRAL and reference lists were searched with no date or language restrictions. Randomised controlled trials comparing use of NSAIDs to placebo in the perioperative or postoperative period were identified. Included studies reported outcomes relevant to gut function: time to pass flatus or stool and time to tolerate an oral diet. The mean difference in time from surgery until passage of flatus, stool and tolerance of diet were meta-analysed using a random-effects model in RevMan 5.3. This study identified 992 relevant articles. Five randomised control trials on patients undergoing elective colorectal surgery met our inclusion criteria, and were meta-analysed. Compared to placebo NSAIDs significantly improved the time to pass flatus (mean difference -9.44 hours, 95% CI: -17.22, -1.65, I^2=70%, p=0.02), time to pass stool (mean difference -12.09 hours, 95% CI: -17.16, -7.02, I^2=0%, p<0.001) and time to tolerate a diet (mean difference -11.95 hours, 95% CI: -18.66, -5.24, I^2=0%, p<0.001). The conclusion was that NSAIDs significantly improve time to gut recovery after elective colorectal surgery. However, present evidence is not adequate to identify whether selective or non-selective NSAIDs should be recommended. Further high-power studies using selective NSAIDs are required.

The fourth study aimed to determine the benefit of gastrografin as a treatment for patients with PPOI by pooling the results of two recent randomised controlled trials that assessed the efficacy of gastrografin compared to placebo given at time of PPOI diagnosis. Anonymised, individual patient data from patients undergoing elective bowel resection for any indication were included, stoma closure was excluded. The primary outcome was duration of PPOI. Secondary outcomes were time to tolerate an oral diet, passage of flatus/stool, requirement and duration of nasogastric tube, length of postoperative stay and rate of postoperative complications. Individual patient data were pooled for analysis (53 gastrografin, 55 placebo). Gastrografin trended towards a reduction in PPOI duration compared to placebo respectively, median 96 hours (IQR 78 hours) vs. median 120 hours (IQR 84 hours), however this result was non-significant (p=0.11). In addition, no significant difference was detected between the two groups for time to passage of flatus/stool (p=0.36) and overall length of stay (p=0.35). Gastrografin conferred a significantly faster time to tolerate an oral diet compared to placebo (median 84 hours vs. median 107 hours, p=0.04). There was no difference in postoperative complications between the two interventions (p>0.05). The conclusion was that gastrografin did not significantly reduce PPOI duration after abdominal surgery, but did significantly reduce the time to tolerate a solid diet. Further studies are required to clarify the definitive role of gastrografin in PPOI.

Finally, the fifth study assessed whether perioperative prucalopride improves postoperative gut function and reduces the incidence of PPOI following elective colorectal surgery. We conducted a double-blind, placebo-controlled randomized trial of Prucalopride 2mg vs. placebo in adults undergoing elective colorectal surgery for all indications except inflammatory bowel disease. Patients with planned ileostomy formation were excluded. Medication was administered preoperatively and continued for up to 6 days. The primary endpoint was GI-2, time to passage of stool and time to tolerate an oral diet. 148 patients were recruited, 74 per arm. Demographic data were the same between groups. There was no difference in median (IQR) time to GI-2 between prucalopride and placebo: 3.5 days (2,5) vs. 4 days (3,5) respectively, p=0.124. Prucalopride improved median time to passage of stool by 1 day (3 vs. 4 days, p=0.027) but not time to diet (2 vs. 2 days, p=0.669) or median length of stay (4 vs. 4 days, p=0.929). In patients who underwent laparoscopic surgery (n=125; 84.5% of the total patient cohort), prucalopride significantly improved median time to GI-2 (3 days (2, 4) vs. placebo (4 days (3, 5), p=0.012. There was no difference in incidence of PPOI, complications, or adverse events between groups. In conclusion, prucalopride did not improve time to overall recovery of gut function after elective colorectal surgery or impact

PPOI. Prucalopride significantly improved time to GI-2 in patients who underwent laparoscopic surgery with an acceptable safety profile.

Conclusions

In conclusion, PPOI presents a major problem for the healthcare system. Using a modern definition of PPOI, it occurs much more frequently than originally reported: in around 25% of patients following elective colorectal surgery. Patients with PPOI suffer significant morbidity, and both the patient and healthcare system bear this burden. PPOI significantly increases healthcare spending across all aspects of the healthcare system. We found that patients who develop PPOI cost nearly $12,000 more than those who don't, and if 1 in 4 patients gets a PPOI, that translates to a phenomenal amount of spending. The mechanisms of PPOI are complex, and our understanding of them is based on a variety of animal models of ileus and largely from in-vitro studies on human tissue. The most significant aspects of PPOI prevention seem to involve amelioration of the postoperative inflammatory response, which opens the door for future methods to reduce PPOI.

The accurate prediction of PPOI remains an ongoing problem. The data did not support the use of the I-Score as a prediction tool for PPOI in an independent validation cohort. Further research is required, perhaps involving machine learning or artificial intelligence techniques, to better characterise each patient's risk profile for PPOI, thus tailoring interventions to the most at-risk groups to provide the maximum benefit.

There are a number of currently available ways to treat or prevent PPOI. Importantly, aside from ERAS, few of them are truly effective. Certainly, there is no identifiable "most effective" treatment or preventative regimen for PPOI. NSAIDs may help reduce postoperative gut dysmotility. However, there is concern in the international community regarding NSAID use and postoperative complications such as anastomotic leak. While there is no current high-quality evidence to suggest COX-2 selective NSAIDs increase the risk of anastomotic leak, their use is still uncertain. The mechanism by which NSAIDs work clearly plays an integral role in PPOI development, and further studies, or different medications, may prove successful and safe in the future.

The treatment of PPOI is difficult. For clinicians, the adoption of a conservative "drip and suck" approach as well as patience and patient reassurance is the gold standard. Understandably, this approach is difficult for patients. There are few therapeutic agents to treat PPOI. Gastrografin did not reduce the duration of PPOI when given at PPOI onset, but did improve time to tolerate a diet. Despite pooling the raw data of 2 randomised trials, the

overall number in this analysis was still low, only 108 patients. It is possible that the pooled analysis was also underpowered to detect a statistically significant reduction in time to PPOI recovery, as the results found a 24 hour trend towards faster recovery with gastrografin. Importantly, gastrografin was safe and further, larger and multi-centre, studies may still prove that gastrografin has benefit in patients with PPOI.

Prucalopride belongs to a new family of therapeutic agents that act on specific serotonin receptors that play a role in gut motility and possibly in the regulation of gut inflammation. Our multi-centre randomised trial did not detect a significant difference in time to GI-2 or in rates of PPOI between prucalopride and placebo. Of interest, was that patients who had laparoscopic surgery did recover their gut function 24 hours faster than those allocated to placebo. This was a post hoc analysis, and the results should therefore be interpreted with caution. The mechanism by which patients in the laparoscopic cohort would benefit more from prucalopride, compared to those who undergo open surgery, is unclear. A further analysis of the inflammatory marker profile in patients who underwent open or laparoscopic surgery may provide an insight into why there was a difference in response to medication between groups.

This thesis has sought to assess the evidence for several treatment and preventative strategies for PPOI. Overall, NSAIDs provide a mild to moderate in recovery of gut function after colorectal surgery, gastrografin was not an effective treatment for PPOI, and prucalopride may benefit a select subset of patients after surgery but further studies are required. It is possible that PPOI cannot be truly prevented, but its effect can be minimised using a multi-modal approach, such as the ERAS protocol. Furthermore, perhaps future studies should focus on high-risk patients instead of treating all patients on an equal footing. As explained previously, there are a few modifiable risk factors for PPOI, but many are not easily modifiable. A more accurate system to predict high-risk patients is warranted, particularly one that can select patients prior to surgery. PPOI remains one of the most common and difficult to manage complications following colorectal surgery, and it will continue to do so until further research finds a way to minimise or prevent it.

Future Directions of Research

The international scientific and medical community understand the burden of PPOI. There are a few ways that future studies could improve our understanding of PPOI pathophysiology and use this to develop treatment and preventative strategies for PPOI. The following section will discuss how future, and current, studies are tackling the problem of PPOI.

Ileus and the gut microbiome

There is growing interest in the role that the gut microbiome plays in influencing patient postoperative complications. Bacterial translocation may potentiate gut inflammation and mast cell degranulation in animal models of ileus. Reducing the volume of intestinal microbiota may be of benefit in reducing the postoperative inflammatory response of the gut, and may reduce PPOI. [8] Recently, attention has turned to mechanical bowel prep (MBP) using oral antibiotics in addition, to reduce patient postoperative morbidity. The role of oral antibiotic prep in colorectal surgery seems to favour reduced surgical site infection and anastomotic leak, but its role in prevention of PPOI is unclear and has not been widely assessed.[397] Retrospective data from the USA suggest that MBP with oral antibiotics, but not MBP on its own, reduced the rate of anastomotic leak (OR = 0.57, 95% CI: 0.35–0.94), surgical site infection (OR = 0.40, 95% CI: 0.31–0.53), and PPOI (OR = 0.71, 95% CI: 0.56–0.90).[108] The rate of PPOI (defined using clinical coding) was 9.2% for patients with MBP and oral antibiotics, 12.3% with MBP alone, and 15.1% with no prep.[108] Another retrospective series in the USA showed that MBP with oral antibiotics reduced PPOI rates to 9.4%, compared to MBP alone (12.1%) or no MBP (14.6%). [398]

Recently, one study collected stool samples from 60 patients undergoing colorectal surgery, and found higher concentrations of Escherichia-Shigella and Bacteroides, and higher lipopolysaccharide levels, in the faeces of patients who developed PPOI.[399] Their conclusion was that modification of the preoperative gut microbiome, in patients with at-risk bacterial profiles, may help reduce postoperative gut inflammation and reduce PPOI. Similarly, a study of 101 patients undergoing elective colorectal resection at the Mayo clinic found significantly higher levels of Bacteroides, Ruminococcus and Parabacteroides on rectal swabs taken preoperatively and on postoperative day 2 in patients who developed PPOI.[400] All patients in this study received MBP with oral antibiotics, which is of particular significance here, as it suggests that MBP with oral antibiotics did not actually change the patient's bacterial phenotype.[400] Perhaps MBP with oral antibiotics simply reduces the

bacteria load in the colon. Our understanding of the role the intestinal microbiome plays in relation to postoperative outcomes is in its infancy. Studies suggest that the intestinal microbiome impacts long term oncological outcomes after colorectal cancer surgery,[401] and plays a role in development of infectious complications, such as anastomotic leak. It is possible that we cannot easily modify a patients microbiome preoperatively, and that an individual's gut microbiome serves more as a predictive tool for postoperative morbidity.

While research into the intestinal microbiome is of significant interest, the evidence is largely based on observational data. The mechanism by which MBP with oral antibiotics may be of benefit is unclear, and the implications of altering patients gut microbiome are not well understood. Further studies are required before clinicians can begin to understand the role the gut microbiome plays in postoperative outcomes, and whether it can be modified for patient benefit.

Vagus nerve and posterior tibial nerve stimulation

As discussed previously, the parasympathetic nervous system, in particularly the vagus nerve, plays an integral role in gut homeostasis and immune function. The vagus is essential for gut motility and is thought to be the main driver of PPOI resolution. The anti-inflammatory effect of the parasympathetic nervous system, in paricular the vagus, has been termed the cholingeric anti-inflammatory pathway. Stimulation alpha-7 nicotinic acetylcholine receptors (a7AChR) on intestinal resident macrophages, by vagal efferents, inactivates them and acts to reduce gut inflammation.[402] Animal studies show that vagus nerve stimulation may ameliorate the effects of PPOI.[403] Lipopolysaccharide (LPS) induced sepsis leads to increased TNF-α production in mice, and this response is significantly reduced in mice with cervical vagus nerve stimulation.[403] Intestinal manipulation reduces gastrointestinal motility in mice, and promotes macrophage infiltration within the muscularis, and this effect is ameliorated by cervical and abdominal vagus nerve stimulation.[403] Transcutaneous auricular vagus nerve stimulation in mice improves intestinal motility and reduces levels of IL-6, and TNF-α after intestinal manipulation.[404] This effect is negated by vagotomy.[404]

A variety of devices have been designed to stimulate the vagus nerve in humans, either in its auricular location or cervical location, which avoids the need for direct vagus stimulation by surgical intervention.[402] Stakenborg assessed the impact of posterior vagus nerve stimulation in 18 patients undergoing hemicolectomy for colon cancer.[403] They found reduced levels of IL6 and IL8 on postoperative day 1 with vagus nerve stimulation done for 2 minutes at the beginning of surgery and for 2 minutes at the end of surgery.[403] There were

no reported side effect or complications noted due to the need for additional dissection to identify the vagus nerve, but postoperative clinical recovery was not reported. Chapman *et al* (2021) recently conducted an RCT of transcutaneous cervical vagus nerve stimulation in 40 patients undergoing surgery for colorectal cancer.[405] Patients underwent 2 minutes of self-administered bilateral cervical vagus nerve stimulation both 5 days preoperatively and 5 days postoperatively. Compliance with the device was good (78.9-90%).[405] While the study did not report a statistical analysis of outcomes, it suggests that cervical vagus nerve stimulation is feasible and can be administered by the patient for prolonged periods prior to surgery, which is likely the optimal time to initiate preventative measures for POI.

The vagus nerve plays a clear role in stimulating intestinal activity and reducing intestinal inflammation in response to surgery, however, vagal innervation reduces in density along the intestinal tract and does not innervate the distal colon. Pelvic splanchnic nerves carry parasympathetic activity to the distal colon and sacral nerve activity can be stimulated indirectly by stimulating the posterior tibial nerve.[406] Tibial nerve stimulation (TNS), therefore, has been used as a treatment for urinary and faecal incontinence, and may be a less invasive treatment for incontience, compared to sacral neuromodulation.[407] Posterior tibial nerve stimulation uses either a transcutaneous or percutanous approach.[407] In a pilot study by Venara *et al* (2018), patients undergoing colectomy or high anterior resection, using a postoperative ERAS protocol, were randomly assigned to TENS (15 patients) to the posterior tibial nerve or placebo (19 patients).[408] Their intention to treat analysis found a non-signficiant trend towards faster time to GI-2, reduced PPOI and reduced incidence in NGT insertion for those receiving posterior tibial nerve stimulation.[408] The study found no difference in levels of COX-2, IL-6 or mPGES1 expressed in the surgical specimen between groups.[408]

In a large single centre double blind randomised control trial by Martelluci *et al* (2021), 170 patients undergoing right hemicolectomy and 170 patient undergoing left hemicolectomy were randomly allocated to tibial nerve stimulation or sham electrical stimulation.[409] Only elective cases were included and open procedures, or procedures with formation of a stoma, were excluded.[409] TNS was commenced 6 hours postoperatively, and continued for 72 hours, at a level of stimulation below sensory threshold. The primary end point was first passage of stool.[409] TNS was found to be safe, and conferred a faster time to first flatus in the right hemicolectomy group (by 9 hours) but not in the left hemicolectomy group.[409] No difference in time to passage of stool or length of postoperative stay was noted between groups.[409] In a subgroup analysis of patients who were unable to tolerate an early diet, patients who underwent right hemicolectomy treated with TNS passed stool on average 24

hours faster than the sham stimulation group.[409] Unfortunately, this study did not use PPOI as a primary endpoint and did not assess time to tolerance of diet, which limits it's impact on the current literature. Importantly, TNS was only started in the postoperative period, which means that any potential anti-inflammatory effect of the treatment would have been missed. However, it highlights the importance of targetted interventions in at-risk populations, and further assessment of TNS in patients prone to PPOI may be warranted. Future improvements to the I-Score model, for example, may provide additional benefit by selectiving those at high or low risk for PPOI development either preoperatively, or in the early postoeprative period. Further studies of TNS in patients underoging laparoscopic surgery with pre-treatment of TNS 3 days prior to surgery are planned, using comprehensive outcomes such as GI-2 and plasma concentrations of relevant inflammatory markers (IL-6, IL-1b).[410] We await their results before considering vagus nerve stimulation of TNS as impactful interventions to prevent PPOI.

An improved understanding of PPOI pathophysiology

One key issue with our understanding of ileus development and PPOI is that most of the evidence for how ileus develops is based on animal models. These animal studies are conducted on carefully selected animals, and intestinal manipulation carried out in pre-specified ways. This is not the reality in the operating room, where each patient's operation is difference than the next for a multitude of reasons. Patient comorbidity plays a major role in PPOI development, but animal studies are not able to account for this. Naturally, it is not possible to perform the level of scientific study on humans in vivo. Fortunately, there are other ways to improve our understanding of the in vivo effects of PPOI, by studying the intestinal motility patterns of patients in the postoperative period. Recently, Wells *et al* (2019) have developed an ambulatory system to collect high-resolution manometric data on colonic motility, that could be used to better define postoperative colonic motility over longer periods of time.[411] In addition, skin-surface electrical recordings, or "electrocolonography", has been piloted in healthy patients as a means to detect cyclical colonic motor activity.[412] Combined, these 2 novel methods to detect colonic motor patterns may provide invaluable information on how the colon recovers after surgery, and may help detect patients at risk of PPOI or new targets for PPOI prevention. An accurate model of how the gut recovers following abdominal surgery has 2 key implications. Firstly, it may allow researchers to develop computer-based models of gut motility, which would allow testing of specific therapeutic strategies electronically, "in silico". Secondly, it may allow the real-time assessment of new medications that improve gut motility, leading to development and

testing of new interventions for PPOI. We await further studies, and importantly, we await further research into the role of gastric and small bowel motility relates to PPOI.

Appendix 1.
Written permission to use Figure 1-1

I hereby give permission for Tony Milne to include the graphic figure 1-1 as an acknowledged piece in his thesis. The figure was originally developed by Ryash Vather as part of his PhD thesis, and published in:

Vather, R., O'Grady, G., Bissett, I. P., & Dinning, P. G. (2014). Postoperative ileus: mechanisms and future directions for research. *Clinical & Experimental Pharmacology & Physiology, 41*(5), 358-370. doi:10.1111/1440-1681.12220

The figure was later updated and published by Cameron Wells:

Wells, C. I., Milne, T. G. E., Seo, S. H. B., Chapman, S. J., Vather, R., Bissett, I. P., & O'Grady, G. (2022). Post-operative ileus: definitions, mechanisms, and controversies. *ANZ J Surg, 92*(1-2), 62-68. doi:10.1111/ans.17297

Dr Ryash Vather

Dr Cameron Wells

Appendix 2.

SYSTEMATIC REVIEW SEARCH STRATEGY (OVID MEDLINE)

1. exp Ileus/
2. exp Intestinal Obstruction/
3. ileus.mp.
4. pseudoobstruct*.mp.
5. pseudo-obstruct*.mp.
6. exp Gastrointestinal Motility/
7. exp Gastrointestinal Transit/
8. exp Peristalsis/
9. ileus$.tw.
10. peristalsis.tw.
11. (gastrointestinal adj3 (motilit* or transit*)).tw.
12. or/1-11
13. exp anti-inflammatory agents/ or exp anti-inflammatory agents, non-steroidal/
14. antiinflam*.mp.
15. anti-inflam*.mp.
16. antiinflam*.tw.
17. exp Postoperative Complications/
18. postoperative.mp.
19. post-operative.mp.
20. post operative.tw.
21. or/17-20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. drug therapy.fs.
27. randomly.ab.
28. trial.ab.
29. groups.ab.
30. or/22-29
31. (animals not (humans and animals)).sh.
32. 30 not 31
33. Celecoxib/
34. Diclofenac/
35. Flurbiprofen/
36. Ibuprofen/
37. Indomethacin/
38. Ketoprofen/
39. Ketorolac/
40. Cyclooxygenase 2 Inhibitors/ or Cyclooxygenase Inhibitors/ or Piroxicam/ or meloxicam.mp.
41. Naproxen/
42. parecoxib.mp.
43. rofecoxib.mp.
44. valdecoxib.mp.
45. Diet/ or diet.mp.
46. flatus.mp. or Flatulence/
47. stool.mp.

48. bowel motion.mp. or Defecation/
49. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 45 or 46 or 47 or 48
50. 17 or 18 or 19 or 20
51. nsaid*.mp.
52. 13 or 14 or 15 or 16 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 51
53. 49 and 50 and 52
54. 32 and 53

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