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Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)
Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

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ABSTRACT

Background
Postoperative adynamic bowel atony interferes with recovery following abdominal surgery. Prokinetic pharmacologic drugs are widely used to accelerate postoperative recovery.

Objectives
To evaluate the benefits and harms of systemic acting prokinetic drugs to treat postoperative adynamic ileus in patients undergoing abdominal surgery.

Search strategy
Trials were identified by computerised searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and the Cochrane Colorectal Cancer Group specialised register. The reference lists of included trials and review articles were tracked and authors contacted.

Selection criteria
Randomised controlled parallel-group trials (RCT) comparing the effect of systemically acting prokinetic drugs against placebo or no intervention.

Data collection and analysis
Four reviewers independently extracted the data and assessed trial quality. Trial authors were contacted for additional information if needed.
Main results

Thirty-nine RCTs met the inclusion criteria contributing a total of 4615 participants. Most trials enrolled a small number of patients and showed moderate to poor (reporting of) methodological quality, in particular regarding allocation concealment and intention-to-treat analysis. Fifteen systemic acting prokinetic drugs were investigated and ten comparisons could be summarized. Six RCTs support the effect of Alvimopan, a novel peripheral mu receptor antagonist. However, the trials do not meet reporting guidelines and the drug is still in an investigational stage. Erythromycin showed homogenous and consistent absence of effect across all included trials and outcomes. The evidence is insufficient to recommend the use of cholecystokinin-like drugs, cisapride, dopamine-antagonists, propranolol or vasopressin. Effects are either inconsistent across outcomes, or trials are too small and often of poor methodological quality. Cisapride has been withdrawn from the market due to adverse cardiac events in many countries. Intravenous lidocaine and neostigmine might show a potential effect, but more evidence on clinically relevant outcomes is needed. Heterogeneity among included trials was seen in 10 comparisons. No major adverse drug effects were evident.

Authors’ conclusions

Alvimopan may prove to be beneficial but proper judgement needs adherence to reporting standards. Further trials are needed on intravenous lidocaine and neostigmine. The remaining drugs cannot be recommended due to lack of evidence or absence of effect.
Most prokinetic drugs routinely used to support bowel recovery after major abdominal surgery are not supported by current research evidence

Postoperative ileus (POI) refers to the delayed recovery of bowel function following abdominal surgery. POI may cause major patient discomfort and delayed recovery. Several drugs are commonly used to treat POI but it is unclear which drugs are supported by patient-oriented research.

Many of the 39 studies assessed in this review enrolled only a small number of patients and date back to before 1990. The novel drug alvimopan shortened bowel recovery, but many studies failed to report methodology according to current guidelines. Erythromycin, cholecystokinin, cisapride, dopamine-antagonists, propranolol or vasopressin are not supported due to lack of evidence or absence of effect. Intravenous lidocaine and neostigmine might show to be beneficial, but more evidence is needed.

BACKGROUND

Delayed return of normal gastrointestinal function due to 'postoperative ileus' (POI) following major abdominal surgery is the main cause for prolonged convalescence leading to extended hospital stay and additional health care costs. In 2002 for instance, total hospital costs attributable to POI has been estimated to be as large as 1.46 billion dollars in the United States in 2002 (Goldstein 2007).

The term 'postoperative ileus' refers to the atony of the bowel which frequently follows abdominal surgery. Delayed recovery of normal peristalsis causes variable clinical symptoms ranging from minor complaints to significant discomfort with painful abdominal distension, cramps, nausea and vomiting. Furthermore, delay in oral food intake affects the immune defence with an increased risk of localised or generalised infections (Moore 1992, Moore 1989).

The pathogenesis of postoperative ileus is multifactorial and not yet completely understood. Activation of the sympathetic nervous system by manipulation of the gut seems to play a major role (Dubois 1974, Resnick 1997(1), Resnick 1997(2)). Release of inflammatory mediators as well as the immigration of leucocytes into the intestinal wall has been shown to correlate with the intestinal trauma and paralysis of intestinal smooth muscles tissue (Kalf 1998, Kalf 1999). Stimulation of opioid receptors by exogenous and endogenous opioids significantly accounts for a delay in postoperative recovery of colonic motility (Frantzides 1992) and prolonged postoperative ileus (Cali 2000). Moreover, peri-operative fluid excess can impair bowel motility due to oedema of the intestinal wall (Lobo 2002).

Impaired bowel motility is most extensive after major abdominal procedures such as colonic segmental resections (Kehlet 2001). Other procedures without bowel resection like cystectomy (Chang 2002), nephrectomy (Kerbl 1994), transabdominal hysterectomy (Wattwil 1989) or abdominal aortic aneurysm surgery (Buckley 2000) may also cause postoperative ileus of on average more than three days. Despite the widespread use of epidural anaesthetics and laparoscopic procedures, POI is still a problem in daily postoperative care (Mann 2000). Therefore, prokinetic drugs are widely administered in surgical wards and Intensive Care Units (ICU’s).

Comprehensive systematic reviews in the field of POI exist for epidural local anaesthetics (Jorgensen 2000), homeopathy (Barnes 1997) or selective opioid receptor antagonists (Tan 2007) but not for the widely used and systematically applied prokinetic drugs.

The aim of this systematic review was therefore to assess the efficacy of systemic prokinetic pharmacologic treatment to shorten the duration of POI and to assess the effectiveness to reduce length of hospital stay in patients undergoing major abdominal surgery.

OBJECTIVES

To evaluate the benefits and harms of different systemically acting prokinetic drugs in the treatment of POI, in patients undergoing abdominal surgery with or without peri- or postoperative epidural anaesthesia or analgesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised and quasi randomised controlled parallel-group trials, published or unpublished, which compared any systemically acting prokinetic drug to placebo or no intervention. Trials with multiple comparison arms were included if subjects were randomly allocated to each treatment arm separately and if the distinction between each treatment arm and the control arm was unambiguous. Unpublished trials were considered when we were able to obtain full-text manuscripts from the author(s). We considered subjective outcomes as time to first flatus only if a trial...
was carried out in a double blind manner (i.e. patients and outcome assessors were blinded to treatment allocation).

**Types of participants**

**Inclusion criteria:**
Adult patients undergoing open or laparoscopic abdominal surgery with or without peri- and postoperative epidural analgesia. Exclusion criteria:
- Trials with patients on postoperative obstructive or mechanical ileus
- Trials with patients on caesarean section or sole inguinal hernia repair.
- Trials with paediatric patients (i.e. age less than 16 years).
- Trials with patients undergoing total or subtotal colectomy or enterostomy *.
- Trials with an observation period of 24 hours or less.

* Assessment of time to passage of first stool is not reliable and POI affects the large bowel in the first place (Clin. Consensus 2006)

**Types of interventions**

We considered systemically acting prokinetic drugs of any type, duration or dose compared to placebo or no intervention. Combinations of prokinetic drugs against placebo or no intervention were considered as well. Trials where treatment of POI was indirect via a reduction of the consumption opioid-based analgesics were not considered for this review. Furthermore, we did not consider drugs with a local mechanism of action (e.g. enemas or local anaesthetic treatment); interventions which primarily alter the perioperative anabolic or catabolic state of the patient (e.g. carbohydrate supplementation or early enteral nutrition); herbal medicine treatments or gum chewing.

The most recent development concerns the drug alvimopan, a peripheral opioid mu-receptor antagonist. Due to its greater affinity for the mu- than the kappa- or sigma-opioid receptors, alvimopan acts as an antagonist of the inhibitory effects of endogenous and exogenous opioids. Cerulein/cheruletide and cholecystokinin were resumed under 'cholecystokinin-like acting drugs' because of their related pharmacodynamic action. Cholecystokinin (CCK) seems to be important in the regulation of gastrointestinal motility (Herbert 2002). The synthetic decapeptide cheruletide from cerulein is suggested to act similar to CCK. Cisapride is a 5 HT4- agonist that facilitates acetylcholine release from the intrinsic plexus and therefore increases gut motility (Tontini 1999). Dihydroergotamine is a alpha-adrenergic blocking agent that increases postoperative bowel motility (Thorup 1983). Metoclopramide and bromopride both act as cholinergic agonists and dopamine-antagonists (Luckey 2003). The macrolide antibiotic erythromycin has been suggested to act as a motilin agonist and directly stimulates enteral smooth muscle by inducing the migrating motor complex (MMC) (Weber 1993, Peeters 1993). The exact mechanism of lidocaine as prokinetic drug is still unknown. Lidocaine may decrease postoperative pain or act directly by inhibition of sympathetic nerve stimulation (Liu 1995, Carpenter 1996, Groudine 1994). Neostigmine acts as a reversible acetylcholinesterase inhibitor which results in an activation of colonic motility (Luckey 2003). The beta-blocking agent propranolol is suggested to act as inhibitor of sympathoadrenergic neurones in the intestinal wall. The drugs were classified as follows:

- Cholinergic agonists: bethanechol, neostigmine
- Benzamides: cisapride*, metoclopramide, bromopride
- Dopamine antagonists: domperidone*
- Peptide hormones: cholecystokinin, ceruletide, vasopressin
- Adrenergic antagonists: propranolol
- Macrolide antibiotic: erythromycin
- Ergotamine derivates: dihydroergotamine
- Systemic application of local anaesthetics
- Prostaglandins
- Vitamines: pantothenic acid, dexpanthenol
- Selective gastrointestinal opioid antagonists

* Withdrawn from the market in the United States (FDA 2006) and most European countries

**Types of outcome measures**

We considered the following outcome measures according to decreasing order of clinical relevance.

1. Composite endpoint of maximum time to either tolerance of solid food or passage of first stool* (GI-2)
2. Composite endpoint of maximum time to either tolerance of solid food or the latest of time to first flatus or time to passage of first stool* (GI-3)
3. Time to passage of first stool*
4. Time to tolerance of regular diet
5. Length of hospital stay
6. Time to passage of first flatus. Trials using as outcome time to a combination of passage of first flatus or stool were treated as time to passage of first flatus.
7. Adverse drug effects
   * if not indicated otherwise, the term bowel movement refers to the passage of stool.

**Search methods for identification of studies**

We used the Cochrane Colorectal Cancer Group search strategy as outlined in detail for each searched database below. The following bibliographic databases were searched to identify relevant trials:

- The Cochrane Central Register of Controlled Trials (CENTRAL), from the Cochrane Library 2007 issue 2. MEDLINE from 1966 to June, 18, 2007 and EMBASE from 1980 to June, 18, 2007. The Cochrane Colorectal Cancer Group specialised register SR-COLOCA and SCISEARCH.
Searches were carried out using medical subject headings (MeSH) and free text words in combination. The highly sensitive search strategy for identifying reports of randomised controlled trials as contained in the Cochrane Reviewer’s Handbook (Dickersin 1994, Robinson 2002) was used. No language restriction was applied.

The reference lists of relevant trials and review articles in the field were reviewed. Additionally, authors of relevant articles and known international experts in the field of POI were contacted to obtain information on any past, ongoing, or planned future trials. Authors of abstracts were asked to provide full reports.

The following search strategies were used for each database:

**EMBASE**

#23 ((laparo*) or (digestive surgery) or (abdom* surgery) or (aortic aneurysm) or (aortic surgery) or (urologic surgical procedures) or (colorectal surgery) or (gynecologic surgical procedures) or (digestive system surgical procedures) or (obsteric surgical procedures) or (post-operative) or (postoperative) or (postoperative complications) or (postoperative care) or (postoperative period)) and ((colon*) or (gut) or (intestin*) or (bowel)) and (paralysis) or (gastrointestinal motility) or (pareisis) or (ileus) or (aton*) or (peristalsis) or (motility) or (adynam*) or (paralytic) and (intestines) or (alvimopan) or (purgative*) or (laxative*) or (dexpanthenol) or (ceruletide) or (procinetic) or (prokinetic) or (selective gastrointestinal opioid antagonists) or (cathartics) or (panthothenic acid) or (prostaglandins) or (anaesthetics) or (dihydroergotamine) or (erythromycin) or (adrenergic antagonists) or (postoperative complications) or (peristalsis) or (defecation) or (intestinal drug therapy) or (digestive system) or (gastrointestinal motility) or (gastrointestinal agents) or (therapeutics) or (drug evaluation) or (drug therapy) or (metoclopramide) or (cisapride) or (benzamides) or (neostigmine) or (cholinergic agents) and (#12 not #16) and (PY:EMBV = 2006-2007) 71

**MEDLINE**

#21 (laparo*) or (digestive surgery) or (abdom* surgery) or (aortic aneurysm) or (aortic surgery) or (urologic surgical procedures) or (colorectal surgery) or (gynecologic surgical procedures) or (digestive system surgical procedures) or (obsteric surgical procedures) or (post-operative) or (postoperative) or (postoperative complications) or (postoperative care) or (postoperative period) 348023

#20 (colon*) or (gut) or (intestin*) or (bowel) 468052

#19 (paralysis) or (gastrointestinal motility) or (pareisis) or (ileus) or (aton*) or (peristalsis) or (motility) or (adynam*) or (paralytic) and (intestines) or (alvimopan) or (purgative*) or (laxative*) or (dexpanthenol) or (ceruletide) or (procinetic) or (prokinetic) or (selective gastrointestinal opioid antagonists) or (cathartics) or (panthothenic acid) or (prostaglandins) or (anaesthetics) or (dihydroergotamine) or (erythromycin) or (adrenergic antagonists) or (postoperative complications) or (peristalsis) or (defecation) or (intestinal drug therapy) or (digestive system) or (gastrointestinal motility) or (gastrointestinal agents) or (therapeutics) or (drug evaluation) or (drug therapy) or (metoclopramide) or (cisapride) or (benzamides) or (neostigmine) or (cholinergic agents) 1698255

Searches and results below from saved search history from EMBASE SS for RCT/CCT are listed below

#17 #12 not #16 1665210

#16 #14 not #15 2675100

#15 #13 and #14 476674

#14 (ANIMAL or NONHUMAN) in DER 3151774

#13 HUMAN in DER 5823446

#12 #9 or #10 or #11 2665088

#11 (SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*) in TLAB 86449

#10 (RANDOM* or CROSSOVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TLAB 471851

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 2452728

#8 “SINGLE-BLIND-PROCEDURE” or all subheadings 6660

#7 “DOUBLE-BLIND-PROCEDURE” or all subheadings 64218

#6 “PHASE-4-CLINICAL-TRIAL” or all subheadings 596

#5 “PHASE-3-CLINICAL-TRIAL” or all subheadings 7423

#4 “MULTICENTER-STUDY” or all subheadings 38817

#3 “CONTROLLED-STUDY” or all subheadings 242081

#2 “RANDOMIZATION” or all subheadings 22563

#1 “RANDOMIZED-CONTROLLED-TRIAL” or all subheadings 19188

Searches and results from saved search history from Medline for RCT/CCT are listed below

#42 #36 and #37 and #38 and #39 and #40 and (PY:MEDS = 2006-2007) 58

Searches and results below from saved search history MKO 079 Medline 11.08.06

#41 #36 and #37 and #38 and #39 and #40 738

#40 (laparo*) or (digestive surgery) or (abdom* surgery) or (aortic aneurysm) or (aortic surgery) or (urologic surgical procedures) or (colorectal surgery) or (gynecologic surgical procedures) or (digestive system surgical procedures) or (obsteric surgical procedures) or (post-operative) or (postoperative) or (postoperative complications) or (postoperative care) or (postoperative period) 348023
Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)

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Data collection and analysis

Study selection
Two reviewers (UT and MKO) scanned the titles and the abstract sections of all citations retrieved by the search procedure. Full text articles were obtained of all titles and abstracts suggestive of being eligible for inclusion if one reviewer considered the citation as potentially relevant. Both reviewers independently assessed the full text reports against the inclusion criteria. Discrepancies for inclusion of trials were resolved by consensus following consultation of a third reviewer.

Data collection
Details on the number of retrieved references, the number of obtained full-text reports and the number of included and excluded references are listed below.
cluded articles were recorded and reported (‘Characteristics of included/excluded studies’ and Figure 1) The lists of included and excluded studies are provided in ‘Table of included studies’ and ‘Table of excluded studies’, respectively. All data were managed and stored in Review Manager software version 4.2; the reason for excluding trials from this review is stated in ‘Table of excluded studies’.
Figure 1. Flow diagram.

1189 citations identified and screened

1114 citations excluded
- Duplicates
- Not randomized
- Review article
- Different topic

75 abstracts retrieved for more detailed evaluation

34 excluded
- Not randomized: 11
- Duplicate publication: 2
- Head-to-head comparison: 5
- Post-hoc analysis: 3
- Inadequate follow up: 1
- Different patients / endpoint: 12

41 RCTs selected for detailed full text review

2 RCT excluded
- Two trials excluded for inadequate follow up.

39 RCTs included in meta-analysis
Data extraction
Four reviewers (UT, LB, RK, MKO) independently performed appraisal of the methodological quality and extracted the data of all included trials in duplicate. Differences in the assessment of quality or data extraction between two reviewers were resolved by consensus. If necessary and possible, additional information was sought from the authors of the trials. Prespecified data extraction forms were used to record all data.

Quality assessment (NHS CRD 2001)
We rated the quality of included trials using the Cochrane approach to assess the quality of eligible trials. The quality items were as follows: random sequence generation, concealment of random allocation, blinding of patients and/or care givers and/or outcome assessors and intention-to-treat analysis. Description was rated as follows: A: adequate, B: unclear, C: clearly inadequate, D: not used. We described trial quality as good if all above-mentioned criteria were adequately reported. If at least two but not all criteria were reported, we assigned ‘moderate’ quality if and less than two were reported we used the attribute ‘poor’. Beyond these criteria, we recorded whether information on the distribution of baseline characteristics was reported according to treatment allocation.

Statistical analysis
The endpoint of primary interest in the evaluation of post-operative ileus was time from treatment initiation until resolution of ileus (i.e. signs of restoration of intestinal motility according to outcome measures 1 to 4 and 6). The measurement unit to summarise and compare treatment effects was therefore time measured in hours or days. We assumed that the resolution times follow a log-normal normal distribution due to the generally short duration until resolution of POI and due to accumulation of resolution times in the early post-operative period. We further assumed that treatment effects for postoperative ileus are multiplicative for the time to resolution of ileus (i.e. subjects with short and subjects with long-lasting ileus were expected to have the same relative benefit). The accelerated failure time (AFT) model allows modelling a multiplicative treatment effect and the acceleration factor equals the ratio of the means as well as the ratio of the medians (Keene 2002) of the intervention group relative to the control group. Therefore we used for the summary effect the ratio of means or the ratio of medians - whatever available - of the intervention and control group, and aggregated the natural logarithm-transformed ratios across trials using the generalized inverse variance method. Similarly, if hazard ratios (HR) were used as in more recent trials of selective opioid receptor antagonists, we aggregated the natural logarithm-transformed HRs using the same method.

If the median and interquartile range was reported, we estimated the standard deviation of the log data per treatment arm with the following formula: \((\log(\text{quartile3}) - \log(\text{quartile1}))/1.349\). We calculated the standard error of the log ratio of the medians by taking the square root of the sum of each standard deviation divided by the number of subjects randomized to the treatment and the control arm, respectively. If the mean and standard deviation was reported, we estimated the standard error of the logarithm of the ratio of the means using the delta method (Friedrich 2005).

If trials reported response rates at different time points, response times were extracted per subject and treatment arm and the log ratio of the medians with the corresponding standard error were estimated using an accelerated failure time model as mentioned above. If standard deviations were not reported or only the range was given, we imputed standard deviations with the method by Furukawa et al (Furukawa 2006).

Statistical heterogeneity of summary estimates was assessed both by calculating a test of heterogeneity (standard chi-squared test) and by using I2 statistic. I2 is an estimate of the amount of variance due to between-trial heterogeneity rather than chance (Higgins 2002, Higgins 2003). It is based on the traditional measure of variance, the Cochran Q statistic (Cochrane 1954). Substantial heterogeneity exists when I2 exceeds 50%. For each hypothesis, we tested the difference in estimates of treatment effect between the two groups using a Z-test (Deeks 2001) and we considered a p-value of 0.05 or less to be statistically significant. All pooled effect estimates are presented with 95% confidence intervals (CI). Funnel plot analysis was not considered since none of the drug categories contained more than five trials. In the case of significant heterogeneity, we used random effect models and compare these to fixed effect models to test the robustness of the findings. Two possible reasons for heterogeneity were pre-specified: (i) Difference of responses according to difference in the quality of the trials; (ii) difference of responses according to clinical heterogeneity (e.g. bowel resection, applied drug doses). The limited number of studies per drug precluded to explore between-trial heterogeneity according to these criteria.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

‘Table of included studies’
A total of 1189 titles and abstracts were retrieved through searching databases and reference tracking. We obtained the full text of 75 articles whereof 34 trials were ineligible. Hence the final trial sample consisted of 39 randomized trials meeting the inclusion criteria for this review (see also Figure 1). The details of included trials are reported in ‘Characteristics of included studies’. The reasons for excluding trials are stated in ‘Characteristics of excluded studies’.

Study design
All trials compared active treatment against placebo or no intervention in a parallel-group randomized manner. Thirty-four trials were described as double blind, one trial was declared as single blinded and five trials did not report on blinding.
Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  

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Participants  
A total of 4615 participants with major abdominal surgery were recruited across all trials. The surgical procedures included major abdominal surgery, major abdominal-vascular surgery, and major abdominal urological and gynaecological surgery (‘Characteristics of included studies’). Reporting of inclusion and exclusion criteria was similar across trials. Patients with advanced diseases, e.g. chronic inflammatory bowel disease, cardiac impairment, renal, pulmonary or liver diseases or insulin dependent diabetes were excluded in twenty-one trials.

Interventions and co-interventions  
Of the 39 included trials, six trials compared opioid receptor antagonists (alvimopan) to placebo (Delaney 2005; Herzog 2006; Ludwig 2006; Taguchi 2001; Viscusi 2006; Wolff 2004), four trials compared cholecystokinin (CCK)-like acting drugs to placebo or no treatment (Alvarez 1979, Ferreira 1980, Frisell 1985, Sadek 1988), seven trials compared cisapride to placebo (Clevers 1991, Hallerbäck 1991, Tollesson 1991(2), Brown 1999, Benson 1994, Roberts 1995, Von Ritter 1987), two trials compared dihydroergotamine to no treatment (Altaparmakov 1984, Thorup 1983), four trials compared dopamine-antagonists (metoclopramide and bromopride) to placebo or no treatment (Cheape 1991, Conte 1983, Jepsen 1986, Tollesson 1991(1)), four trials compared erythromycin to placebo (Bonacini 1993, Lightfoot 2007, Smith 2000, Wilkinson 2002), three trials compared systemically applied lidocaine to placebo (Groudine 1998, Kuo 2006, Rimbäck 1990), two trials compared neostigmine to placebo (Hallerbäck 1987(1), Orlando 1994), two trials compared propranolol to placebo or no treatment (Ferraz 2001, Hallerbäck 1987(2)) and two trials compared the combined administration of propranolol and neostigmine to placebo (Garcia 1993, Hallerbäck 1987(1)). Twenty-two trials initiated the test drug on the day of surgery and sixteen trials initiated the drug regimen on the first postoperative day (POD). Two trials did not specify the time point of drug treatment initiation (Clevers 1991, Woods 1993). Duration of drug treatment varied between a single dose regimen (Ferreira 1980, Sadek 1988) to permanent application until hospital discharge (Brown 1999; Ludwig 2006; Viscusi 2006; Wolff 2004). One trial did not specify the duration of drug administration (Hallerbäck 1987(2)). Follow-up durations ranged from 33 hours (Alvarez 1979) until hospital discharge or 30 days post surgery (Herzog 2006). Physicians were allowed to administer co-medication to treat POI in five trials (Delaney 2005; Hallerbäck 1987(2); Herzog 2006; Sadek 1988, Smith 2000). Type of anaesthesia and analgesia used was properly reported in twenty-four trials. In twelve trials anesthetic techniques and use of analgesia remains unclear. One trial did not allow the administration of morphine, morphine-like, anticholinesterase or sympatholytic drugs during the course of the study (Manani 1982). In seven trials analgesic treatment consisted of opioid-based patient controlled analgesia (PCA) (Delaney 2005; Herzog 2006; Ludwig 2006; Smith 2000; Taguchi 2001; Viscusi 2006; Wolff 2004). Intra- and postoperative epidural analgesia reduces GI recovery times (Jorgensen 2000). Six trials reported to allow for intra- or postoperative epidural analgesia with opioids (Clevers 1991, Jepsen 1986, Kuo 2006, Lightfoot 2007, Wilkinson 2002, Woods 1993) and one trial with local anaesthetics (Lightfoot 2007). The remaining trials use intramuscular or subcutaneous analgesic application or did not report further details.

Outcomes  
In addition to the outcomes of this review, various additional outcomes were measured, e.g. electromyographic analysis with either continuous manometric recording or radio opaque marker to study transit times. (Altaparmakov 1984, Benson 1994, Rimbäck 1990, Roberts 1995, Tollesson 1991(1), Tollesson 1991(2)) (‘Characteristics of included studies’). Wolff et al (Wolff 2004) used GI-2 and GI-3 as novel outcomes of POI recovery for the first time. GI-3 was defined as the later of either time to tolerance of solid food or time to passage of the first of flatus or stool. Because of the subjectiveness and large variability of the component flatus (Bungard 1999), the GI-2 composite end point was introduced. GI-2 was defined as the later of time to either tolerance of solid food or first stool. Four trials reported GI-2 and GI-3 outcomes (Delaney 2005; Herzog 2006; Viscusi 2006; Wolff 2004). Ludwig et al. (Ludwig 2006) used solely GI-3 as outcome. Twenty-three trials reported on time to passage of first stool, thirteen trials on time to tolerance of regular diet, twenty-four trials on time to passage of first flatus and nineteen trials on length of hospital stay. Thirty-one trials reported adverse drug reactions in different levels of detail. The majority of the included trials did not specify surgical complications and the rate of surgical re-interventions (‘Characteristics of included studies’). Twenty trials reported resolution or incidence of nausea or vomiting.

Risk of bias in included studies  
‘Characteristics of included studies’  
Seventy-five percent of the trials were performed before the year 2000 and 68% before the year 1990. The number of patients per trial was small and ranged between 14 for the smallest (Roberts 1995) and 666 patients for the largest trial (Viscusi 2006). Only
eight trials enrolled more than 100 patients (Conte 1983; Delaney 2005; Herzog 2006; Ludwig 2006; Smith 2000; Taguchi 2001; Viscusi 2006; Wolff 2004). The reporting of methodological quality of the included trials was variable but often poor. In the majority of the trials the method of randomisation was not specified. Three trials used inadequate methods (Groudine 1998 and Woods 1993 used quasi-randomisation; Mieny 1972 used random number tables). Allocation was concealed in 7 of 40 trials (Brown 1999, Friisell 1985, Kuo 2006, Lightfoot 2007, Manani 1982, Taguchi 2001, Smith 2000). The remaining trials did not state or use concealment of random allocation. The intention-to-treat principle (ITT) was applied in only three trials (Taguchi 2001, Kuo 2006, Lightfoot 2007). Nine trials did not report the use of the ITT principle but the reported number of patients available for data analyses was in agreement with the number of initially randomized patients (Altaparmakov 1984, Brown 1999, Hakansson 1985, Mieny 1972, Rimbaek 1990, Roberts 1995, Tollesson 1991(1), Tollesson 1991(2), Von Ritter 1987). Five trials (Delaney 2005; Herzog 2006; Ludwig 2006; Viscusi 2006; Wolff 2004) reported effect estimates based on a ‘modified-intention-to-treat population’, which does not correspond to an intention to treat analysis. Withdrawals were excluded from the analysis in twenty-one trials and eleven trials did not report on the occurrence of withdrawals. Twelve trials described blinding procedures in detail, while five did not provide information on blinding at all (Alvarez 1979; Ferraz 2001; Ferreira 1980; Thorup 1983; Woods 1993). Twenty-two trials declared to be double-blind, but did not provide any details about the used blinding methods. Only eight trials included information on sample size calculations (Brown 1999; Cheape 1991; Hallerbäck 1991; Herzog 2006; Jepsen 1986; Kuo 2006; Lightfoot 2007; Smith 2000).

**Effects of interventions**

In ‘Characteristics of included studies’ we provide a summary of each included trial. Results of pooled analyses are shown in the section ‘Analysis’ and adverse drug reactions are reported in ‘Additional Tables’.

**Selective opioid antagonists (alvimopan) versus placebo**

Six trials reported on the effect of alvimopan (Delaney 2005; Herzog 2006; Ludwig 2006; Taguchi 2001; Viscusi 2006; Wolff 2004). Methodological quality was good in only one trial where the method of random sequence generation, concealment of random allocation, double blinding, number of withdrawals and the use of the intention-to-treat principle was properly reported (Taguchi 2001). All remaining trials showed methodological or reporting deficiencies. Except reporting of attrition, none of the trials properly described the randomization method used, only one trial detailed on blinding (Herzog 2006) and none of the trials properly applied the intention to treat principle (modified intention-to-treat principle). Of note, authors of alvimopan trials used Cox models to analyze the effect of treatment against placebo on time to recovery. Acceleration of time to recovery in e.g. the treatment arm compared to the control arm corresponds to a larger hazard in the treatment arm compared to the control arm what appears as a hazard ratio larger than unity.

**Recovery of gastrointestinal function: composite endpoints GI-2 and GI-3 (Comparison 01, outcome 01, outcome 02)**

Five trials used the composite endpoint GI-2 (Delaney 2005; Herzog 2006; Ludwig 2006; Viscusi 2006; Wolff 2004) and four trials the composite endpoint GI-3 (Delaney 2005; Herzog 2006; Viscusi 2006; Wolff 2004) as primary efficacy endpoint. Subjects in the intervention groups received either alvimopan 12mg or 6mg on the day of operation or on the first postoperative day (POD). The trials by Herzog et al and Ludwig et al used alvimopan 12mg as single active treatment group.

The alvimopan 12 mg against placebo comparison contained a total of 2181 patients (Delaney 2005; Herzog 2006; Ludwig 2006; Viscusi 2006; Wolff 2004), the alvimopan 6 mg against placebo comparison a total of 1034 patients (Delaney 2005; Viscusi 2006; Wolff 2004).

The pooled hazard ratio for recovery of gastrointestinal function according to the GI-2 outcome for alvimopan 12 mg compared to placebo was 1.59 (95% CI 1.33, 1.90). A large effect seen with the trial by Herzog et al (Herzog 2006) lead to between-trial heterogeneity ($I^2=67\%$) within this comparison. The pooled hazard ratio of alvimopan 6 mg compared to placebo was 1.41 (95% CI 1.22, 1.63) for the same outcome (Delaney 2005; Ludwig 2006; Viscusi 2006; Wolff 2004).

The pooled hazard ratio of GI-3 recovery for 12mg alvimopan against placebo was 1.30 (95% CI 1.16, 1.46), and 1.31 (95% CI 1.15, 1.50) for 6 mg alvimopan against placebo (test for heterogeneity $I^2=0\%$ for both comparisons).

**Time to passage of first stool (Comparison 01, outcome 03)**

Four trials assessed the outcome time to passage of first stool. Three trials compared 12mg alvimopan to placebo (Delaney 2005; Herzog 2006; Viscusi 2006) and three trials compared 6mg alvimopan to placebo (Delaney 2005; Taguchi 2001; Viscusi 2006). The pooled analyses of the outcome time to first stool included a total of 1238 patients in the 12 mg alvimopan against placebo comparison and a total of 782 patients in the 6 mg alvimopan against placebo comparison.

The pooled hazard ratio for passage of first stool for alvimopan 12mg compared to placebo was 1.74 (95% CI 1.29, 2.34). The pooled hazard ratio for alvimopan 6mg compared to placebo was 1.60 (95% CI 1.32, 1.92) for the same outcome.

**Time to tolerance of regular diet (Comparison 01, outcome 04)**

Four trials reported on tolerance of regular diet. Three trials compared 12mg alvimopan against placebo (Delaney 2005; Herzog 2006; Viscusi 2006) and three trials compared 6mg alvimopan against placebo (Delaney 2005; Taguchi 2001; Viscusi 2006). The pooled results for 12 mg alvimopan compared to placebo in-
cluded a total of 1238 patients and a total of 782 patients were assigned to the 6mg alvimopan against placebo comparison. The pooled hazard ratio for the 12mg alvimopan against placebo comparison was 1.14 (95% CI 1.00, 1.29) and 1.57 (95% CI 1.04, 2.37) for the 6mg alvimopan against placebo comparison. The trial from Taguchi et al contributed to heterogeneity of the treatment effect estimates of the 6mg against placebo comparison ($I^2 = 81.7\%$).

**Length of hospital stay**

*(Comparison 01, outcome 05)*

Five trials reported length of hospital stay. Five trials (Delaney 2005; Herzog 2006; Ludwig 2006; Viscusi 2006; Wolff 2004) studied 12mg alvimopan against placebo and four trials investigated 6mg alvimopan against placebo (Delaney 2005; Taguchi 2001; Viscusi 2006; Wolff 2004). The pooled analysis included a total of 2181 patients into the 12mg alvimopan against placebo comparison and 1086 patients contributed to the 6mg alvimopan against placebo comparison. The pooled hazard for length of hospital stay was larger for both the 12mg alvimopan against placebo comparison and the 6mg alvimopan against placebo comparison (HR 1.31 (95% CI 1.20, 1.43) and HR 1.38 (95% CI 1.22, 1.57), respectively).

**Time to passage of first flatus**

*(Comparison 01, outcome 06)*

Two trials reported the time to passage of first flatus (Herzog 2006; Taguchi 2001). The pooled analysis included a total of 562 patients into both the alvimopan and placebo groups. The treatment effect was heterogeneous across trials and showed a non-significant trend towards reduction of time to passage of first flatus (HR 1.67 (95% CI 0.86, 3.23), $I^2 = 77.0\%$).

Taguchi et al. also studied the effect alvimopan 1mg against placebo (Taguchi 2001). The analysis included a total of 52 patients and did not show a significant reduction of time to resolution of POI (the HR for time to tolerance of regular diet was 1.30 (95% CI 0.69, 2.46) and the HR for length of hospital stay was 1.40 (95% CI 0.78, 2.60)). We did not incorporate the data from the 1mg alvimopan against placebo comparison into pooled analyses.

**Summary of effect and dose-response considerations**

The effect of alvimopan was consistent across all endpoints, except for time to first flatus which was only reported in two trials who showed heterogeneous effects. There was no clear dose-response relationship. Alvimopan 12mg against placebo did not show a larger effect which was consistent across different endpoints than alvimopan 6mg against placebo. None of the trials reported whether the proportional hazards assumption was fulfilled or violated. Except the trial from Taguchi (Taguchi 2001), the (reporting of) methodological quality of the trials was moderate.

**Cholecystokinin-like acting drugs (cerulein and ceruletide) versus placebo or no treatment**

Four trials assessed the effect of cholecystokinin-like drugs (Alvarez 1979, Ferreira 1980, Frisell 1985, Sadek 1988) on several endpoints. Methodological quality was moderate in one trial where the method of random sequence generation, concealment of random allocation, double blinding and number of withdrawals was properly reported (Frisell 1985). None of the remaining trials properly reported on the randomization process and only two trials detailed on attrition (Ferreira 1980, Sadek 1988). None of the trials on cholecystokinin-like acting drugs properly applied an intention to treat analysis.

**Time to passage of first stool**

*(Comparison 02, outcome 03)*

Four trials reported the effect on passage of first stool (Alvarez 1979, Ferreira 1980, Frisell 1985, Sadek 1988). Pooled analysis of cholecystokinin-like drugs included a total of 257 patients in both the intervention and control arm. The pooled ratio of the mean time to passage of first stool showed a small and non-significant advantage of cholecystokinin-like drugs compared to placebo (0.86 (95% CI 0.71, 1.04)). The effect was heterogeneous ($I^2 = 84.8\%$) due to a large effect of the trial by Ferreira et al (Ferreira 1980).

**Time to tolerance of regular diet and length of hospital stay**

*(Comparison 02, outcome 04 and outcome 05)*

Two trials assessed tolerance of regular diet and length of hospital stay (Alvarez 1979, Sadek 1988). The pooled analyses included a total of 141 patients within both comparison groups. The analysis showed a small but significant acceleration of the time to tolerance of regular diet (pooled ratio of means of 0.93 (95% CI 0.90, 0.97)) and similarly significant acceleration of length of hospital stay (pooled ratio of the mean of 0.81 (95% CI 0.68, 0.97) for cholecystokinin-like drugs compared to control.

**Time to passage of first flatus**

*(Comparison 02, outcome 06)*

Two trials assessed the outcome time to passage of first flatus (Frisell 1985, Sadek 1988). The pooled analysis of this comparison included a total of 148 patients. The analysis showed a non-significant reduction of time to passage of first flatus compared to control subjects compared to control subjects with a pooled ratio of the means of 0.77 (95% CI 0.55, 1.08). Two trials were excluded from the analysis of time to first flatus (Alvarez 1979, Ferreira 1980) since no information on blinding was available (see 'Criteria for considering studies for this review').

* includes the combination of time to first flatus or stool

**Summary of effect**

There is inconsistent evidence of a reduction of recovery times for the group of cholecystokinin-like drugs. The effect did not reach significance for time to passage of first stool and time to passage of flatus, but for the outcomes tolerance of regular diet and length of hospital stay. These inconsistent results are based on small trials of moderate to poor methodological quality.

**Cisapride versus placebo**

Cisapride showed a significant acceleration of the time to passage of first stool in a heterogeneous random effects model. The effect was not consistent across endpoints; in particular the effect did neither significantly replicate in a homogenous fixed-effects model for the outcome time to first flatus nor for other endpoints. All cisapride trials were of moderate to poor quality.

**Dihydroergotamine versus no treatment**
Two trials studied the effect of dihydroergotamine compared to no treatment (Altaparmakov 1984; Thorup 1983). Methodological quality was poor in both trials with no information available on the process of randomization. One trial properly applied the intention to treat principle (Thorup 1983), the other (Altaparmakov 1984) stated patient withdrawals.

**Time to passage of first stool**
(Comparison 04, outcome 03)
Both trials reported time to passage of first stool (Altaparmakov 1984; Thorup 1983). The analysis of this comparison included a total of 123 patients allocated to dihydroergotamine or no treatment. The pooled ratio of the mean time to passage of first stool was lower in subjects treated with dihydroergotamine but the reduction was far from being significant (ratio of the means 0.71 (95% CI 0.43, 1.18)). Effect estimates across the two trials were heterogeneous and therefore the random effects model was used ($I^2 = 88.2\%$).

**Summary of effect**
The two low quality trials did not show a significant reduction of time to passage of first stool in favour of dihydroergotamine compared to no treatment.

**Dopamine-antagonists (metoclopramide and bromopride) versus placebo**
Four trials studied the effect of dopamine-antagonists (Cheape 1991, Conte 1983, Jepsen 1986, Tollesson 1991(1) ). Methodological quality was poor in all included trials and all quality criteria but attrition were poorly reported. No information on the randomization process was reported and only one trial applied the intention-to-treat principle (Tollesson 1991(1) ). Withdrawals were stated and excluded (Jepsen 1986, Conte 1983).

**Time to passage of first stool and time to tolerance of regular diet**
One small trial reported time to passage of first stool (Tollesson 1991(1) ), with in total 20 patients assigned to either metoclopramide or placebo. Time to passage of stool was similar in patients treated with metoclopramide compared to control (ratio of the means 0.96 (95% CI 0.68, 1.37)). One trial reported on time to tolerance of regular diet (Cheape 1991). Ninety-three patients were in total allocated to treatment or control. The effect in favour of metoclopramide compared to control was small and not significant (ratio of the means 0.90 (95% CI 0.80, 1.02)).

**Time to passage of first flatus**
(Comparison 05, outcome 06)
Three trials investigated the effect on time to passage of first flatus (Conte 1983, Jepsen 1986, Tollesson 1991(1) ) with a total of...
239 patients assigned to the treatment or control group. The results were heterogeneous across trials due to a significant effect of the largest trial (Conte 1983) \((I^2 = 64.3\%)\). Conte et al included patients undergoing abdominal surgery with and without bowel resection (Conte 1983). Lightfoot included patients with surgery of the aorta and iliac arteries (Lightfoot 2007) and Tollesson enrolled elective cholecystectomy patients (Tollesson 1991(1)). The pooled analysis did not reveal a significant reduction of the time to passage of first flatus in patients treated with dopamine-antagonists compared to placebo (pooled ratio of the means of 0.94 (95% CI 0.66, 1.33)).

* includes the combination of time to first flatus or stool

**Summary of effect**

We did not find evidence of an effect of dopamine-antagonists on the resolution of POI. The absence of significant effects was consistent across endpoints, however, the evidence for the ‘harder endpoints’ time to stool or tolerance of regular diet is based on only one trial each. The quality of all trials was poor.

**Erythromycin versus placebo**

Four trials studied the effect of erythromycin (Bonacini 1993, Lightfoot 2007, Smith 2000, Wilkinson 2002). Methodological quality was moderate in three trials where the randomization process and the number of withdrawals was properly reported (Lightfoot 2007, Smith 2000, Wilkinson 2002). Only one trial applied an intention-to-treat analysis (Lightfoot 2007).

*Time to passage of first stool*

(Comparison 06, outcome 03)

Three trials reported on the passage of first stool (Bonacini 1993, Lightfoot 2007, Smith 2000) including a total of 233 patients enrolled into erythromycin or placebo. There was a homogenous lack of effect across all trials with a pooled ratio of the mean time to passage of first stool 0.99 (95% CI 0.90, 1.08) for erythromycin compared to placebo.

*Time to tolerance of regular diet, length of hospital stay and time to passage of first flatus*

(Comparison 06, outcome 04, 05 and 06)

Three trials assessed tolerance of regular diet (Bonacini 1993, Lightfoot 2007, Smith 2000) and four trials length of hospital stay (Bonacini 1993, Lightfoot 2007, Smith 2000, Wilkinson 2002). For the outcome time to tolerance of regular diet, a total of 233 patients were available in the erythromycin and placebo groups and a total of 254 patients for the length of hospital stay comparison. There was neither evidence of effect of erythromycin against placebo on time to tolerance of regular diet (pooled ratio of the means of 1.04 (95% CI 0.93, 1.15)) nor on length of hospital stay (pooled ratio of the means of 1.00 (95% CI 0.90, 1.11)).

Four trials assessed time to passage of first flatus (Bonacini 1993, Lightfoot 2007, Smith 2000, Wilkinson 2002) in a total of 254 patients. Similar to other endpoints, the analysis showed no reduction of erythromycin compared to control for time to passage of first flatus (pooled ratio of the means of 0.95 (95% CI 0.88, 1.03)).

* includes the combination of time to first flatus or stool

**Summary of effect**

There is evidence of absence of a treatment effect of erythromycin on time to recovery of post-operative bowel function. The absence of effect was homogenous and consistent across all endpoints. The overall quality of included trials was moderate.

**Systemic administration of lidocaine versus placebo**

Three trials analysed the effect of systemic lidocaine compared to placebo (Groudine 1998, Kuo 2006, Rimbiöck 1990). Methodological quality varied across included trials. Information on the randomization process was detailed in two trials (Groudine 1998, Kuo 2006), but one (Groudine 1998) used a quasi randomization scheme. Two trials properly applied the intention to treat principle (Rimböck 1990, Kuo 2006).

*Time to passage of first stool and time to passage of first flatus*

(Comparison 07, outcome 03 and 06)

Two small trials reported on time to passage of first stool (Groudine 1998, Rimbiöck 1990) with a total of 68 patients allocated to lidocaine or placebo. The analysis showed a significant reduction of the mean time to passage of first stool in treated subjects compared to control (pooled ratio of the means 0.83 (95% CI 0.73, 0.95)). Similarly, three trials assessed time to passage of first flatus (Kuo 2006, Groudine 1998, Rimbiöck 1990) in 108 patients. Consistent with time to first stool, time to passage of first flatus was reduced in favour of the active group compared to control (pooled ratio of the means 0.82 (95% CI 0.73, 0.92)).

* includes the combination of time to first flatus or stool

**Length of hospital stay**

(Comparison 07, outcome 05)

Two small trials investigated length of hospital stay (Kuo 2006, Groudine 1998) in 38 patients receiving lidocaine or placebo. Random effects meta-analysis of the two heterogeneous trials \((I^2 = 73.6\%)\) did not show a significant effect on length of hospital stay in favour of active treatment (pooled ratio of the means of 0.89 (95% CI 0.73, 1.10)).

**Summary of effect**

Systemic treatment with lidocaine might eventually be effective to support restoration of POI. The evidence is based on small trials, but the treatment effect is consistent for time to passage of first stool and time to passage of first flatus. However, the evidence is insufficient to judge the effect on length of hospital stay and data of randomized comparisons on tolerance of regular diet are not available. All included trials were of moderate quality. Sensitivity analysis excluding the study with quasi-randomisation did not change the conclusions drawn for lidocaine.

**Neostigmine versus placebo**

Two trials assessed the effect of neostigmine against placebo (Hallerbäck 1987(1); Orlando 1994). The trials showed methodological or reporting deficiencies. Except reporting of attrition, none of the trials properly reported the randomization process and none of the trials properly applied the intention to treat principle.

*Time to passage of first stool and time to passage of first flatus*

Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)
One trial reported on time to passage of first stool (Hallerbäck 1987(1)) in 35 patients. The median time to first stool was 75 hours in neostigmine treated subjects compared to 93 hours in control group subjects. The reduction was statistically significant yielding a ratio of the medians of 0.81 (95% CI 0.65, 0.99) for neostigmine to control. One trial reported on time to passage of first flatus (Orlando 1994). The comparison included a total of 39 patients. Orlando et al assessed the endonasal application of neostigmine for a period of 4 days and found a borderline significant reduction in time to passage of first flatus (ratio of the means 0.57 (95% CI 0.33, 1.01)). * includes the combination of time to first flatus or stool

Propranolol versus placebo

Two trials assessed the effect of propranolol against placebo (Ferraz 2001, Hallerbäck 1987(2)). The two trials were of poor methodological quality. Except reporting of attrition, none of the trials properly reported the requested quality criteria.

Time to passage of first stool or time to passage of first flatus* (Comparison 09, outcome 06)

One trial reported time to passage of first stool (Hallerbäck 1987(2)) and two trials reported on time to passage of first flatus (Ferraz 2001, Hallerbäck 1987(2)). The comparison regarding the outcome time to passage of first stool enrolled a total of 39 patients to propranolol or placebo. The median time to evacuation of stool was reported as 74.5 hours in treated patients and 120 hours in control patients (ratio of the medians 0.37 (95% CI 0.29, 0.46). The effect of the drug was not consistent over the two trials including a total of 66 patients for the outcome time to passage of first flatus. The results were homogenous over both trials and failed to show a significant on acceleration of time to passage of first flatus in the treatment group compared to the control group (pooled ratio of the means 0.91 (95% CI 0.74, 1.11)). * includes the combination of time to first flatus or stool

Propranolol combined with neostigmine versus placebo

Two trials were carried out to assess the combination of propranolol and neostigmine compared to placebo (Garcia 1993, Hallerbäck 1987(1)). Both trials showed methodological and reporting deficiencies. Except reporting of withdrawals, no further details on the requested methodological quality criteria were given.

Time to passage of first stool and time to passage of first flatus* (Comparison 08, outcome 03 and outcome 06)

Both trials enrolled a total of 70 patients into the propranolol/neostigmine or placebo group. The pooled analysis showed heterogeneity of effects ($I^2 = 71.0\%$) and failed to show a significant association of the drug combination against placebo with time to passage of first stool (pooled ratio of the means 0.85 (95% CI 0.62, 1.16)). Similarly, Garcia-Caballero et al. (Garcia 1993) compared time to passage of first flatus in 37 patients receiving the same drug combination or placebo. The median time to flatus was 48 hours in the treatment arm and 60 hours in the control arm and failed to show a significant effect (ratio of the means of 0.80 (95% CI 0.61, 1.05)).

* includes the combination of time to first flatus or stool

Summary of effect

There is insufficient evidence for any of neostigmine, propranolol or the combination of neostigmine and propranolol. The effect of neostigmine is based on two small trials, both of low methodological quality. The effect of propranolol in contrast was inconsistent with an effect on time to stool but no replication on time to flatus. Similarly, the combination of both drugs did not enhance recovery times beyond chance, based on two low-quality trials.

Other drugs

Four trials (Hakansson 1985, Manani 1982, Mieny 1972, Woods 1993) could not be assigned to any of the drug classes mentioned in the methods section. Methodological quality was moderate in one trial where the method of random sequence generation, concealment of random allocation, double blinding and number of withdrawals was reported (Manani 1982). All remaining trials showed methodological or reporting deficiencies. None properly described the randomization process; only one trial detailed on blinding (Mieny 1972) but two trials, however, applied an intention to treat analysis (Mieny 1972, Hakansson 1985). Mieny et al and Woods et al used quasi randomization (Mieny 1972, Woods 1993).

One trial analysed the effect of postoperative albumin replacement (Woods 1993). The comparison enrolled 69 patients. Albumin replacement was administrated according to serum albumin levels in the treatment group. The approach used in the control group, which had no albumin replacement, was unclear. Time to regular diet and time to hospital discharge was similar in both groups (220 hours for albumin versus 202 hours for no treatment and 9 days versus 8 days, respectively). Blinding was not reported, therefore time to passage of first flatus was not considered according to the protocol.

Manani et al (Manani 1982) investigated systemic administration of fructose-1,6-diphosphate. They compared 100 patients. Fructose-1,6-diphosphate reduced the time to first flatus (ratio of the means 0.84 (95% CI 0.72, 0.98)). However, the control group received fructose which is chemically similar to Fructose-1,6-diphosphate.

Pantothen Acid was studied by Mieny et al (Mieny 1972). Eighty-nine patients undergoing cholecystectomy were included. There was no difference in time to first flatus between pantothen acid treated patients and control group patients (ratio of means 1.00 (95% CI 0.85, 1.17)).

Another trial investigated vasopressin (Hakansson 1985). They enrolled 60 patients undergoing major abdominal surgery. Time to hospital discharge and time to passage of first flatus was not significantly different in the treatment group compared to the control group (ratio of means 1.14(95% CI 0.86, 1.52) and 0.72 (95% CI0.45, 1.14), respectively).

Summary of effect of 'other drugs'

There is insufficient evidence for a conclusive judgement of the effect of albumin, pantothen acid, fructose 1,6 diphosphate or...
vasopressin. All single trials were of small size. Except the trial of Manani on Fructose-1, 6-diphosphate which was of adequate methodological quality, the quality of the remaining trials was poor.

**Summary of adverse drug reactions**

There was large variability in the degree of reporting of adverse drug reactions, especially in older trials. Also, some trials did not report adverse drug reactions according to treatment allocation (Table 1). Moreover, adverse events associated with cisapride occurred in the post-marketing period and lead to withdrawal of the drug from the market. For alvimopan, we only found a small and non-significantly increased risk of headache in treated patients. Frisell (Frisell 1985) and Sadek (Sadek 1988) reported increased adverse drug reactions (nausea and vomiting) for cholecystokinin-like drugs and Orlando (Orlando 1994) reported mild side effects associated with neostigmine. The remaining trials reported, if any, balanced risk of adverse drug reactions between active and control arms.

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<td>infections 28/296 (9.4)</td>
<td>infections 28/153 (18.3)</td>
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<td>Nausea 182/296 (61.5)</td>
<td>Nausea 104/153 (67.9)</td>
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<td>Vomiting 60/296 (20.2)</td>
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<td>Abdominal distension 41/296 (13.8)</td>
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<td>Tachycardia 31/296 (10.5)</td>
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<td>n</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Adverse events</td>
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<tr>
<td>Herzog 2006</td>
<td>413/106*</td>
<td>Alvimopan, 12mg</td>
<td>Placebo</td>
<td>Serious adverse events (life-threatening) 23/413 (5.6) Mild: Nausea 298/413 (72.2) Vomiting 129/413 (31.2) Abdominal distension 34/413 (8.2) Hypertension 28/413 (6.8) Headache 55/413 (13.3) Tachycardia 21/413 (5.1) Constipation 94/413 (22.8)</td>
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<td>Alvimopan 12mg</td>
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<td>Serious adverse events not reported Mild: Nausea 190/329 (57.8) Vomiting 46/329 (14.0) Abdominal pain 19/329 (5.8) Hypertension 36/329 (10.9) Tachycardia 27/329 (8.2) Postoperative ileus 24/329 (7.3)</td>
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<td>Taguchi 2001</td>
<td>52/26</td>
<td>ADL 8-2689 (Alvimopan), 1mg and 6mg</td>
<td>Placebo</td>
<td>Mild: Nausea 27% in 6mg- and 67% in 1mg in alvimopan group Vomiting 0% in 6mg- and 26% in 1mg in alvimopan group</td>
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<tr>
<td>Source</td>
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<td>Treatment</td>
<td>Treatment Details</td>
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<td>Mild:</td>
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<tr>
<td>Viscusi 2006</td>
<td>441/224*</td>
<td>Alvimopan, 6mg and 12mg</td>
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<td>30/441 (6.8) (5.9 in 6mg group)</td>
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<td>Wolff 2004</td>
<td>345/165*</td>
<td>Alvimopan, 6mg and 12mg</td>
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<td>17/345 (5) (no details reported)</td>
<td>Nausea 199/345 (57.7)</td>
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</table>
| Alvarez 1979 | 25/25   | Cerulein 0.3mcg/kg | No Treatment | 18 Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review) Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
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<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
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<th>Severe:</th>
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<td>Ferreira 1980</td>
<td>30/30</td>
<td>Cerulein 2ng/kg/min</td>
<td>No Treatment</td>
<td>Nausea 1/30 (3.3)</td>
<td>Vomiting 1/30 (3.3)</td>
<td>Colic pain 1/30 (3.3)</td>
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<td>Frisell 1985</td>
<td>27/30</td>
<td>Cholecystokinin 75 IU</td>
<td>Placebo</td>
<td>Nausea 15/27 (55.5)</td>
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<td>Benson 1994</td>
<td>11/12</td>
<td>Cisapride 30mg</td>
<td>Placebo</td>
<td>Mild: Hypokalemia 2/11 (18.2) (3.0-3.5mmol/l)</td>
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<td>Mild: Hypokalemia 3/12 (25) (3.0-3.5mmol/l)</td>
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<td>Brown 1999</td>
<td>17/18</td>
<td>Cisapride 20mg</td>
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<td>Mild: Wound infection 3/17 (17.6)</td>
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<td>Clevers 1991</td>
<td>17/20</td>
<td>Cisapride 30mg</td>
<td>Placebo</td>
<td>Severe nausea 17/17 (100)</td>
<td>Repeated vomiting 10/17 (58.8)</td>
<td>Reinsertion of nasogastric tube</td>
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<td>Study Year</td>
<td>Total Number</td>
<td>Drug Dose</td>
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<td>Trial Reported</td>
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<tr>
<td>Hallerbäck 1991</td>
<td>36/33</td>
<td>Cisapride 30mg</td>
<td>Placebo</td>
<td>Severe: Prolonged ileus 1/36 (2.7)</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<tr>
<td>Roberts 1995</td>
<td>7/7</td>
<td>Cisapride 20mg and 30mg</td>
<td>Placebo</td>
<td>Not reported</td>
<td>Not reported</td>
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<td>Tollesson 1991(2)</td>
<td>20/20</td>
<td>Cisapride 10mg</td>
<td>Placebo</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<td>Von Ritter 1987</td>
<td>17/15</td>
<td>Cisapride 10mg</td>
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<td>Not reported</td>
<td>Not reported</td>
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<td>Altaparmakov 1984</td>
<td>23/23</td>
<td>Dihydroergotamine</td>
<td>No Treatment</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<tr>
<td>Thorup 1983</td>
<td>43/34</td>
<td>Dihydroergotamine</td>
<td>No Treatment</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<tr>
<td>Cheape 1991</td>
<td>40/53</td>
<td>Metoclopramide 10mg</td>
<td>Placebo</td>
<td>Severe: Death 1/40 (2.5) Reoperation 1/40 (2.5) Prolonged ileus 7/40 (17.5)</td>
<td>Reoperation 1/53 (1.9) Prolonged ileus 8/53 (15.1)</td>
<td></td>
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<tr>
<td>Tollesson 1991(1)</td>
<td>10/10</td>
<td>Metoclopramide 20mg</td>
<td>Placebo</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<tr>
<td>Conte 1983</td>
<td>84/80</td>
<td>Bromopride 20mg</td>
<td>No Treatment</td>
<td>Mild: Nausea 36/84 (42.9)</td>
<td>Mild: Nausea 51/80 (63.8)</td>
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## Table 1. Adverse drug reactions (Adr)

(Continued)

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<tr>
<th>Study</th>
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<th>Drug</th>
<th>Placebo</th>
<th>Severe:</th>
<th>Mild:</th>
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<tr>
<td>Bonancini 1993</td>
<td>41/36</td>
<td>Erythromycin</td>
<td>Placebo</td>
<td>Abdominal pain 41/84 (48.8)</td>
<td>Abdominal pain 55/80 (68.8)</td>
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<td></td>
<td></td>
<td>250mg</td>
<td></td>
<td>Gastrointestinal bleeding 1/41 (2.4)</td>
<td>Gastrointestinal bleeding 1/36 (2.7)</td>
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<td></td>
<td></td>
<td></td>
<td>Vomiting 3/41 (7.3)</td>
<td>Vomiting 2/36 (5.5)</td>
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<td></td>
<td></td>
<td>Abdominal pain 2/41 (4.9)</td>
<td>Abdominal pain 2/36 (5.5)</td>
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<tr>
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<td></td>
<td>Skin rash 3/41 (7.3)</td>
<td>Skin rash 1/36 (2.7)</td>
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<td>Lightfoot 2006</td>
<td>11/11</td>
<td>Erythromycin</td>
<td>Placebo</td>
<td>Mild: Nausea (=2days) 4 (36)</td>
<td>Mild: Nausea (=2days) 2 (18)</td>
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<td>125mg</td>
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<td>Vomiting (=2days) 3 (27)</td>
<td>Vomiting (=2days) 1 (9)</td>
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<td></td>
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<td></td>
<td>Abdominal pain (=2days) 2 (18)</td>
<td>Abdominal pain (=2days) 0 (0)</td>
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<td></td>
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<td></td>
<td>QTc prolongation (=2days) 1 (9)</td>
<td>QTc prolongation (=2days) 1 (9)</td>
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<tr>
<td>Smith 2000</td>
<td>65/69</td>
<td>Erythromycin</td>
<td>Placebo</td>
<td>Mild: Severe Nausea 17/65 (26.1)</td>
<td>Mild: Severe Nausea 18/69 (26.1)</td>
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<td></td>
<td>200mg</td>
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<td>Vomiting 11/65 (16.9)</td>
<td>Vomiting 11/69 (15.9)</td>
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<td></td>
<td>Skin rash 1/65 (1.5)</td>
<td>Skin rash 0/69 (0)</td>
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<td></td>
<td></td>
<td>Cardiac arrhythmia 0/65 (0)</td>
<td>Cardiac arrhythmia 11/69 (15.9)</td>
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<td>Wilkinson 2002</td>
<td>11/10</td>
<td>Erythromycin</td>
<td>Placebo</td>
<td>Severe: Venous thrombosis 0/11 (0)</td>
<td>Severe: Venous thrombosis 1/10 (1)</td>
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<td></td>
<td></td>
<td>250mg</td>
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<td>Mild: Nausea 1/11 (0.91)</td>
<td>Mild: Nausea 1/10 (1)</td>
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<td></td>
<td>Wound infection Superficial 1/11 (0.91)</td>
<td>Wound infection Superficial 1/10 (1)</td>
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<td>Groudine 1998</td>
<td>18/20</td>
<td>Lidocaine 1.5</td>
<td>Placebo</td>
<td>Mild: Fever 1/18 (5.6)</td>
<td>Mild: Fever 2/20 (10)</td>
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<td></td>
<td></td>
<td>mg/kg Bolus,</td>
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<td></td>
<td></td>
<td>Infusion 3mg/min</td>
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<td></td>
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<td>&gt;70kg, 2mg/min</td>
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<tr>
<td></td>
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<td>&lt;70kg</td>
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<tr>
<td></td>
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<td>mg Bolus, 3mg/min</td>
<td></td>
<td>Vomiting 7/15</td>
<td>Vomiting 8/15</td>
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<td>Patients</td>
<td>Treatment</td>
<td>Control</td>
<td>Drug Reaction</td>
<td>Severe</td>
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<tr>
<td>Kuo 2006</td>
<td>20/20</td>
<td>Lidocaine 2mg/kg Bolus, Infusion 3mg/kg/h</td>
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<td>Sedation 2/15 (13.3)</td>
<td>(46.6)</td>
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<td>Orlando 1994</td>
<td>19/20</td>
<td>Neostigmine 2x 5.4mg</td>
<td>Placebo</td>
<td>Bradycardia 3/20 (15)</td>
<td>Nausea or vomiting 5/20 (25)</td>
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<td>Hallerbäck 1987(1)</td>
<td>I(Pro/Neo):21 II(N): 22 III(P): 19</td>
<td>Propranolol 10 mg and 80mg Neostigmine 0.5mg</td>
<td>Placebo</td>
<td>Nausea 1/21 (4.8) Pulmonary obstruction and itching 1/22 (4.5)</td>
<td>Not reported</td>
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<td>Ferraz 2001</td>
<td>12/15</td>
<td>Propranolol 40mg</td>
<td>No Treatment</td>
<td>Severe: Primary peritonitis 1/12 (8.3) Arrhythmia 1/12 (8.3)</td>
<td>Severe: Reoperation 2/15 (13.3)</td>
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<td>Garcia 1993</td>
<td>17/20</td>
<td>Propranolol 7.5mg iv or 80mg Neostigmine 0.5mg</td>
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<td>Not reported</td>
<td>Not reported</td>
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<td>Propranolol 4mg and 10mg</td>
<td>Placebo</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
<td>Trial reported: Treatment was without adverse drug reactions</td>
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<tr>
<td>Woods 1993</td>
<td>37/32</td>
<td>Albumin</td>
<td>No Treatment</td>
<td>Death 1/37 (2.7) Mild: Respiratory insufficiency and Bronchitis 5/37 (13.5)</td>
<td>Total complication rate (31.3)</td>
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<tr>
<td>Study</td>
<td>Total Complication Rate (35.1%)</td>
<td>Treatment Group</td>
<td>Adverse Drug Reactions</td>
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<tr>
<td>Manani 1982</td>
<td>50/50</td>
<td>Fructose-1,6 diphosphate 5g Placebo (Fructose)</td>
<td>Mild: Nausea and/or Vomiting reported to resolve earlier in treatment group</td>
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<td>Mieny 1972</td>
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<td>Panthothenic Acid Placebo</td>
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<tr>
<td>Hakansson 1985</td>
<td>30/30</td>
<td>Vasopressin, 10IE No Treatment</td>
<td>Trial reported: Treatment was without serious adverse drug reactions</td>
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</table>

*Safety population
- Data in parentheses are numbers with percentages
Discussion

Prokinetic acting drugs are often prescribed for patients with symptoms of postoperative ileus (POI) or to step up recovery on a regular basis following abdominal surgery. We reviewed efficacy and effectiveness outcomes of 15 systemically acting prokinetic drugs used in patients with POI. More than half of all trials were published before the year 1990 and such older trials can therefore not satisfy current methodological and reporting criteria which were mainly introduced after the year 2000 (Moher 2001).

Six RCTs reported on alvimopan and the summary estimate indicates a shortened recovery period of gastrointestinal (GI) function and time to hospital discharge of alvimopan when compared to placebo. Alvimopan is still an investigational drug which has not yet passed the regulatory affairs. Moreover safety concerns have been issued recently with alvimopan in patients taking opioids for chronic non-cancer pain (www.biospace.com). The quality of reporting of the alvimopan trials does not, except the study from Taguchi et al. (Taguchi 2001) comply with current reporting standards (Moher 2001). Although these are recent trials, we judged the methodological quality as only moderate. Cholecystokininin-like prokinetic drugs like cerulein/cheruletide and cholecystokinin showed inconsistent evidence to reduce recovery time of post-operative bowel function and trials were of poor quality. Three trials of intravenous lidocaine and two trials of neostigmine showed a small effect of GI recovery with reduced time to passage of first flatus and passage of first stool. The evidence for both drugs, however, is insufficient for other patient relevant outcomes and sufficiently powered trials of high-quality are needed to confirm these preliminary data. There is insufficient evidence of generally low to moderate quality for the use of propranolol, propranolol and neostigmine and cisapride. None of the drugs showed a consistent effect over several clinically relevant outcomes. Moreover, cisapride has been withdrawn from the market in many countries since 2000 due to serious cardiac events (Tonini 1999). We found clear evidence for the absence of effects of erythromycin on post-operative bowel recovery in four trials of moderate quality. These findings were consistent across trials and different outcomes. RCTs of different drugs like dopamine-antagonists, dihydroergotamine, albumin replacement, vasopressin and pantothen acid were most of poor methodological quality and failed to demonstrate any effect on restoration of postoperative ileus. Only Manani (Manani 1982) showed that fructose 1, 6 diphosphate reduced time to passage of first flatus in a trial of moderate methodological quality. But the drug did not receive attention in later randomised trials.

Alvimopan selectively blocks opioid effects throughout the gastrointestinal tract without affecting the analgesic effects of opioid medications (Delaney 2005; Greenwood-Van 2004; Schmidt 2001; Viscusi 2006; Wolff 2004). Although the most promising drug to accelerate recovery of bowel function following abdominal surgery, it is currently unclear whether and to which extent the found effect estimates suffer from bias. All trials compute effect estimates based on ‘modified intention to treat populations’, a subset of the ITT population that received the protocol-specified surgery and had at least one on- treatment primary efficacy evaluation (Delaney 2005; Herzog 2006; Ludwig 2006; Viscusi 2006; Wolff 2004). Subjects who did not receive the protocol specified surgery were excluded after randomization, what is debatable. The exclusions add an arbitrary element to the trials (Senn 1997). Effect estimates based on ITT could have been provided at least as sensitivity analysis (Fowler 2006, Heritier 2003). Further, the Cox proportional hazard model was used for statistical analysis. Since recovery times are thought to be shortened, the hazard ratio of a beneficial effect is above unity what makes the clinical interpretation not wrong but unusual. No trial reported in the statistical analysis whether the proportional hazard assumption was fulfilled. If not, the length of follow-up employed becomes critical because the hazard will accordingly increase or decrease. As a result, the hazard ratios tend to be more discrepant from unity in trials with short follow-up compared to trials with longer follow-up (Keene 2002). Two of the included studies (Herzog 2006; Wolff 2004) received funding of pharmaceutical companies, which were involved in the development of the compound, and some co-authors were employees of the sponsors (Delaney 2005; Herzog 2006; Ludwig 2006; Taguchi 2001; Viscusi 2006; Wolff 2004).

N-methylaltrexone (MNTX) is another mu opioid antagonist with effects restricted to the periphery. We identified one ongoing trial that currently evaluates the efficacy of MNTX in the treatment of postoperative ileus. Asimadoline, a peripherally acting kappa opioid agonist is currently tested regarding POI in one phase II trial in patients with segmental colonic resection (see ‘Characteristics of ongoing studies’).

Cerulein or ceruletide are dekapeptides with similar pharmacodynamic properties as cholecystokinin. The evidence for an effect of this class of drugs was inconsistent. The treatment effects were heterogeneous and did not show a significant effect on the outcome time to stool or time to flatus. Based on only two trials and in contradiction with the first outcome, cerulein or ceruletide reduced time to tolerance of regular diet and length of hospital stay. The quality of all included trials was poor and complicates the interpretation of the inconsistent results.

Cisapride did not show a consistent prokinetic effect across endpoints and the results are based on work with overall poor reporting quality. In 2000 cisapride was withdrawn from the market in the USA and in many other countries because of reports of serious, and in many cases fatal, cardiac events (Layton 2003, Barbey 2000). The drug is included in this review since it is still approved in some countries (Greece, Serbia, Poland, South Africa).

Although dopamine-antagonists are widely used to positively influence postoperative bowel motility, the trial evidence is of poor
methodological quality and pooled analyses did not demonstrate a significant effect of the drug.

Erythromycin showed no effect on time to recovery of bowel function in four trials, irrespective of the endpoint considered. We found preliminary evidence of intravenously applied lidocaine and neostigmine on time to first flatus or stool, but the effect on other patient relevant outcomes is unclear and needs further attention. The trials were very small and only of poor to moderate quality. We suppose the currently ongoing trials to be of adequate power and methodological quality to provide further evidence of these drugs in patients undergoing major abdominal surgery (Asimadoline, Lidocaine, Lidocaine/Ketamin, Methylaltrexone).

Single trial evidence was available for albumin, pantothen acid, fructose 1,6 diphosphate and vasopressin. However, the small study sizes, the poor reporting quality (except the trial of Manani (Manani 1982)) and the outdated information makes recommendation of any of these drugs impossible.

Many important aspects of drug treatment for POI can not be addressed with the current evidence. It would be interesting, for example, to know whether differential drug effects exist in patients with or without epidural analgesia (Jorgensen 2000) or in patients who had open or laparoscopic surgery (Schwenk 2005). Such subgroup analyses, however, need adequate power or specific research questions and are not possible to address currently. Similarly, the influence of postoperative opioid consumption, either as an effect modifier or if unbalanced as confounder, can not be addressed. Only alvimopan trials reported, that the effect was apparently not influenced by the amount of opioids given (Delaney 2005; Herzog 2006; Ludwig 2006; Taguchi 2001; Tollesson 1991(2); Wolff 2004).

Limitations of this review

Most included trials are of small size and therefore prone to effect overestimation due to publication bias. Since the number of trials per comparison was usually very limited, formal assessment of publication bias was impossible.

AUTHORS’ CONCLUSIONS

Implications for practice

Pharmacological agents to decrease POI are commonly used in post-surgical management. Evidence for the majority of these agents is based on small trials of limited methodological quality compromising the interpretation of study findings. Adequately powered trials of high methodological quality are required to prove beneficial effects of any compound currently used for POI or under investigation for POI.

Limited evidence from few small trials of moderate to poor quality indicates that intravenous use of lidocaine and neostigmine may show effects on time to recovery from POI, but more evidence on patient-relevant outcomes is needed from trials with rigorous design. For cholecystokinin-like acting drugs, cisapride, dopaminergic antagonists, pantothen acid, propranolol or vasopressin the evidence is insufficient to recommend their use for the treatment of POI. For all these compounds effects are either inconsistent across different outcomes, study sample sizes are too small to be conclusive, or the methodological quality of eligible trials is too poor. Cisapride has been withdrawn from the market due to adverse cardiac events in most countries worldwide. Erythromycin has no effect on GI recovery following abdominal surgery. Alvimopan may be likely to reduce time to recovery of bowel function following major abdominal surgery. However, current evidence is based on 6 trials of reasonable size but most studies do not follow current reporting standards what makes judgement of potential bias or the influence of potential conflicts of interests impossible. The compound is not yet approved for the treatment of POI.

Implications for research

Trial protocols should use an explicit rational when to start therapy for POI, should provide sufficiently long intervention and follow-up duration (Kehlet 2006) and use uniform endpoint reporting according to time to GI-2 and GI-3 criteria. In addition, such protocols should prohibit the use of other prokinetic drugs and use standardized protocols for pain medication with an appropriate stratified randomisation scheme for patients with epidural analgesia and laparoscopic operation techniques.

Pharmacologic treatment of POI, if proven to be effective, should furthermore be contrasted against the multimodal or proactive POI management (Kehlet 2001).

Applied methodological work should elicit statistical time-to-event models most suited and clinically meaningful to report drug effects of POI data.

ACKNOWLEDGEMENTS

Mette Agervist of the Danish Cochrane Colorectal Cancer group for giving assistance with electronic database searches.

Toshi A Furukawa of the Department of Psychiatry and Cognitive-Behavioural Medicine, Nagoya City University, Japan for giving assistance with translating Japanese articles and applying the imputation method.

Marcel Wolbers of the Basel Institute for Clinical Epidemiology, University Hospital Basel, Switzerland, for providing statistical support.
References to studies included in this review

Altaparmakov 1984 [published data only]

Alvarez 1979 [published data only]

Benson 1994 [published data only]

Bonacini 1993 [published data only]

Brown 1999 [published data only]

Cheape 1991 [published data only]

Clevens 1991 [published data only]

Conte 1983 [published data only]

Delaney 2005 [published data only]

Ferraz 2001 [published data only]

Ferreira 1980 [published data only]

Frisell 1985 [published data only]

Garcia 1993 [published data only]

Graudine 1998 [published data only]

Hakansson 1985 [published data only]

Hallerbäck 1987(1) [published data only]

Hallerbäck 1987(2) [published data only]

Hallerbäck 1991 [published data only]

Herzog 2001 [published data only]

Jepsen 1986 [published data only]

Kuo 2006 [published data only]
Lightfoot 2007  [published data only]

Ludwig 2006  [published data only]

Manani 1982  [published data only]

Miény 1972  [published data only]

Orlando 1994  [published data only]

Rimbäck 1990  [published data only]

Roberts 1995  [published data only]

Sadek 1988  [published data only]

Smith 2000  [published data only]

Taguchi 2001  [published data only]

Thorup 1983  [published data only]

Tollesson 1991(1)  [published data only]

Tollesson 1991(2)  [published data only]

Viscusi 2006  [published data only]

Von Ritter 1987  [published data only]

Wilkinson 2002  [published data only]

Wolff 2004  [published data only]

Woods 1993  [published data only]

References to studies excluded from this review

Aloisio 1976  [published data only]

Baig 2004  [published data only]

Boghaert 1987  [published data only]

Chan 2005  [published data only]
Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)

Chen JH 2005  [published data only]

Chen JY 2005

Chen JH 2005

Clevers 1988  [published data only]

Costa 1994  [published data only]

Colvers 1988  [published data only]

Costa 1994  [published data only]

Cyba 1985  [published data only]

Davidson 1979  [published data only]

Delaney 2006  [published data only]

Delaney 2007  [published data only]

Fanning 1999  [published data only]

Ferraz 1995  [published data only]

Gales 1999  [published data only]

Garcia-Caballero 1993  [published data only]

Jensen 1990  [published data only]

Kasperek 2007  [published data only]

Kawaguchi 1985  [published data only]

Kivalo 1970  [published data only]

Kreis 2001  [published data only]

Lykkegaard-Nielsen 1983  [published data only]

Madsen 1983  [published data only]

Madsen 1986  [published data only]

Myrhøj 1988  [published data only]

Nio 1980  [published data only]

Noblett 2006  [published data only]
References to ongoing studies

Asimadoline [published data only]
Asimadoline for the treatment of post-operative ileus [A randomized, double-blind, placebo-controlled study evaluating asimadoline on the duration of PO in subjects undergoing laparoscopic/ handwritten-assisted lap segmental colon resection secondary to colon cancer, polypectomy or diverticulitis]. Information obtained from ClinicalTrials.gov on June 26, 2007. Massachusetts, United States, Record first received February 27, 2007. [: Study ID numbers: ASMP2004, ClinicalTrials.gov identifier: NCT00443040]

Lidocaine [published data only]

Lidocaine/Ketamin [published data only]

Methylnaltrexone [published data only]
Study of intravenous (iv) methylnaltrexone bromide (MNTX) in the treatment of post-operative ileus (POI) [A phase III, double blind, randomized, parallel-group, placebo-controlled study of intravenous (iv) methylnaltrexone bromide (MNTX) in the treatment of post-operative ileus (POII)]. Information obtained from ClinicalTrials.gov on June 26, 2007. New York, United States, Record first received: November 16, 2006. [: Study ID numbers: MNTX 3301, ClinicalTrials.gov identifier: NCT00401375]

Additional references

Barbey 2000

Barnes 1997

Buckley 2000

Bungard 1999

Cali 2002

Carpenter 1996

Carpenter 2001

Chang 2002
Clinical consensus 2006

Dickersin 1994

Dubois 1974

FDA 2006

Deeks 2001

Dickersin 1994

Dubois 1974

Furukawa 2006

Goldstein 2007

Greenwood-Van 2004

Groudine 1994

Herbert 2002

Heritier 2003

Higgins 2002

Higgins 2003

Jorgensen 2000

Kalff 1998

Kalff 1999

Keene 2002
Keene ON. Alternatives to the hazard ratio in summarizing efficacy in time-to-event studies: an example from influenza trials. Statistics in Medicine 2002;21(23):3687–3700. [MEDLINE: 56]

Kehlet 2001

Kehlet 2006
Kerbl 1994

Layton 2003

Liu 1995

Lobo 2002

Lucky 2003

Mann 2000

Moher 2001

Moore 1989

Moore 1992

NHS CRD 2001

Peeters 1993

Resnick 1997(1)

Resnick 1997(2)

Robinson 2002

Schwenk 2005

Senn 1997

Tan 2007

Tonini 1999

Wattwil 1989

Weber 1993

www.biospace.com

* Indicates the major publication for the study
### Characteristics of included studies  
[ordered by study ID]

**Altaparmakov 1984**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Parallel group RCT</td>
</tr>
<tr>
<td>Randomisation</td>
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<tr>
<td>Time point of randomisation</td>
<td>Before surgery</td>
</tr>
<tr>
<td>Blinding</td>
<td>Double blind, no details given</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>Yes, details not reported</td>
</tr>
<tr>
<td>Reporting of patient baseline characteristics</td>
<td>Yes</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>Not stated</td>
</tr>
<tr>
<td>Sample size calculation</td>
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</table>

<table>
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<tr>
<th>Participants</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>Unclear, Bulgaria, Germany</td>
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<tr>
<td>Number eligible</td>
<td>Not stated</td>
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<tr>
<td>Number enrolled</td>
<td>46</td>
</tr>
<tr>
<td>Number in intervention group</td>
<td>23</td>
</tr>
<tr>
<td>Number in control group</td>
<td>23</td>
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<tr>
<td>Number of withdrawals</td>
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<tr>
<td>Inclusion criteria</td>
<td>Not reported</td>
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<tr>
<td>Exclusion criteria</td>
<td>Not reported</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Elective cholecystectomy</td>
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<table>
<thead>
<tr>
<th>Interventions</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Study drug</td>
<td>Dihydroergotamine with Heparin</td>
</tr>
<tr>
<td>Dose</td>
<td>0.5mg and 5000IE</td>
</tr>
</tbody>
</table>
| Administration            | - Route: 12 hours interval, Heparin subcutaneous administration  
- Start: 1. POD         |
| - Duration: 5 days        | Control: 5000IE Heparin subcutaneous       |
|                            | Planned follow up duration: 5 days         |
| Co-Medication for ileus   | allowed at discretion of the physician: Not reported |
| Type of anaesthesia       | Not reported                               |
| Type of analgesia         | Not reported                               |

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electromyographic analysis</td>
<td></td>
</tr>
<tr>
<td>Time to passage of first bowel movement</td>
<td></td>
</tr>
<tr>
<td>Occurrence of Bowel Sounds</td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
</tr>
</tbody>
</table>

| Notes                     | POI defined as postoperative gut motility depressed |

### Risk of bias

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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
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<td>Unclear</td>
<td>B - Unclear</td>
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</table>

Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  
Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Before surgery
Blinding: Not reported
Intention-to-treat analysis: No
Reporting of patient baseline characteristics: Yes
Withdrawals: Not stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, Mexico
Number eligible: Not stated
Number enrolled: 50
Number in intervention group: 25
Number in control group: 25
Number of withdrawals: Not reported
Inclusion criteria: Abdominal surgery
Exclusion criteria: Not reported
Type of surgery: Cholecystectomy, vagotomy, pyloroplasty, hernioplasty, adhesiolysis, explorative laparotomy, appendectomy, gastrectomy, exploration biliary tract, jejunal bypass, pseudocystogastrostomy

Interventions
Study drug: Cerulein
Dose: 0.3mcg/kg body weight
Administration:
- Route: 4h interval, intravenous administration
- Start: 1. POD, 1h after operation
- Duration: Maximum of 33h
Control: No treatment
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: Not reported
Type of analgesia: Not reported

Outcomes
Time to passage of first bowel sounds
Time to passage of first flatus
Time to passage of first stool
Time to first oral intake
Length of hospital stay
Time to first mobilization out of bed

Notes

Risk of bias

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<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Benson 1994

**Methods**
- Design: Parallel group RCT
- Randomisation: No details available
- Time point of randomisation: Before surgery
- Blinding: Single blind, outcome assessor blinded
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

**Participants**
- Setting: Single centre trial, United Kingdom
- Number eligible: Not stated
- Number enrolled: 29
- Number in intervention group: 13 (11)
- Number in control group: 16 (12)
- Number of withdrawals (intervention/placebo): 2/4
- Inclusion criteria: Not reported
- Exclusion criteria: Previous abdominal surgery (exception: appendectomy, herniorrhaphy), disease or medication associated with alteration of the gastrointestinal motility
- Type of surgery: Major abdominal surgery

**Interventions**
- Study drug: Cisapride
- Dose: 30mg
- Administration:
  - Route: 8 hours interval, rectal administration
  - Start: 1. POD
  - Duration: Maximum of 92 hours
- Control: Placebo
- Planned follow up duration: Until first flatus or 92 hours
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: GA
- Type of analgesia: Meperidin bolus, intravenous; Meperidin infusion, subcutaneous (1.0mg/kg over 3 hours)

**Outcomes**
- Electromyographic analysis
- Continuous manometric recording
- Time to passage of first flatus
- Occurrence of bowel sounds
- Adverse effects

**Notes**
- Data extracted from figures

**Risk of bias**

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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
### Bonacini 1993

**Methods**
- Design: Parallel group RCT
- Randomisation: No details available
- Time point of randomisation: After surgery
- Blinding: Double blind, Surgical staff blinded
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

**Participants**
- Setting: Single centre trial, USA
- Number eligible: Not stated
- Number enrolled: 80
- Number in intervention group: 41 (41)
- Number in control group: 39 (36)
- Number of withdrawals: 3 - allocation stated
- Inclusion criteria: Operations that involved the opening of the peritoneal cavity
- Exclusion criteria: Not reported
- Type of surgery: Standard open cholecystectomy, celiotomy, major operation

**Interventions**
- Study drug: Erythromycin
- Dose: 250mg
- Administration:
  - Route: 8 hour interval, intravenous administration
  - Start: 1. POD
  - Duration: 3 days
- Control: Placebo
- Planned follow up duration: Until resolution of 'ileus symptoms'
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: GA
- Type of analgesia: Meperidine, application form unclear

**Outcomes**
- Time to passage of first stool/bowel movement
- Time to passage of first flatus
- Time to first tolerated oral intake
- Length of hospital stay

**Notes**

### Risk of bias

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<td>Allocation concealment</td>
<td>Unclear</td>
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</table>

### Brown 1999

**Methods**
- Design: Parallel group RCT
- Randomisation: Sealed opaque envelopes, numbered medication kits distributed by pharmacy
### Brown 1999

(Continued)

Time point of randomisation: Before surgery  
Blinding: Double blind, patient and care giver blinded  
Intention-to-treat analysis: Yes, no details reported  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Not stated  
Sample size calculation: Used

**Participants**  
Setting: Single centre trial, USA  
Number eligible: Not stated  
Number enrolled: 35  
Number in intervention group: 17  
Number in control group: 18  
Number of withdrawals: Not reported  
Inclusion criteria: Elective or emergent colorectal surgery with resection of a portion of the large bowel  
Exclusion criteria: Extraintestinal surgery, preoperative intestinal motility disorder, diabetes with known gastroparesis  
Type of surgery: Left and right hemicolecotomy

**Interventions**  
Study drug: Cisapride  
Dose: 20mg  
Administration:  
- Route: 6 hour interval, oral administration  
- Start: 1. POD  
- Duration: Until hospital discharge  
Control: Placebo  
Planned follow up duration: Not reported  
Type of anaesthesia: Not reported  
Type of analgesia: Not reported

**Outcomes**  
Time to passage of first stool/bowel movement  
Time to regular diet intake  
Length of hospital stay  
Hospital cost analysis  
Adverse effects

**Notes**  
Military population

### Risk of bias

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<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<td>A - Adequate</td>
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</table>

### Cheape 1991

**Methods**  
Design: Parallel group RCT  
Randomisation: No details available
Cheape 1991

Time point of randomisation: Before surgery
Blinding: Double blind, no details given
Intention-to-treat analysis: No
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Used

Participants
Setting: Single centre, USA
Number eligible: 100
Number enrolled: 93
Number in intervention group: 40
Number in control group: 53
Number of withdrawals (intervention/placebo): 3/4
Inclusion criteria: Major elective intraabdominal colorectal surgery
Exclusion criteria: Need for 2nd laparotomy, improper dose/interval of metoclopramide administration, insertion/ removal of the nasogastric tube, death
Type of surgery: Abdominal/segmental colectomy, abdominoperineal resection, ileoanal reservoir, small bowel resection, relocation of stoma, colostomy creation, strictureplasty, rectopexy, gastrocolic fistula resection, colocutaneous fistula resection

Interventions
Study drug: Metoclopramide
Dose: 10 mg
Administration:
- Route: 8 hour interval, intravenous administration
- Start: Day of operation
- Duration: Until regular diet was tolerated
Control: Placebo
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: Not reported
Type of analgesia: Not reported

Outcomes
Time to toleration of regular diet
Adverse effects

Notes
Prolonged ileus defined as an ileus greater than 7 days duration

Risk of bias

Item | Authors’ judgement | Description
--- | --- | ---
Allocation concealment? | Unclear | B - Unclear

Clevers 1991

Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Unclear
Participants
Setting: Single centre trial, The Netherlands
Number eligible: Not stated
Number enrolled: 40
Number in intervention group: 19 (17)
Number in control group: 21 (20)
Number of withdrawals (intervention/placebo): 2/1
Inclusion criteria: Elective major surgery- developing moderate or severe nausea or vomiting in the postoperative days
Exclusion criteria: Operation of esophagus, stomach, emergency surgery, intrabdominal infections, intestinal obstruction
Type of surgery: Elective major abdominal surgery (colonic surgery, abdominal vascular surgery, various abdominal procedures)

Interventions
Study drug: Cisapride
Dose: 30 mg
Administration:
- Route: 6 hour interval, rectal administration
- Start: unclear
- Duration: Maximum 48 hours
Control: Placebo
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: GA, GA with epidural anaesthesia
Type of analgesia: Morphine, epidural anaesthesia

Outcomes
Time to passage of first flatus
Time to passage of first stool
Time to tolerance of normal diet
Time to mobilization out of bed
Occurrence of bowel sounds
Adverse effects

Notes

Risk of bias

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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
Conte 1983

Methods
Design: Parallel group RCT  
Randomisation: No details available  
Time point of randomisation: Unclear  
Blinding: Double blind, no details given  
Intention-to-treat analysis: No  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Stated  
Sample size calculation: Not used.

Participants
Setting: Single centre trial, Italy  
Number eligible: Not stated  
Number enrolled: 166  
Number in intervention group: 86 (84)  
Number in control group: 80  
Number of withdrawals (intervention/no treatment): 2/0  
Inclusion criteria: Major/minor abdominal surgery-with or without opening of the gastrointestinal tract  
Exclusion criteria: Not reported  
Type of surgery: Appendectomy, cholecystectomy, herniotomy, gastric resection, cholecystojjunostomy, laparocele, hemicolecotomy, intrahepatoduodenogastrojejunostomy, fistula biliodigestive, hyster- and adnexectomy

Interventions
Study drug: Bromopride  
Dose: 20 mg  
Administration:  
- Route: 14h/20h (1. POD)- 6/14/22h (2. POD), intramuscular administration  
- Start: Day of operation  
- Duration: 2 days  
Control: No treatment  
Planned follow up duration: Not reported  
Co-Medication for ileus allowed at discretion of the physician: Not reported  
Type of anaesthesia: Not reported  
Type of analgesia: Not reported

Outcomes
Time to passage of first flatus or stool (canalization time)  
Adverse effects

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
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<td>B - Unclear</td>
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</tbody>
</table>

Delaney 2005

Methods
Design: Parallel group RCT  
Randomisation: Stratified by type of surgery, (1:1:1 ratio)
Delaney 2005

Time point of randomisation: Before surgery
Blinding: Double blind, no details given
Intention-to-treat analysis: No-stated MITT-population*
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Not used

Participants
Setting: Multi centre trial, USA
Number eligible: Not stated
Number enrolled: 451
Number in intervention (6 mg) group: 152 (141)
Number in intervention (12 mg) group: 146 (138)
Number in control group: 153 (145)
Number excluded post randomisation (intervention A/intervention B/placebo): 27, allocation not stated
Inclusion criteria: Male or female between 18-80 years undergo laparotomy (partial colectomy, total abdominal hysterectomy)
Exclusion criteria: Anterior resection, opioid taking within 4 weeks, severe cardiovascular, pulmonary, renal, hepatic, hematological, systemic disease, pregnancy, laboratory abnormalities, complete bowel obstruction, inflammatory bowel disease
Type of surgery: Partial colectomy, total abdominal hysterectomy

Interventions
Study drug: Alvimopan
Dose A: 6mg
Dose B: 12mg
Administration:
- Route: 2 hours before surgery, 12 hour interval, oral administration
- Start: On the day of surgery
- Duration: Until hospital discharge or maximum of 7 days
Control: Placebo
Planned follow up duration: Until hospital discharge or maximum of 10 POD
Co-Medication for ileus allowed at discretion of the physician: Not allowed (‘prophylactic antiemetics after surgery’)
Type of anaesthesia: Not reported
Type of analgesia: Patient-controlled analgesia with opioids, intravenous

Outcomes
GI-3
GI-2
Time to passage of first stool
Time to first tolerance of solid food
Length of hospital stay
Adverse effects

Notes
*Modified intention to treat -population- all treated patients who received the protocol-specified surgeries of bowel resection or radical or simple hysterectomy and had one on-treatment primary efficacy evaluation.

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
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</tbody>
</table>

Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Ferraz 2001

#### Methods
- **Design:** Parallel group RCT
- **Randomisation:** No details available
- **Time point of randomisation:** Unclear
- **Blinding:** Not reported
- **Intention-to-treat analysis:** No
- **Reporting of patient baseline characteristics:** Yes
- **Withdrawals:** Stated
- **Sample size calculation:** Not used.

#### Participants
- **Setting:** Single centre trial, Brazil
- **Number eligible:** Not stated
- **Number enrolled:** 35
- **Number in intervention group:** 14 (12)
- **Number in control group:** 21 (15)
- **Number of withdrawals (intervention/no treatment):** 2/6
- **Inclusion criteria:** Hepatosplenic schistosomiasis with indication of splenectomy
- **Exclusion criteria:** Chronic diarrhea or constipation, autoimmune disease., inflammatory bowel disease., diverticular disease, diabetes mellitus, chagas disease, drug use (laxatives, constipants, antidepressive drugs, calcium-channelblockers), contraindication to propranolol use
- **Type of surgery:** Splenectomy, division of left gastric vein, postoperative endoscopic sclerosis of oesophageal varices

#### Interventions
- **Study drug:** Propranolol
- **Dose:** 40 mg
- **Administration:**
  - **Route:** Initially 40mg, dose adjustment to achieve decrease in cardiac frequency, oral administration
  - **Start:** Prior to operation
  - **Duration:** Until decrease of 20% in cardiac frequency
- **Control:** No treatment
- **Planned follow up duration:** Until clinical recovery of ileus
- **Co-Medication for ileus allowed at discretion of the physician:** Not reported
- **Type of anaesthesia:** GA
- **Type of analgesia:** Tenoxicam

#### Outcomes
- **Time to passage of first flatus or stool**
- **Adverse effects**

#### Notes
- Precise timing of drug initiation unclear. Dose range 80-160mg

### Risk of bias

<table>
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<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Ferreira 1980

**Methods**
- **Design:** Parallel group RCT
- **Randomisation:** No details available
- **Time point of randomisation:** After surgery
- **Blinding:** Not reported
- **Intention-to-treat analysis:** No
- **Reporting of patient baseline characteristics:** Yes
- **Withdrawals:** Stated
- **Sample size calculation:** Not used

**Participants**
- **Setting:** Single centre trial, Spain
- **Number eligible:** Not stated
- **Number enrolled:** 60
- **Number in intervention group:** 30 (29)
- **Number in control group:** 30
- **Number of withdrawals (intervention/no treatment):** 1/0 - allocation stated
- **Inclusion criteria:** Not reported
- **Exclusion criteria:** Not reported
- **Type of surgery:** Laparotomy and surgical procedures not involving the digestive tube (gall-bladder, spleen), gastrostomy, duodenotomy, hiatal hernia repair, and surgical procedures involving the digestive tube

**Interventions**
- **Study drug:** Cerulein
- **Dose:** 2ng/kg/min
- **Administration:**
  - **Route:** Single dose, intravenous administration
  - **Start:** 24 hours after surgery
- **Control:** No treatment
- **Planned follow up duration:** Not reported
- **Co-Medication for ileus allowed at discretion of the physician:** Not reported
- **Type of anaesthesia:** Not reported
- **Type of analgesia:** Not reported

**Outcomes**
- **Time to passage of first flatus**
- **Time to passage of first stool**
- **Time of restoration of peristalsis and removal of nasogastric tube**
- **Adverse effects**

**Notes**
- Stratified reporting of results in patients with and patients without bowel resection

### Risk of bias

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<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
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### Frisell 1985

**Methods**
- **Design:** Parallel group RCT
- **Randomisation:** Patients were consecutively numbered, each number corresponded to box containing a set
Frisell 1985

(Continued)

- of coded vials for infusion
- Time point of randomisation: After surgery
- Blinding: Double blind, patient and care giver were blinded
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

Participants

- Setting: Single centre trial, Sweden
- Number eligible: Not stated
- Number enrolled: 60
- Number in intervention group: 30 (27)
- Number in control group: 30
- Number of withdrawals (intervention/placebo): 3- allocation stated
- Inclusion criteria: Not reported
- Exclusion criteria: Previous abdominal surgery (except appendectomy), history of laxatives
- Type of surgery: Elective cholecystectomy

Interventions

- Study drug: Cholecystokinin
- Dose: 75 IDU 10 ml
- Administration:
  - Route: 8 hour interval, intravenous administration
  - Start: 1. POD
  - Duration: 2 days
- Control: Placebo
- Planned follow up duration: Not reported
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: Not reported
- Type of analgesia: Not reported

Outcomes

- Time to passage of first flatus
- Time to passage of first stool
- Time to evaluate barium contrast medium in the caecum
- Adverse effects

Notes

Risk of bias

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<td>A - Adequate</td>
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</table>

Garcia 1993

Methods

- Design: Parallel group RCT
- Randomisation: No details available
- Time point of randomisation: Before surgery
Garcia 1993

(Continued)

Blinding: Double blind, no details given
Intention-to-treat analysis: No
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, Spain
Number eligible: Not stated
Number enrolled: 100-included, 96 analysed
Number in intervention group: 20 (17)
Number in control group: 20
Number of withdrawals(intervention/ no treatment): 3/0
Inclusion criteria: Patients with cholecystolithiasis
Exclusion criteria: Treatment with digitalis or verapamil, history of cardiac insufficiency or impairment, hypotension or bradycardia, insulin-dependent diabetes, chronic bronchitis, obstructive peripheral arteriopathy
Type of surgery: Elective cholecystectomy

Interventions
Study drug A: Propranolol
Trial drug B: Neostigmine
- Dose A: 7.5mg iv or 80mg oral
- Dose B: 0.5mg
Administration:
- Route A and B: 8 hour interval if intravenous administration; 12 hour interval if oral administration, 12 hour interval, subcutaneous administration
- Start: Day of operation
- Duration: Until passage of flatus or stool
Control: No treatment
Planned follow up duration: Until passage of first stool
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: GA
Type of analgesia: Magnesium noramidopirinometasulphate (NSAID) 6g/day

Outcomes
Time to passage of first flatus
Time to passage of first stool
Occurrence of bowel sounds
Adverse effects

Notes
Allocation in 5 groups:
I: Control: conventional cholecystectomy (CC), no additional treatment
II: CC with intraoperative local injection 20ml 0.5% bupivacaine
III: CC with postoperative instilling of 7.5mg propranolol/8h i.v. and 0.5mg of neostigmine/12h s.c.
IV: II+III
V: Laparoscopic cholecystectomy without additional treatment

Risk of bias

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<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
### Methods

- **Design**: Parallel group RCT
- **Randomisation**: Quasi-randomisation (even-numbered intervention, odd-numbered control)
- **Time point of randomisation**: Before surgery
- **Blinding**: Double blind, nursing staff, surgeons and patients
- **Intention-to-treat analysis**: No
- **Reporting of patient baseline characteristics**: Yes
- **Withdrawals**: Stated
- **Sample size calculation**: Not used

### Participants

- **Setting**: Single centre trial, USA
- **Number eligible**: Not stated
- **Number enrolled**: 40
- **Number in intervention group**: 19 (18)
- **Number in control group**: 20
- **Number of withdrawals (intervention/placebo)**: 2/0
- **Inclusion criteria**: Not reported
- **Exclusion criteria**: Preexisting disorder of the gastrointestinal tract, using of enemas, opioids, anticholinergic medication chronically, ASA physical Status > III
- **Type of surgery**: Radical retropubic prostatectomy
- **Number of withdrawals (intervention/placebo)**: 2/0

### Interventions

- **Study drug**: Lidocaine
- **Dose**: 1.5 mg/kg bolus, infusion 3mg/min >70kg, 2mg/min <70kg
- **Administration**:
  - **Route**: Until 60 minutes after end of operation, intravenous administration
  - **Start**: With operation
  - **Duration**: 60 minutes
- **Control**: Placebo
- **Planned follow up duration**: Until hospital discharge
- **Co-Medication for ileus allowed at discretion of the physician**: Not reported
- **Type of anesthesis**: GA
- **Type of analgesia**: Ketorolac bolus 30mg, 15mg/6 hours, intravenous; Morphine, no further details available

### Outcomes

- **Time to passage of first stool/bowel movement**
- **Time to passage of first flatus**
- **Length of hospital stay**
- **Amount of analgesia used**
- **Adverse effects**

### Notes

- **Only male patients**

### Risk of bias

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</table>
Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: After surgery
Blinding: Double blind, no details given
Intention-to-treat analysis: Yes, no details reported
Reporting of patient baseline characteristics: Yes
Withdrawals: Not stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, Denmark
Number eligible: Not stated
Number enrolled: 60
Number in intervention group: 30
Number in control group: 30
Number of withdrawals(intervention/no treatment): Not reported
Inclusion criteria: Uremia, cardiac, pulmonary disease, neurological disorder, mental retardation
Type of surgery: Elective abdominal surgery

Interventions
Study drug: Vasopressin
Dose: 10IE
Administration:
- Route: 4 hour interval, intramuscular administration
- Start: 1. POD
- Duration: Until passage of first flatus
Control: No treatment
Planned follow up duration: Until passage of first flatus
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: Not reported
Type of analgesia: Not reported

Outcomes
Time to passage of first flatus

Notes

Risk of bias

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Hallerbäck 1987(1)

Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Before surgery
Blinding: Double blind, no details given
Intention-to-treat analysis: No
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, Sweden
Number eligible: Not stated
Number enrolled: 62
Number in intervention group A: 21 (16)
Number in intervention group B: 22 (18)
Number in control group: 19 (17)
Number of withdrawals (intervention A/intervention B/placebo): 5/4/2
Inclusion criteria: Not reported
Exclusion criteria: Obstructive pulmonary disease, cardiac decompensation, cardiac arrhythmias, pregnancy or lactation, insulin-treated diabetes, renal or hepatic insufficiency, treatment with beta-blocking agents, treatment with anticholinergic agents, choledochotomy and/or duodenotomy, postoperative peritonitis due to bile leakage or infection
Type of surgery: Elective cholecystectomy

Interventions
Study drug A: Propranolol and Neostigmine
Study drug B: Neostigmine
- Dose A: 10 mg, after occurrence of flatus: change to 80mg tablets
- Dose B: 0.5mg
Administration:
- Route A: both 12 hour interval, intravenous administration
- Route B: 12 hour interval, subcutaneous administration
- Start: Day of operation
- Duration: Until passage of first stool
Control: Placebo
Planned follow up duration: Until passage of first stool
Co-Medication for ileus allowed at discretion of the physician: Not allowed (No enemas or laxatives were used before and after operation)
Type of anaesthesia: GA
Type of analgesia: Preanesthetic medication pethidine chloride 50mg, intramuscular

Outcomes
Time to passage of first stool
Blood pressure and heart rate
Number of analgesic injections
Adverse effects

Notes

Risk of bias

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<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
**Methods**

Design: Parallel group RCT  
Randomisation: No details available. Allocation method to different propranolol dosages unclear  
Time point of randomisation: Before surgery  
Blinding: Double blind, no details given  
Intention-to-treat analysis: No  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Stated  
Sample size calculation: Not used  

**Participants**

Setting: Single centre trial, Sweden  
Number eligible: Not stated  
Number enrolled: 40  
Number in intervention group A: 10  
Number in intervention group B: 10  
Number in control group: 19  
Number of withdrawals(intervention A/ intervention B/placebo): 1-allocation stated  
Inclusion criteria: Obstructive pulmonary disease, cardiac decompensation, cardiac arrhythmias, insulin-treated diabetes, renal or hepatic insufficiency, treatment with beta-blocking agents  
Type of surgery: Elective colonic surgery  

**Interventions**

Study drug: Propranolol  
- Dose A: 4mg, after occurrence of flatus changed to 40mg tablets  
- Dose B: 10mg, after occurrence of flatus changed to 80mg tablets  
Administration:  
- Route A: 12 hour interval, intravenous administration  
- Start A: 1. POD  
- Start B: 30 minutes before operation  
- Duration: Not reported  
Control: Placebo  
Planned follow up duration: Until passage of first stool or flatus  
Co-Medication for ileus allowed at discretion of the physician: Not allowed ('laxative drugs, enemas after surgery')  
Type of anaesthesia: Not reported  
Type of analgesia: Not reported  

**Outcomes**

Time to passage of first flatus  
Time to passage of first stool  
Occurrence of bowel sounds  
Measurement of the abdominal circumference  
Blood pressure and heart rate  
Number of analgesic injections  
Adverse effects  

**Notes**

Outcome reporting stratified for age and type of surgery  
Numbers in tables and text not consistent  

**Risk of bias**

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Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  
Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Hallerbäck 1987(2)

(Continued)

Allocation concealment? Unclear B - Unclear

Hallerbäck 1991

Methods

- Design: Parallel group RCT
- Randomisation: No details available
- Time point of randomisation: Before surgery
- Blinding: Double blind, no details given
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Used

Participants

- Setting: Multi centre trial, Sweden
- Number eligible: Not stated
- Number enrolled: 74
- Number in intervention group: 36
- Number in control group: 33
- Number of withdrawals (intervention/placebo): 2/3
- Inclusion criteria: No bowel movement over 48h after completion of the operation
- Exclusion criteria: Diabetes, previous operation with vagotomy, pregnancy or lactation, renal or hepatic insufficiency, severe pulmonary disease, cardiac decompensation, psychiatric disease or drug abuse, enterostomy, treatment with cholinergic or anticholinergic agents, treatment with adrenoceptor stimulating/blocking agents, postoperative complications (anastomotic leakage or intraabdominal sepsis), epidural anaesthesia
- Type of surgery: Elective colonic surgery (fundoplicatio, gastric resection, cholecystectomy, choledochotomy, small/large bowel resection)

Interventions

- Study drug: Cisapride
- Dose: 30 mg
- Administration:
  - Route: 8 hour interval, rectal administration
  - Start: 48 hours after surgery
  - Duration: Until passage of stool, total of seven suppositories, maximum 56 hours
- Control: Placebo
- Planned follow up duration: Not reported
- Co-Medication for ileus allowed at discretion of the physician: Not allowed ('laxative drugs, enemas after surgery')
- Type of anaesthesia: GA
- Type of analgesia: Piritramine 10-15mg, intramuscular; Dextropropoxyhene 32.5mg, tablets; Paracetamol 0.325g, tablets

Outcomes

- Time to passage of first of stool
- Number of analgesic injections
- Adverse effects

Notes

Stratified reporting of results in patients with and patients without bowel resection

Risk of bias

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Herzog 2006

Methods
- Design: Parallel group RCT
- Randomisation: No details available (4:1 ratio)
- Time point of randomisation: Before surgery
- Blinding: Double blind, investigators, research facility staff, clinical monitors and patients
- Intention-to-treat analysis: No-stated MITT-population*
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Used

Participants
- Setting: Teaching Hospital, USA
- Number eligible: Not stated
- Number enrolled: 519
- Number in intervention group: 413 (408)
- Number in control group: 106 (102)
- Number of withdrawals (intervention/placebo): 33/12
- Inclusion criteria: Woman, age 18 or older, scheduled for patient controlled analgesia
- Exclusion criteria: Opioid exposure within two weeks before study entry, complete bowel obstruction, previous or planned colectomy, colostomy or ileostomy, increased risk of postoperative mortality
- Type of surgery: Simple total abdominal hysterectomy

Interventions
- Study drug: Alvimopan
- Dose: 12mg
- Administration:
  - Route: 12 hours interval, oral administration
  - Start: 1. POD
  - Duration: Maximum 7 days
- Control: Placebo
- Planned follow up duration: 30 days after the last dose of the study drug
- Co-Medication for ileus allowed at discretion of the physician: Not allowed (‘concomitant cathartics’)
- Type of anaesthesia: Not reported
- Type of analgesia: Morphine, patient controlled analgesia, no further details available

Outcomes
- GI-3
- GI-2
- Time to passage of first stool/bowel movement
- Time to passage of first flatus
- Time to passage of first stool
- Time to tolerance of first solid food
- Length of hospital stay
- Amount of analgesia used
- Adverse effects

Notes
*Modified intention to treat population (MITT)-population: included all randomly assigned and treated patients who underwent simple total abdominal hysterectomy and who had >1 on-treatment evaluations for flatus, bowel movement or tolerance of solid food.
Herzog 2006

(Continued)

Data extracted from figures

Risk of bias

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Jepsen 1986

Methods

Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Unclear
Blinding: Double blind, no details given
Intention-to-treat analysis: Unclear
Reporting of patient baseline characteristics: Unclear
Withdrawals: Stated
Sample size calculation: Used

Participants

Setting: Single centre trial, Denmark
Number eligible: Not stated
Number enrolled: 60
Number in intervention group: 30
Number in control group: 30(25)
Number of withdrawals (intervention/placebo): 0/5
Inclusion criteria: Not reported
Exclusion criteria: Not reported
Type of surgery: Implantation of prosthesis (arteriosclerotic stenosis in the aorta and iliacal arteries)

Interventions

Study drug: Metoclopramide
Dose: 10mg
Administration:
- Route: 6 hour interval, intravenous administration
- Start: Immediately after operation
- Duration: Maximum 5 days
Control: Placebo
Planned follow up duration: 5 days
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: Not reported
Patient controlled analgesia: Morphine 4mg/8h, epidural analgesia

Outcomes

Time to passage of first flatus
Amount of gastric drainage
Vomiting
Oral intake of fluids
Adverse effects

Notes

Risk of bias
### Kuo 2006

**Methods**
- **Design:** Parallel group RCT
- **Randomisation:** Computer generated randomisation list
- **Time point of randomisation:** Before surgery
- **Blinding:** Double blind, identical packages
- **Intention-to-treat analysis:** Yes
- **Reporting of patient baseline characteristics:** Yes
- **Withdrawals:** Not stated
- **Sample size calculation:** Used

**Participants**
- **Setting:** Single centre trial, Taiwan
- **Number eligible:** Not stated
- **Number enrolled:** 60 - 40 analysed
- **Number in intervention group:** 20
- **Number in control group:** 20
- **Number of withdrawals(intervention/placebo):** Not reported
- **Inclusion criteria:** Colon cancer
- **Exclusion criteria:** Other systemic diseases: diabetes mellitus, hypertension, opioid or non steroidal anti-inflammatory drugs within 1 week before surgery
- **Type of surgery:** Colon surgery, not in detail reported

**Interventions**
- **Study drug:** Lidocaine
- **Dose A:** 2mg/kg
- **Dose B:** 3mg/kg/h
- **Administration:**
  - **Route A:** 10 minutes intravenous administration
  - **Route B:** after Route A was completed, via epidural catheter,
  - **Start:** 30 minutes before surgery
  - **Duration:** Throughout the surgical procedure not stated how long
- **Control:** Placebo
- **Planned follow up duration:** 72 hours
- **Co-Medication for ileus allowed at discretion of the physician:** Not reported
- **Type of anaesthesia:** GA
- **Type of analgesia:** Morphine 0.1mg/ml, ropivacaine 0.2%, patient controlled epidural analgesia

**Outcomes**
- **Time to passage of first flatus**
- **Length of hospital stay**
- **PCEA, trigger time, - delivery time, - consumption**
- **Postoperative pain relief**
- **Adverse effects**

**Notes**
- I: TEA - thoracic epidural anaesthesia
- II: IV - Lidocaine intravenous
- III: C - Control group

### Risk of bias

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**Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)**

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Allocation concealment? Yes  

Lightfoot 2007

Methods

Design: Parallel group RCT  
Randomisation: Using “permuted blocks method”  
Time point of randomisation: Unclear  
Blinding: Double blind, no details given  
Intention-to-treat analysis: Yes  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Stated  
Sample size calculation: Used

Participants

Setting: Single centre trial, USA  
Number eligible: 27  
Number enrolled: 22  
Number in intervention group: 11  
Number in control group: 11  
Number of withdrawals (intervention/placebo): 5 - allocation not stated  
Inclusion criteria: Patients undergoing cystectomy with urinary diversion secondary to bladder cancer or interstitial cystitis  
Exclusion criteria: Not reported  
Type of surgery: Neobladder, ileal conduit, Indiana pouch

Interventions

Study drug: Erythromycin  
Dose: 125mg  
Administration:  
- Route: 8 hour interval, intravenous administration  
- Start: 1. POD  
- Duration: Until maximum of 21 doses (=7 days)  
Control: Placebo  
Planned follow up duration: Not reported  
Co-Medication for ileus allowed at discretion of the physician: Not reported  
Type of anaesthesia: GA  
Type of analgesia: Local anesthetics per epidural analgesia

Outcomes

Time to passage of first stool/bowel movement  
Time to passage of first flatus  
Time to tolerance of regular diet  
Length of hospital stay  
Amount of analgesia and narcotics used  
Adverse effects

Notes

Placebo group: solely male

Risk of bias

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</tbody>
</table>
### Methods
Design: Parallel group RCT  
Randomisation: No details available  
Time point of randomisation: Before surgery  
Blinding: Double blind, no details given  
Intention-to-treat analysis: No- stated MITT-population*  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Not stated  
Sample size calculation: Not used

### Participants
Setting: Multi centre trial, USA  
Number eligible: Not stated  
Number enrolled: 654  
Number in intervention group: 329 (317)  
Number in control group: 325 (312)  
Number excluded post randomisation (intervention A/placebo): 25, allocation not stated  
Inclusion criteria: Adult patients (= 18 years of age) undergoing laparotomy (small or large bowel resection with primary anastomosis, scheduled for postoperative pain management with opioid based intravenous patient controlled analgesia  
Exclusion criteria: Undergoing total colectomy, colostomy, ileostomy or ileal pouch-anal anastomosis, complete bowel obstruction, history of total colectomy, gastrectomy, gastric bypass, short bowel syndrome or multiple previous abdominal operations performed by laparotomy, current opioid use or exposure (>3 doses) within one week of study entry  
Type of surgery: laparotomy (small or large bowel resection with primary anastomosis)

### Interventions
Study drug: Alvimopan  
Dose: 12mg  
Administration:  
- Route: 30 to 90 minutes before surgery, 12 hour interval, oral administration  
- Start: On the day of surgery  
- Duration: Until hospital discharge, maximum of 7 days  
Control: Placebo  
Planned follow up duration: Until hospital discharge or maximum of 10 days  
Co-Medication for ileus allowed at discretion of the physician: Not reported  
Type of anaesthesia: Not reported  
Type of analgesia: Opioid based patient controlled analgesia, no further details available

### Outcomes
GI-3 (but not reported)  
GI-2  
Time until actual discharge (Length of hospital stay)  
Time to hospital discharge order written  
Incidence of POI*-related morbidity  
Daily opioid consumption  
Adverse effects

### Notes
*Modified intention to treat population- all randomised and treated patients who received the protocol-specified surgery and had = one efficacy evaluation.  
Alvimopan trial 314. Information abstracted from poster presented at the American College of Surgeons 92nd Annual Clinical Congress.
Ludwig 2006

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Manani 1982

Methods
- Design: Parallel group RCT
- Randomisation: Sealed opaque envelopes
- Time point of randomisation: Before surgery
- Blinding: Double blind, patient and attending staff were blinded
- Intention-to-treat analysis: Unclear
- Reporting of patient baseline characteristics: Inadequate
- Withdrawals: Stated
- Sample size calculation: Not used

Participants
- Setting: Single centre trial, Italy
- Number eligible: Not stated
- Number enrolled: 150, 100 hysterectomy or cholecystectomy patients, 50 arthrodesis patients
- Number in intervention group: 50
- Number in control group: 50
- Number of withdrawals (intervention/placebo): 4 in vertebral arthrodesis group
- Inclusion criteria: uterine fibromatosis (hysterectomy), scoliosis (vertebral arthrodesis), cholecystic calculosis (cholecystectomy), ASA class I
- Exclusion criteria: Reoperations, hyper- or hypotension, additional complicating disease, bowel anastomosis
- Type of surgery: Hysterectomy, cholecystectomy, (vertebral arthrodesis)

Interventions
- Study drug: Fructose-1,6 diphosphate
- Dose: 5g
- Administration:
  - Route: 8 hour interval, intravenous administration
  - Start: On the day of operation
  - Duration: Until passage of first flatus
- Control: Fructose
- Planned follow up duration: Until passage of first flatus
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: GA
- Type of analgesia: No Morphine or morphine-like, anticholinesterase or sympatholytic substances

Outcomes
- Time to passage of first stool or flatus (canalization time)
- Effect on nausea and vomiting
- Adverse effects

Notes
- Subgroup of 50 vertebral arthrodesis patients not considered for this review.
- Only hysterectomy and cholecystectomy subgroup considered for analysis.
- Placebo: Fructose

Risk of bias
Manani 1982

(Continued)

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Mieny 1972

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<tr>
<td>Design: Parallel group RCT</td>
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<td>Randomisation: Random number tables</td>
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<tr>
<td>Time point of randomisation: After surgery</td>
</tr>
<tr>
<td>Blinding: Double blind, no details given</td>
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<tr>
<td>Intention-to-treat analysis: Yes, no details reported</td>
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<td>Reporting of patient baseline characteristics: Not reported</td>
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<td>Withdrawals: Not stated</td>
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<tr>
<td>Sample size calculation: Not used</td>
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<table>
<thead>
<tr>
<th>Participants</th>
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<tbody>
<tr>
<td>Setting: Single centre trial, South Africa</td>
</tr>
<tr>
<td>Number eligible: Not stated</td>
</tr>
<tr>
<td>Number enrolled: 89</td>
</tr>
<tr>
<td>Number in intervention group: 44</td>
</tr>
<tr>
<td>Number in control group: 45</td>
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<tr>
<td>Number of withdrawals (intervention/placebo): Not reported</td>
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<tr>
<td>Inclusion criteria: Not reported</td>
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<tr>
<td>Exclusion criteria: Exploration of the common bile duct, other intraabdominal procedures</td>
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<tr>
<td>Type of surgery: Elective cholecystectomy</td>
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<table>
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<tr>
<th>Interventions</th>
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<tbody>
<tr>
<td>Study drug: Panthothenic Acid</td>
</tr>
<tr>
<td>Dose: 500mg</td>
</tr>
<tr>
<td>Administration:</td>
</tr>
<tr>
<td>- Route: 24 hour interval, intravenous administration</td>
</tr>
<tr>
<td>- Start: Immediately after surgery</td>
</tr>
<tr>
<td>- Duration: Maximum 3 days</td>
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<tr>
<td>Control: Placebo</td>
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<tr>
<td>Planned follow up duration: Not reported</td>
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<tr>
<td>Co-Medication for ileus allowed at discretion of the physician: Not reported</td>
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<tr>
<td>Type of anaesthesia: Not reported</td>
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<tr>
<td>Type of analgesia: Not reported</td>
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<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to passage of first flatus</td>
</tr>
<tr>
<td>Time to return of mixing sounds and propulsive sounds</td>
</tr>
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Notes

Risk of bias

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<th>Item</th>
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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</table>
**Orlando 1994**

**Methods**
- Design: Parallel group RCT
- Randomisation: Randomisation list, no details available
- Time point of randomisation: Unclear
- Blinding: Double blind, no details given
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

**Participants**
- Setting: Single centre trial, Italy
- Number eligible: Not stated
- Number enrolled: 40
- Number in intervention group: 20 (19)
- Number in control group: 20
- Number of withdrawals (intervention/placebo): 1/0
- Inclusion criteria: Not in detail reported (abdominal surgery)
- Exclusion criteria: Allergy against anticholinergic drugs, bromides, bowel obstruction, obstruction or infection within the urinary passage
- Type of surgery: Cholecystectomy, emergency abdominal surgery with opening the peritoneum

**Interventions**
- Study drug: Neostigmine
- Dose: 2 Puffs (5.4mg/puff)
- Administration:
  - Route: 4 hour interval, endonasal administration
  - Start: On the day of operation
  - Duration: Maximum 4 days
- Control: Placebo
- Planned follow up duration: Not reported
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: Not reported
- Type of analgesia: Not reported

**Outcomes**
- Time to passage of first flatus or stool (canalization time)
- Adverse effects

**Notes**

**Risk of bias**

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<td>D - Not used</td>
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</table>

**Rimbäck 1990**

**Methods**
- Design: Parallel group RCT
- Randomisation: No details available
- Time point of randomisation: Before surgery
Rimbäck 1990

(Continued)

Blinding: Double blind, no details given
Intention-to-treat analysis: Yes, no details reported
Reporting of patient baseline characteristics: Yes
Withdrawals: Not stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, Sweden
Number eligible: Not stated
Number enrolled: 30
Number in intervention group: 15
Number in control group: 15
Number of withdrawals (intervention/placebo): Not reported
Inclusion criteria: Stool frequency between 3 stools daily and 3 stools weekly
Exclusion criteria: Laxatives or drugs with effect on the gastrointestinal motility, history of gastrointestinal disease or complication to surgery, possibility of pregnancy
Type of surgery: Elective cholecystectomy

Interventions
Study drug: Lidocaine
Dose: 100 mg bolus, 3mg/min
Administration:
- Route: Bolus, then continuous infusion over 24 hours, intravenous administration
- Start: 30 minutes before surgery
- Duration: 24 hours after surgery
Control: Placebo
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: GA
Type of analgesia: Meperidine, intramuscular

Outcomes
Electromyographic analysis
Radioopaque marker to study transit time
Time to passage of first flatus
Time to passage of first stool
Amount of analgesia used
Blood pressure and heart rate
Adverse effects

Notes
Data extracted from figures

Risk of bias

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<tr>
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<td>Unclear</td>
<td>B - Unclear</td>
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</table>

Roberts 1995

Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Before surgery
Blinding: Double blind, identical packages of suppositories and tablets
Intention-to-treat analysis: Yes, no details reported
Reporting of patient baseline characteristics: Not reported
Withdrawals: Not stated
Sample size calculation: Not used

Participants
Setting: Teaching Hospital, United Kingdom
Number eligible: Not stated
Number enrolled: 14
Number in intervention group: 7
Number in control group: 7
Number of withdrawals (intervention/placebo): Reported in relation to manometric outcomes: 5 - allocation stated
Inclusion criteria: Not reported
Exclusion criteria: Drugs with effect on the gastrointestinal motility, disseminated malignant disease, neurologic or benign colonic disease, previous gastrointestinal surgery (except appendectomy)
Type of surgery: Distal left colonic anastomosis (localized colonic malignancy)

Interventions
Study drug: Cisapride
- Dose A: 20mg
- Dose B: 30mg
Administration:
- Route A: 8 hour interval/day, oral administration
- Route B: 8 hour interval/day, rectal administration
- Start A: 1 day before surgery
- Start B: On the day of surgery
- Duration: Until passage of first flatus
Control: Placebo
Planned follow up duration: Until passage of first flatus
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: GA
Type of analgesia: Pethidine bolus 0.7-1mg/kg, 1mg/kg/3h, subcutaneous infusion

Outcomes
Electromyographic analysis
Continuous manometric recording
Time to passage of first flatus
Occurrence of bowel sounds

Notes

Risk of bias

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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
### Methods
- **Design:** Parallel group RCT
- **Randomisation:** Sealed envelopes, no further details available
- **Time point of randomisation:** Unclear
- **Blinding:** Double blind, no details given
- **Intention-to-treat analysis:** No
- **Reporting of patient baseline characteristics:** Yes
- **Withdrawals:** Stated
- **Sample size calculation:** Not used

### Participants
- **Setting:** Teaching Hospital, United Kingdom
- **Number eligible:** Not stated
- **Number enrolled:** 96
- **Number in intervention group:** 47
- **Number in control group:** 44
- **Number of withdrawals (intervention/placebo):** 5- allocation not stated
- **Inclusion criteria:** Not reported
- **Exclusion criteria:** Drugs with effect on the gastrointestinal motility within 1 month of surgery, major resections of the small and large intestines, significant renal, hepatic or cardiac disease, history of pancreatitis
- **Type of surgery:** Elective abdominal surgery

### Interventions
- **Study drug:** Ceruletide
- **Dose:** 2.5ng /kg/min
- **Administration:**
  - Route: Single dose, intravenous administration
  - Start: 1. POD
  - Duration: 1 hour
- **Control:** Placebo
- **Planned follow up duration:** Until resolution of ileus
- **Co-Medication for ileus allowed at discretion of the physician:** Allowed (stemetil (prochlorperazine) 12.5mg, intramuscular)
- **Type of anaesthesia:** Not reported
- **Type of analgesia:** Morphine 10mg i.m./4h, intramuscular

### Outcomes
- **Time to passage of first flatus**
- **Time to passage of first stool**
- **Time to first solid food**
- **Incidence of nausea and vomiting**
- **Postoperative complications**

### Notes

### Risk of bias

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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
**Methods**

Design: Parallel group RCT  
Randomisation: Using of a randomisation book  
Time point of randomisation: Before surgery  
Blinding: Double blind, identical packages, nursing and research staff, physicians and patients blinded  
Intention-to-treat analysis: No  
Reporting of patient baseline characteristics: Yes  
Withdrawals: Stated  
Sample size calculation: Used for endpoint nasogastric intubation

**Participants**

Setting: Single centre trial, USA  
Number eligible: Not stated  
Number enrolled: 150  
Number in intervention group: 75 (65)  
Number in control group: 75 (69)  
Number of withdrawals (intervention/placebo): 10/6  
Inclusion criteria: Primary resection of the colon or rectum  
Exclusion criteria: Preoperative factors (History of allergic reaction to erythromycin, -major abdominal or pelvic surgery (excluding appendectomy, cholecystectomy, hysterectomy), planned hepatic resection, metastatic disease, medication known to interact with erythromycin, history of ventricular arrhythmias, baseline QTc(QT/RR) >460ms, ejection fraction <30%), operative factors (need for ileostomy, resection incorporating the upper gastrointestinal tract, gross fecal spillage, need to leave nasogastric tube in, unexpected intra-abdominal adhesions)  
Type of surgery: Elective colorectal resection

**Interventions**

Study drug: Erythromycin  
Dose: 200 mg  
Administration:  
- Route: 6 hour interval, intravenous administration  
- Start: 1. POD  
- Duration: Until tolerance of solid food or maximum 5 days  
Control: Placebo  
Planned follow up duration: Not reported  
Co-Medication for ileus allowed at discretion of the physician: Allowed (cimetidine)  
Type of anaesthesia: Not reported  
Type of analgesia: Morphine, patient controlled analgesia

**Outcomes**

Time to passage of first stool/bowel movement  
Time to passage of first flatus  
Time to first solid food  
Length of hospital stay  
NG tube replacement  
12-lead ECG serial evaluations  
Adverse effects

**Notes**

**Risk of bias**

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<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
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</table>
**Methods**
- Design: Parallel group RCT
- Randomisation: Computer generated randomisation list generated by hospital pharmacy
- Time point of randomisation: Before and on the day of surgery
- Blinding: Double blind, identical packages, patient, care giver and assessor of outcome blinded
- Intention-to-treat analysis: Yes
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

**Participants**
- Setting: Single centre trial, USA
- Number eligible: 185
- Number enrolled: 79
- Number in intervention group A: 26
- Number in intervention group B: 26
- Number in control group: 26
- Number of withdrawals (intervention A/intervention B/placebo): 8/0/4
- Inclusion criteria: Age 18-78 years, generally healthy or well-controlled systemic disease
- Exclusion criteria: Treatment with corticosteroids or immunosuppressive drugs within 2 weeks before surgery, opioid analgesics within 4 weeks before surgery, likely to receive nonsteroidal anti-inflammatory drugs after surgery, Crohn's disease, history of abdominal radiation therapy, history of treatment with vinca alkaloids
- Type of surgery: Partial colectomy or total abdominal hysterectomy (simple or radical)

**Interventions**
- Study drug: ADL 8-2689 (Alvimopan)
  - Dose A: 1mg
  - Dose B: 6mg
- Administration:
  - Route: 2 hours before surgery, 12 hour interval, oral administration
  - Start: On the day of operation
  - Duration: Until first bowel movement or hospital discharge or maximum of 7 days
- Control: Placebo
- Planned follow up duration: Not reported
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: GA
- Type of analgesia: Morphine hydrochloride, patient controlled analgesia, intravenous

**Outcomes**
- Time to passage of first stool/bowel movement
- Time to passage of first flatus
- Time to tolerance of solid food
- Length of hospital stay
- Time until ready for discharge
- Time until actual discharge
- Amount of analgesia used
- Adverse effects

**Notes**

**Risk of bias**

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<th>Item</th>
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Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  
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Taguchi 2001

(Continued)

Allocation concealment?  Yes  A - Adequate

Thorup 1983

Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Before surgery
Blinding: Not reported
Intention-to-treat analysis: No
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Not used

Participants
Setting: Teaching Hospital, Denmark
Number eligible: Not stated
Number enrolled: 85
Number in intervention group: 43
Number in control group: 34
Number of withdrawals: 5/3
Inclusion criteria: Major abdominal surgery
Exclusion criteria: Peripheral arterial insufficiency, hepatic failure, suspected dihydroergotamine intolerance
Type of surgery: Major abdominal surgery (biliary-, colonic-, gastric operations and others)

Interventions
Study drug: Dihydroergotamine
Dose: 0.5mg
Administration:
- Route: 1-2 hours before surgery, 12 hour interval, subcutaneous administration
- Start: On the day of operation
- Duration: 7 days
Control: No details reported
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Allowed (oral bisacodyl, rectal DSS-dioctyl sodium sulfosuccinate)
Type of anaesthesia: Not reported
Type of analgesia: Not reported

Outcomes
Time to passage of first flatus
Time to passage of first stool
Number of doses laxatives used

Notes

Risk of bias

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<tr>
<td>Allocation concealment?</td>
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<td>B - Unclear</td>
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</table>

Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  
Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Methods
- **Design:** Parallel group RCT
- **Randomisation:** No details available
- **Time point of randomisation:** Unclear
- **Blinding:** Double blind, detail only given for radiologist assessing marker outcomes
- **Intention-to-treat analysis:** Yes, no details reported
- **Reporting of patient baseline characteristics:** Yes
- **Withdrawals:** Not stated
- **Sample size calculation:** Not used

### Participants
- **Setting:** Unclear, Sweden
- **Number eligible:** Not stated
- **Number enrolled:** 20
- **Number in intervention group:** 10
- **Number in control group:** 10
- **Number of withdrawals (intervention/placebo):** Not reported
- **Inclusion criteria:** Stool frequency between 3 stools daily and 3 stools weekly
- **Exclusion criteria:** Hepatic, renal, cardiovascular or hormonal diseases, laxatives and drugs with effect on the gastrointestinal motility, history of gastrointestinal diseases or complications to surgery, possibility to pregnancy
- **Type of surgery:** Elective cholecystectomy

### Interventions
- **Study drug:** Metoclopramide
- **Dose:** 20 mg
- **Administration:***
  - **Route:** 8 hour interval, intravenous administration
  - **Start:** Immediately after operation
  - **Duration:** Maximum of 10 injections or 4 days
  - **Control:** Placebo
  - **Planned follow up duration:** Until passage of first flatus or stool
  - **Co-Medication for ileus allowed at discretion of the physician:** Not reported
  - **Type of anaesthesia:** GA
  - **Type of analgesia:** Pethidine, intramuscular

### Outcomes
- **Electromyographic analysis**
- **Radioopaque marker to study transit time**
- **Time to passage of first flatus**
- **Time to passage of first stool**
- **Adverse effects**

### Notes
- Data extracted from figures

### Risk of bias

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</table>
Methods
Design: Parallel group RCT
Randomisation: No details available
Time point of randomisation: Unclear
Blinding: Double blind, no details given
Intention-to-treat analysis: Yes, no details reported
Reporting of patient baseline characteristics: Yes
Withdrawals: Not stated
Sample size calculation: Not used

Participants
Setting: Unclear, Sweden
Number eligible: Not stated
Number enrolled: 40
Number in intervention group: 20
Number in control group: 20
Number of withdrawals (intervention/placebo): Not reported
Inclusion criteria: Stool frequency between 3 stools daily and 3 stools weekly
Exclusion criteria: Hepatic, renal, cardiovascular disease, laxatives and drugs with effect on the gastrointestinal motility, history of gastrointestinal diseases or complications to surgery, possibility to pregnancy
Type of surgery: Elective cholecystectomy

Interventions
Study drug: Cisapride
Dose: 10 mg
Administration:
- Route: 12-24 hour interval, intravenous administration
- Start: On the day of operation
- Duration: Maximum of 6 injections
Control: Placebo
Planned follow up duration: Until passage of first flatus or stool
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: GA
Type of analgesia: Morphine, intramuscular

Outcomes
Electromyographic analysis
Radioopaque marker to study transit time
Time to passage of first flatus
Time to passage of first stool
Adverse effects

Notes

Risk of bias

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<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
### Viscusi 2006

#### Methods
- Design: Parallel group RCT
- Randomisation: No details available (1:1:1 ratio)
- Time point of randomisation: Before surgery
- Blinding: Double blind, no details given
- Intention-to-treat analysis: No- stated MITT-population*
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

#### Participants
- Setting: Multi centre Phase III trial, USA
- Number eligible: Not stated
- Number enrolled: 666
- Number in intervention group A: 220
- Number in intervention group B: 222 (221)
- Number in control group: 224
- Number excluded post randomisation (intervention A/intervention B/placebo): 51- allocation not stated
- Inclusion criteria: Age >18 years, laparotomy for partial small or large bowel resection, simple or radical total abdominal hysterectomy
- Exclusion criteria: Pregnancy, acute treatment with opioids less than 1 week before the study or chronic treatment with opioids less than 2 weeks before study, complete bowel obstruction or colectomy, colostomy, ileostomy, any other condition known to be associated with an increased risk of postoperative morbidity
- Type of surgery: Partial small or large bowel resection, simple or radical total abdominal hysterectomy

#### Interventions
- Study drug: Alvimopan
  - Dose A: 6mg
  - Dose B: 12mg
- Administration:
  - Route: 2 hours before surgery, 12 hour interval, oral administration
  - Start: 1. POD
  - Duration: until hospital discharge or maximum of 7 days
- Control: Placebo
- Planned follow up duration: Until hospital discharge or maximum of 10 POD
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: Not reported
- Type of analgesia: Opioid based patient controlled analgesia

#### Outcomes
- GI-3
- GI-2
- Time to passage of first stool/bowel movement
- Time to tolerance of solid food
- Length of hospital stay
- Amount of analgesic use
- Adverse effects

#### Notes
- *Modified intention to treat (MITT) -population: included all randomized patients who had a protocol-specified surgery, took at least one dose of study drug, and had an efficacy assessment (bowel movement, flatus, or solid food)

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**Risk of bias**

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*Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)*

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### Viscusi 2006

(Continued)

| Allocation concealment? | Unclear | B - Unclear |

### Von Ritter 1987

| Methods | Design: Parallel group RCT  
Randomisation: No details available  
Time point of randomisation: Unclear  
Blinding: Double blind, no details given  
Intention-to-treat analysis: Yes, no details reported  
Reporting of patient baseline characteristics: No  
Withdrawals: Not stated  
Sample size calculation: Not used |

| Participants | Setting: Single centre trial, South Africa  
Number eligible: Not stated  
Number enrolled: 32  
Number in intervention group: 17  
Number in control group: 15  
Number of withdrawals (intervention/placebo): Not reported  
Inclusion criteria: Not reported  
Exclusion criteria: Not reported  
Type of surgery: Biliary-, upper gastrointestinal tract-, colon-, miscellaneous surgery |

| Interventions | Study drug: Cisapride  
Dose: 10mg  
Administration:  
- Route: 4/6/8/12 hour interval, intravenous/intramuscular administration  
- Start: 1. POD  
- Duration: 48 hours  
Control: Placebo  
Planned follow up duration: Until passage of first flatus  
Co-Medication for ileus allowed at discretion of the physician: Not reported  
Type of anaesthesia: Not reported  
Type of analgesia: Not reported |

| Outcomes | Time to passage of first flatus  
Onset and intensity of borborygmi  
Color of gastric aspirate |

| Notes | Data extracted from figures |

### Risk of bias

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</table>
### Wilkinson 2002

**Methods**
- Design: Parallel group RCT
- Randomisation: Computer generated randomisation list
- Time point of randomisation: Before surgery
- Blinding: Double blind, surgical team, nursing staff and nuclear medicine staff were blinded
- Intention-to-treat analysis: No
- Reporting of patient baseline characteristics: Yes
- Withdrawals: Stated
- Sample size calculation: Not used

**Participants**
- Setting: Single centre trial, USA
- Number eligible: Not stated
- Number enrolled: 22
- Number in intervention group: 11
- Number in control group: 11 (10)
- Number of withdrawals (intervention/placebo): 1 - allocation not stated
- Inclusion criteria: Not reported
- Exclusion criteria: Not reported
- Type of surgery: Elective gastric bypass

**Interventions**
- Study drug: Erythromycin
- Dose: 250 mg
- Administration:
  - Route: 8 hour interval, intravenous administration
  - Start: 1. POD
  - Duration: Up to 2. POD
- Control: Placebo
- Planned follow up duration: Not reported
- Co-Medication for ileus allowed at discretion of the physician: Not reported
- Type of anaesthesia: Not reported
- Type of analgesia: Intrathecal narcotics, epidural analgesia, morphine, patient controlled analgesia

**Outcomes**
- Time to passage of first flatus
- Length of hospital stay
- HIDA (hepatic iminodiacetic acid)-Scan to evaluate bile excretion and proximal small bowel motility
- Adverse effects

**Notes**

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### Wolff 2004

**Methods**
- Design: Parallel group RCT
- Randomisation: No details available
Wolff 2004

(Continued)

Time point of randomisation: Before surgery
Blinding: Double blind, no details given
Intention-to-treat analysis: No-stated MITT-population*
Reporting of patient baseline characteristics: Yes
Withdrawals: Stated
Sample size calculation: Not used

Participants

Setting: Multi centre trial, USA
Number eligible: Not stated
Number enrolled: 510
Number in intervention group A: 169 (155)
Number in intervention group B: 176 (165)
Number in control group: 165 (149)
Number of withdrawals (intervention A/intervention B/placebo): 14/11/16
Inclusion criteria: Age > 18 years, partial small or large bowel resection with primary anastomosis, or radical total abdominal hysterectomy, postoperative pain management with patient-controlled analgesia with opioids, nasogastric tube removed at the end of surgery
Exclusion criteria: Not reported
Type of surgery: Partial small or large bowel resection with primary anastomosis, radical total abdominal hysterectomy

Interventions

Study drug: Alvimopan
- Dose A: 6 mg
- Dose B: 12 mg
Administration:
- Route: 2 hours before surgery, then 1. POD: 12 hour interval, oral administration
- Start: Day of surgery
- Duration: Until hospital discharge or maximum of 7 days
Control: Placebo
Planned follow up duration: Until hospital discharge or maximum of 10 days
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anaesthesia: Not reported
Type of analgesia: Opioid based patient controlled analgesia, intravenous

Outcomes

GI-3
GI-2
Length of hospital stay
Amount of analgesic used
Adverse effects

Notes

*Modified intention to treat (MITT)-population: included all treated patients who received protocol-specified surgeries and had at least one on-treatment primary efficacy evaluation (flatus, bowel movement, or tolerating solid food).

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Woods 1993

Methods
Design: Parallel group RCT
Randomisation: Quasi-randomisation with even and odd numbered patients
Time point of randomisation: Before surgery
Blinding: Not reported
Intention-to-treat analysis: Unclear
Reporting of patient baseline characteristics: Inadequate
Withdrawals: Stated
Sample size calculation: Not used

Participants
Setting: Single centre trial, USA
Number eligible: Not stated
Number enrolled: 83
Number in intervention group: 37
Number in control group: 32
Number of withdrawals(intervention/no treatment): 14- allocation not stated
Inclusion criteria: Not reported
Exclusion criteria: Not reported
Type of surgery: Elective abdominal aortic aneurysma resections, aorto-femoral, aorto-iliacal bypass

Interventions
Study drug: Albumin
Dose: Not reported. Albumin substitution if blood level <3.5 g/dl, replacement calculated, using the NIH-Formula
Administration:
- Route: Repeated administration, scheme not stated intravenous administration
- Start: Not in detail reported
- Duration: Until achievement of albumin level >3.5gm/dl
Control: No treatment
Planned follow up duration: Not reported
Co-Medication for ileus allowed at discretion of the physician: Not reported
Type of anesthesia: Not reported
Type of analgesia: Narcotics, patient controlled analgesia, epidural

Outcomes
Time to passage of first flatus
Time to first solid food intake
Length of hospital stay
Amount of analgesic used
Albumin, hemoglobin, potassium, chloride, sodium levels
Adverse effects

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td>No</td>
<td>C - Inadequate</td>
</tr>
</tbody>
</table>

Data in parentheses are numbers analysed unless otherwise indicated

RCT = Randomised controlled trial, GA = General anaesthesia, POD = postoperative day, PCEA = Patient controlled epidural analgesia
CCE = Cholecystectomy, DCO = Hospital discharge order, ASA classification = American Society of Anesthesiologists physical status classification
**Characteristics of excluded studies**  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloisio 1976</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Baig 2004</td>
<td>Duplicate Publication.</td>
</tr>
<tr>
<td>Boghaert 1987</td>
<td>Inadequate follow-up duration (maximum 2 hours).</td>
</tr>
<tr>
<td>Chan 2005</td>
<td>Effect of metoclopramide on intra-peritoneal chemotheraphy (IPC) induced ileus.</td>
</tr>
<tr>
<td>Chen JH 2005</td>
<td>Effect of water soluble contrast medium on POI*. Intervention not systemic pharmacologic treatment directed to treat POI*.</td>
</tr>
<tr>
<td>Chen JY 2005</td>
<td>Indirect effect of ketorolac on POI* indirect via opiate dose reduction.</td>
</tr>
<tr>
<td>Clevers 1988</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Costa 1994</td>
<td>Study population cesarean section.</td>
</tr>
<tr>
<td>Cyba 1985</td>
<td>Head to head comparison of ceruletide and neostigmine.</td>
</tr>
<tr>
<td>Davidson 1979</td>
<td>Effect of metoclopramide on postoperative ileus. Outcome not according to protocol: number of doses of metoclopramide or placebo until resolution of ileus.</td>
</tr>
<tr>
<td>Fanning 1999</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Ferraz 1995</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Gales 1999</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Garcia-Caballero 1993</td>
<td>Duplicate publication.</td>
</tr>
<tr>
<td>Jensen 1990</td>
<td>Study population inguinal hernia repair.</td>
</tr>
<tr>
<td>Kasparek 2007</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Kawaguchi 1985</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Kivalo 1970</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Kreis 2001</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Lykkegaard-Nielsen</td>
<td>Head to head comparison of ceruletide and metoclopramide.</td>
</tr>
<tr>
<td>Madsen 1983</td>
<td>Inadequate follow-up duration (maximum 24 hours).</td>
</tr>
<tr>
<td>Madsen 1986</td>
<td>Head to head comparison between ceruletide and neostigmine.</td>
</tr>
<tr>
<td>Myrhøj 1988</td>
<td>Inadequate follow-up duration (maximum 9 hours).</td>
</tr>
<tr>
<td>Nio 1980</td>
<td>Head-to-head comparison of prostaglandin F and panthothenic acid. Not randomised trial.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Olesen 1985</td>
<td>Head-to-head comparison of morphine and pethidine.</td>
</tr>
<tr>
<td>Olsen 1985</td>
<td>Intervention not systemic pharmacologic treatment directed to treat POI*.</td>
</tr>
<tr>
<td>Schmidt 2001</td>
<td>Review article on alvimopan. Not randomised trial.</td>
</tr>
<tr>
<td>Seta 2001</td>
<td>Not randomised trial.</td>
</tr>
<tr>
<td>Sinatra 2006</td>
<td>Effect of Rofecoxib on POI* indirect via opioid dosage reduction.</td>
</tr>
<tr>
<td>Thunedborg 1993</td>
<td>Study on healthy volunteers.</td>
</tr>
<tr>
<td>van Berge 1997</td>
<td>Study on healthy volunteers.</td>
</tr>
</tbody>
</table>

\*POI = postoperative ileus

---

**Characteristics of ongoing studies** [ordered by study ID]

**Asimadoline**

**Trial name or title**
A Randomized, Double-Blind, Placebo-Controlled Study Evaluating Asimadoline on the Duration of POI in Subjects Undergoing Laparoscopic/Hand-Assisted Lap Segmental Colonic Resection Secondary to Colon Cancer, Polypectomy or Diverticulitis

**Methods**

**Participants**
Subjects undergoing laparoscopic/hand-assisted lap segmental colonic resection secondary to colon cancer, polypectomy or diverticulitis

**Interventions**
Drug: Asimadoline

**Outcomes**
No details available

**Starting date**
January 2007

**Contact information**
Lahey Clinic
Burlington
Massachusetts, United States
01805
Status: Recruiting
Contact: Nancy Shinopulos
tel: 781-744-3035
nancy.m.shinopulos@lahey.org
### Lidozone

**Trial name or title**  
A prospective evaluation of the addition of intraoperative intravenous lidocaine infusion to general anesthetic in total abdominal hysterectomy

**Methods**

**Participants**  
Patients undergoing elective total abdominal hysterectomy

**Interventions**  
Drug: Lidocaine 1.5 mg/kg bolus, followed by continuous intravenous infusion at 3.0 mg/kg/hr

**Outcomes**

Primary outcomes:
- Length of hospital stay
- Total opioid use at 48 hours postoperatively

Secondary outcomes:
- Intraoperative data: BIS scores (to control depth of anesthesia)
- Intraoperative serum lidocaine levels
- Intraoperative opioid use
- Opioid use in the recovery room
- Patient Controlled Analgesia (PCA) morphine requirements postoperatively up to 48 hours
- Oral pain controlling medication use up to 48 hours postoperatively if IV PCA discontinued before 48 hours
- Verbal Analogue Scale (VAS) pain scores in recovery room and during first 2 days post-operatively
- Incidence of side effects that can be attributed to local anesthetic toxicity;
- Incidence of nausea and vomiting and anti-emetic use up to 48 hours postoperatively
- Time of first flatus and first bowel movement.

**Starting date**  
November 2006

**Contact information**  
ILIA Charapov MD  
tel: 613-2605795  
charapov@rogers.com  
The Ottawa Hospital  
Ottawa  
Ontario, Canada  
K1H 8L6

**Notes**

ClinicalTrials.gov identifier:  
NCT00443040  
Study ID numbers:  
ASMP2004
### Lidocaine/Ketamin

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>A randomised controlled trial of lidocaine infusion plus ketamine injection versus placebo to decrease postoperative ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Patients undergoing elective or urgent colon surgery with an anastomotic procedure</td>
</tr>
<tr>
<td>Interventions</td>
<td>Drug: Lidocaine infusion plus ketamine injection or placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcomes:</td>
</tr>
<tr>
<td></td>
<td>- Mean time after surgery to completion of the following postoperative markers:</td>
</tr>
<tr>
<td></td>
<td>- Drinking and retaining 500ml clear fluids</td>
</tr>
<tr>
<td></td>
<td>- Presence of bowel sounds</td>
</tr>
<tr>
<td></td>
<td>- Passage of flatus</td>
</tr>
<tr>
<td></td>
<td>- Passage of stool</td>
</tr>
<tr>
<td></td>
<td>Secondary outcomes:</td>
</tr>
<tr>
<td></td>
<td>- Outcome pain after cough by VAS</td>
</tr>
<tr>
<td></td>
<td>- Narcotic usage</td>
</tr>
<tr>
<td></td>
<td>- Nausea</td>
</tr>
<tr>
<td></td>
<td>- Vomiting</td>
</tr>
<tr>
<td></td>
<td>- Infection, dehiscence and other surgical complications</td>
</tr>
<tr>
<td></td>
<td>- Time to readiness for discharge from hospital</td>
</tr>
<tr>
<td>Starting date</td>
<td>September 2005</td>
</tr>
<tr>
<td>Contact information</td>
<td>William PS McKay MD</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
</tr>
<tr>
<td></td>
<td>Saskatoon Health Region</td>
</tr>
<tr>
<td></td>
<td>University of Saskatchewan</td>
</tr>
<tr>
<td></td>
<td>410 22nd Street East</td>
</tr>
<tr>
<td></td>
<td>Saskatoon</td>
</tr>
<tr>
<td></td>
<td>Saskatchewan, Canada</td>
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<tr>
<td></td>
<td>S7K 5T6</td>
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<td>Notes</td>
<td>ClinicalTrials.gov identifier: NCT00229567</td>
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<tr>
<td></td>
<td>Study ID numbers:</td>
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<td></td>
<td>Bio-REB 03-1316</td>
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</table>
## Methylnaltrexone

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>A phase 3, double-blind, randomized, parallel-group, placebo-controlled study of intravenous (IV) methylnaltrexone bromide (MNTX) in the treatment of post-operative ileus (POI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Patients must be scheduled for a segmental colectomy</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Drug: Methylnaltrexone</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>No details available</td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td>Not available</td>
</tr>
</tbody>
</table>
| **Contact information** | David Jacobs MD  
etl: 914-784-1800  
djacobs@progenics.com  
Progenics Pharmaceuticals  
Tarrytown  
New York, United States  
10591 |
| **Notes**           | ClinicalTrials.gov identifier: NCT00401375  
Study ID numbers:  
MNTX 3301 |
DATA AND ANALYSES

Comparison 1. Alvimopan versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 GI-2</td>
<td>5</td>
<td>3215</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.52 [1.35, 1.71]</td>
</tr>
<tr>
<td>1.1 12mg Alvimopan versus Placebo</td>
<td>5</td>
<td>2181</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.59 [1.33, 1.90]</td>
</tr>
<tr>
<td>1.2 6mg Alvimopan versus Placebo</td>
<td>3</td>
<td>1034</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.41 [1.22, 1.63]</td>
</tr>
<tr>
<td>2 GI-3</td>
<td>4</td>
<td>2586</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.30 [1.19, 1.42]</td>
</tr>
<tr>
<td>2.1 12mg Alvimopan versus Placebo</td>
<td>4</td>
<td>1552</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.30 [1.16, 1.46]</td>
</tr>
<tr>
<td>2.2 6mg Alvimopan versus Placebo</td>
<td>3</td>
<td>1034</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.31 [1.15, 1.50]</td>
</tr>
<tr>
<td>3 Time to passage of first stool</td>
<td>4</td>
<td>2020</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.70 [1.43, 2.02]</td>
</tr>
<tr>
<td>3.1 12mg Alvimopan versus Placebo</td>
<td>3</td>
<td>1238</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.74 [1.29, 2.34]</td>
</tr>
<tr>
<td>3.2 6mg Alvimopan versus Placebo</td>
<td>3</td>
<td>782</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.60 [1.32, 1.92]</td>
</tr>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>4</td>
<td>2020</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.25 [1.06, 1.48]</td>
</tr>
<tr>
<td>4.1 12mg Alvimopan versus Placebo</td>
<td>3</td>
<td>1238</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.14 [1.00, 1.29]</td>
</tr>
<tr>
<td>4.2 6mg Alvimopan versus Placebo</td>
<td>3</td>
<td>782</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.57 [1.04, 2.37]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>6</td>
<td>3267</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.33 [1.24, 1.43]</td>
</tr>
<tr>
<td>5.1 12mg Alvimopan versus Placebo</td>
<td>5</td>
<td>2181</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.31 [1.20, 1.43]</td>
</tr>
<tr>
<td>5.2 6mg Alvimopan versus Placebo</td>
<td>4</td>
<td>1086</td>
<td>Hazard Ratio (Fixed, 95% CI)</td>
<td>1.38 [1.22, 1.57]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>2</td>
<td>562</td>
<td>Hazard Ratio (Random, 95% CI)</td>
<td>1.67 [0.86, 3.23]</td>
</tr>
</tbody>
</table>

Comparison 2. Cholecystokinin-like acting drugs versus Placebo or No treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>4</td>
<td>257</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.86 [0.71, 1.04]</td>
</tr>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>2</td>
<td>141</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.93 [0.90, 0.97]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>2</td>
<td>141</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.81 [0.68, 0.97]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>2</td>
<td>148</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.77 [0.55, 1.08]</td>
</tr>
</tbody>
</table>
### Comparison 3. Cisapride versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>4</td>
<td>181</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.72 [0.54, 0.97]</td>
</tr>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>2</td>
<td>72</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.89 [0.71, 1.10]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>2</td>
<td>72</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.86 [0.72, 1.01]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>5</td>
<td>146</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.89 [0.79, 1.01]</td>
</tr>
</tbody>
</table>

### Comparison 4. Dihydroergotamine versus No treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>2</td>
<td>123</td>
<td>Ratio of the Medians (Random, 95% CI)</td>
<td>0.71 [0.43, 1.18]</td>
</tr>
</tbody>
</table>

### Comparison 5. Dopaminantagonists versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>1</td>
<td>20</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.96 [0.68, 1.37]</td>
</tr>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>1</td>
<td>93</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.90 [0.80, 1.02]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>3</td>
<td>239</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.94 [0.66, 1.33]</td>
</tr>
</tbody>
</table>

### Comparison 6. Erythromycin versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>3</td>
<td>233</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.99 [0.90, 1.08]</td>
</tr>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>3</td>
<td>233</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>1.04 [0.93, 1.15]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>4</td>
<td>254</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>1.00 [0.90, 1.11]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>4</td>
<td>254</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.95 [0.88, 1.03]</td>
</tr>
</tbody>
</table>
### Comparison 7. Lidocaine versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>2</td>
<td>68</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.83 [0.73, 0.95]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>2</td>
<td>78</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.89 [0.73, 1.10]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>3</td>
<td>108</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.83 [0.79, 0.88]</td>
</tr>
</tbody>
</table>

### Comparison 8. Neostigmine versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>1</td>
<td>35</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.80 [0.65, 0.99]</td>
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<tr>
<td>6 Time to passage of first flatus</td>
<td>1</td>
<td>39</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.57 [0.33, 1.01]</td>
</tr>
</tbody>
</table>

### Comparison 9. Propranolol versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>1</td>
<td>39</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.37 [0.29, 0.46]</td>
</tr>
<tr>
<td>6 Time to first passage of flatus</td>
<td>2</td>
<td>66</td>
<td>Ratio of the Means (Fixed, 95% CI)</td>
<td>0.91 [0.74, 1.11]</td>
</tr>
</tbody>
</table>

### Comparison 10. Propranolol and Neostigmine versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Time to passage of first stool</td>
<td>2</td>
<td>70</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.85 [0.62, 1.16]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>1</td>
<td>37</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.80 [0.61, 1.05]</td>
</tr>
</tbody>
</table>
### Comparison 11. Albumin versus No treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Time to tolerance of regular diet</td>
<td>1</td>
<td>69</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>1.11 [0.95, 1.29]</td>
</tr>
<tr>
<td>5 Length of hospital stay</td>
<td>1</td>
<td>69</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>1.09 [0.88, 1.34]</td>
</tr>
</tbody>
</table>

### Comparison 12. Fructose 1,6 Disphosphate versus Fructose

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Time to passage of first flatus</td>
<td>1</td>
<td>100</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>0.84 [0.72, 0.98]</td>
</tr>
</tbody>
</table>

### Comparison 13. Pantothen acid versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Time to passage of first flatus</td>
<td>1</td>
<td>89</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>1.00 [0.85, 1.17]</td>
</tr>
</tbody>
</table>

### Comparison 14. Vasopressin versus Placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Length of hospital stay</td>
<td>1</td>
<td>60</td>
<td>Ratio of the Means (Random, 95% CI)</td>
<td>1.14 [0.86, 1.52]</td>
</tr>
<tr>
<td>6 Time to passage of first flatus</td>
<td>1</td>
<td>60</td>
<td>Ratio of the Medians (Random, 95% CI)</td>
<td>0.72 [0.45, 1.14]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Alvimopan versus Placebo, Outcome 1 GI-2.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 1 Alvimopan versus Placebo  
**Outcome:** 1 GI-2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Subtotal (95% CI)</th>
<th>Heterogeneity: Tau²</th>
<th>Chi²</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.27 (0.1423)</td>
<td></td>
<td>10.5%</td>
<td>1.31 [ 0.99, 1.73 ]</td>
<td>0.03</td>
<td>12.12</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.802 (0.1198)</td>
<td></td>
<td>12.7%</td>
<td>2.23 [ 1.76, 2.82 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ludwig 2006</td>
<td>317</td>
<td>312</td>
<td>0.4054 (0.083)</td>
<td></td>
<td>17.3%</td>
<td>1.50 [ 1.27, 1.76 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.3074 (0.121)</td>
<td></td>
<td>12.6%</td>
<td>1.36 [ 1.07, 1.72 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>165</td>
<td>149</td>
<td>0.5128 (0.1283)</td>
<td></td>
<td>11.8%</td>
<td>1.67 [ 1.30, 2.15 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64.9%</td>
<td>1.59 [ 1.33, 1.90 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: Tau² = 0.03; Chi² = 12.12, df = 4 (P = 0.02); I² = 67%  
Test for overall effect: Z = 5.09 (P < 0.00001) |
| 2 6mg Alvimopan versus Placebo    |           |         |                    |              |        |                   |                     |       |    |     |
| Delaney 2005                      | 141       | 145     | 0.3784 (0.1411)    |              | 10.6%  | 1.46 [ 1.11, 1.93 ] |                     |       |    |     |
| Viscusi 2006                      | 220       | 224     | 0.3364 (0.1175)    |              | 13.0%  | 1.40 [ 1.11, 1.76 ] |                     |       |    |     |
| Wolff 2004                        | 155       | 149     | 0.322 (0.1312)     |              | 11.5%  | 1.38 [ 1.07, 1.78 ] |                     |       |    |     |
| **Subtotal (95% CI)**             |           |         |                   |              | 35.1%  | 1.41 [ 1.22, 1.63 ] |                     |       |    |     |
| Heterogeneity: Tau² = 0.0; Chi² = 2 (P = 0.96); I² = 0.0%  
Test for overall effect: Z = 4.62 (P < 0.00001) |
| **Total (95% CI)**                |           |         |                   |              | 100.0% | 1.52 [ 1.35, 1.71 ] |                     |       |    |     |
| Heterogeneity: Tau² = 0.01; Chi² = 13.85, df = 7 (P = 0.05); I² = 49%  
Test for overall effect: Z = 7.01 (P < 0.00001) |
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (SE)</td>
<td>IV ,Random, 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.27 (0.1423)</td>
<td>1.31 [0.99, 1.73]</td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.802 (0.1198)</td>
<td>2.23 [1.76, 2.82]</td>
<td></td>
</tr>
<tr>
<td>Ludwig 2006</td>
<td>317</td>
<td>312</td>
<td>0.4054 (0.083)</td>
<td>1.50 [1.27, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.3074 (0.121)</td>
<td>1.36 [1.07, 1.72]</td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>165</td>
<td>149</td>
<td>0.5128 (0.1283)</td>
<td>1.67 [1.30, 2.15]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.59 [1.33, 1.90]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.03; Chi² = 12.12, df = 4 (P = 0.02); I² =67%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.09 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (SE)</td>
<td>IV ,Random, 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.3784 (0.1411)</td>
<td>1.46 [1.11, 1.93]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.3364 (0.1175)</td>
<td>1.40 [1.11, 1.76]</td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>155</td>
<td>149</td>
<td>0.322 (0.1312)</td>
<td>1.38 [1.07, 1.78]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.41 [1.22, 1.63]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.0; Chi² = 0.09, df = 2 (P = 0.96); I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.62 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Analysis 1.2. Comparison 1 Alvimopan versus Placebo, Outcome 2 GI-3.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 1 Alvimopan versus Placebo  
**Outcome:** 2 GI-3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (SE)</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.0%</td>
<td>1.28 [0.99, 1.65]</td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>138 145 0.2468 (0.1287)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408 102 0.1484 (0.1216)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221 224 0.2311 (0.1026)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>165 149 0.4317 (0.123)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57.3%</td>
<td>1.30 [1.16, 1.46]</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 2.88, df = 3 (P = 0.41); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 4.44 (P &lt; 0.00001)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.5%</td>
<td>1.45 [1.13, 1.85]</td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>141 145 0.3715 (0.1257)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220 224 0.2151 (0.1059)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>155 149 0.2468 (0.1261)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.7%</td>
<td>1.31 [1.15, 1.50]</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 0.95, df = 2 (P = 0.62); I² = 0.0%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.97 (P = 0.000073)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.30 [1.19, 1.42]</td>
</tr>
<tr>
<td>Heterogeneity: Ch² = 3.85, df = 6 (P = 0.70); I² = 0.0%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.95 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Ch² = 0.01, df = 1 (P = 0.92); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)  
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### Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)

#### Comparison: Alvimopan versus Placebo

#### Outcome: GI-3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N =</td>
<td>N =</td>
<td></td>
<td>(IV,Fixed,95% CI)</td>
<td>(IV,Fixed,95% CI)</td>
</tr>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td>138</td>
<td>145</td>
<td>0.2468 (0.1287)</td>
<td>1.28 [0.99, 1.65]</td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.1484 (0.1216)</td>
<td>1.16 [0.91, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.2311 (0.1026)</td>
<td>1.26 [1.03, 1.54]</td>
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</tr>
<tr>
<td>Wolff 2004</td>
<td>165</td>
<td>149</td>
<td>0.4317 (0.123)</td>
<td>1.54 [1.21, 1.96]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.30 [1.16, 1.46]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.88, df = 3 (P = 0.41); I² = 0.0%

Test for overall effect: Z = 4.44 (P < 0.00001)

---

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N =</td>
<td>N =</td>
<td></td>
<td>(IV,Fixed,95% CI)</td>
<td>(IV,Fixed,95% CI)</td>
</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td>141</td>
<td>145</td>
<td>0.3715 (0.1257)</td>
<td>1.45 [1.13, 1.85]</td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.2151 (0.1059)</td>
<td>1.24 [1.01, 1.53]</td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>155</td>
<td>149</td>
<td>0.2468 (0.1261)</td>
<td>1.28 [1.00, 1.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.31 [1.15, 1.50]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0.0%

Test for overall effect: Z = 3.97 (P = 0.000073)
### Analysis 1.3. Comparison 1 Alvimopan versus Placebo, Outcome 3 Time to passage of first stool.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 1 Alvimopan versus Placebo

**Outcome:** 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.3852 (0.1401)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.8458 (0.1216)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.4187 (0.1185)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57.7 %</td>
<td>1.74 [ 1.29, 2.34 ]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.05; Chi² = 8.50; df = 2 (P = 0.01); I² = 76%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 3.68 (P = 0.00024)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.4382 (0.1383)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26</td>
<td>26</td>
<td>1.0647 (0.4144)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.4317 (0.1162)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.3 %</td>
<td>1.60 [ 1.32, 1.92 ]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 2.21; df = 2 (P = 0.33); I² = 10%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.92 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>1.70 [ 1.43, 2.02 ]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.03; Chi² = 11.49; df = 5 (P = 0.04); I² = 56%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 5.95 (P &lt; 0.00001)</td>
<td></td>
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</tr>
</tbody>
</table>
### Alvimopan versus Placebo

**Outcome:** Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.3852 (0.1401)</td>
<td>1.47</td>
<td>[1.12, 1.93]</td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.8458 (0.1216)</td>
<td>2.33</td>
<td>[1.84, 2.96]</td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.4187 (0.1185)</td>
<td>1.52</td>
<td>[1.20, 1.92]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>1.74</strong></td>
<td>[<strong>1.29, 2.34</strong>]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 76\%$

Test for overall effect: $Z = 3.68$ ($P = 0.00024$)

### Alvimopan versus Placebo

**Outcome:** Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.4382 (0.1383)</td>
<td>1.55</td>
<td>[1.18, 2.03]</td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26</td>
<td>26</td>
<td>1.0647 (0.4144)</td>
<td>2.90</td>
<td>[1.29, 6.53]</td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.4317 (0.1162)</td>
<td>1.54</td>
<td>[1.23, 1.93]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>1.60</strong></td>
<td>[<strong>1.32, 1.92</strong>]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 10\%$

Test for overall effect: $Z = 4.92$ ($P < 0.00001$)
### Analysis 1.4. Comparison 1 Alvimopan versus Placebo, Outcome 4 Time to tolerance of regular diet.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 1 Alvimopan versus Placebo

**Outcome:** 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio W</th>
<th>Weight Hazard Ratio</th>
<th>Hazard Ratio IV</th>
<th>Random,95% CI</th>
<th>Weight IV</th>
<th>Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.1133 (0.1238)</td>
<td>17.7 %</td>
<td>1.12 [ 0.88, 1.43 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.0861 (0.1083)</td>
<td>19.4 %</td>
<td>1.09 [ 0.88, 1.35 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.1823 (0.1034)</td>
<td>20.0 %</td>
<td>1.20 [ 0.98, 1.47 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>57.0 %</td>
<td>1.14 [ 1.00, 1.29 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.44, df = 2 (P = 0.80); I^2 =0.0$

Test for overall effect: $Z = 2.03 (P = 0.042)$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio W</th>
<th>Weight Hazard Ratio</th>
<th>Hazard Ratio IV</th>
<th>Random,95% CI</th>
<th>Weight IV</th>
<th>Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.2623 (0.1242)</td>
<td>17.6 %</td>
<td>1.30 [ 1.02, 1.66 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26</td>
<td>26</td>
<td>1.3083 (0.3267)</td>
<td>5.5 %</td>
<td>3.70 [ 1.95, 7.02 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.1739 (0.1043)</td>
<td>19.9 %</td>
<td>1.19 [ 0.97, 1.46 ]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>43.0 %</td>
<td>1.57 [ 1.04, 2.37 ]</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.10; \chi^2 = 10.95, df = 2 (P = 0.004); I^2 =82$

Test for overall effect: $Z = 2.14 (P = 0.032)$

| Total (95% CI) |           |         |                        | 100.0 %        | 1.25 [ 1.06, 1.48 ] |                |               |               |               |

Heterogeneity: $\tau^2 = 0.03; \chi^2 = 13.39, df = 5 (P = 0.02); I^2 =63$

Test for overall effect: $Z = 2.65 (P = 0.0080)$

0.5 1 2

Favours control Favours treatment

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Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults (Review)

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## Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 1 Alvimopan versus Placebo

**Outcome:** 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td></td>
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</tr>
<tr>
<td>Delaney 2005</td>
<td>138</td>
<td>145</td>
<td>0.1133 (0.1238)</td>
<td>1.12 [0.88, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408</td>
<td>102</td>
<td>0.0861 (0.1083)</td>
<td>1.09 [0.88, 1.35]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>221</td>
<td>224</td>
<td>0.1823 (0.1034)</td>
<td>1.20 [0.98, 1.47]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.14 [1.00, 1.29]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.0; \ \chi^2 = 0.44, \ df = 2 (P = 0.80); \ I^2 = 0.0\%

Test for overall effect: \( Z = 2.03 (P = 0.042) \)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.2623 (0.1242)</td>
<td>1.30 [1.02, 1.66]</td>
<td></td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26</td>
<td>26</td>
<td>1.3083 (0.3267)</td>
<td>3.70 [1.95, 7.02]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.1739 (0.1043)</td>
<td>1.19 [0.97, 1.46]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.57 [1.04, 2.37]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.10; \ \chi^2 = 10.95, \ df = 2 (P = 0.004); \ I^2 = 82\%

Test for overall effect: \( Z = 2.14 (P = 0.032) \)
## Analysis 1.5. Comparison 1 Alvimopan versus Placebo, Outcome 5 Length of hospital stay.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: 1 Alvimopan versus Placebo
Outcome: 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
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</thead>
<tbody>
<tr>
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<td>N N (SE)</td>
<td>IV Fixed, 95% CI</td>
<td>IV Fixed, 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 12mg Alvimopan versus Placebo</td>
<td>Delaney 2005</td>
<td>138 145</td>
<td>0.1655 (0.1219)</td>
<td>9.3%</td>
<td>1.18 [0.93, 1.50]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herzog 2006</td>
<td>408 102</td>
<td>0.1222 (0.1213)</td>
<td>9.4%</td>
<td>1.13 [0.89, 1.43]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ludwig 2006</td>
<td>317 312</td>
<td>0.3364 (0.0733)</td>
<td>25.7%</td>
<td>1.40 [1.21, 1.62]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viscusi 2006</td>
<td>221 224</td>
<td>0.27 (0.1026)</td>
<td>13.1%</td>
<td>1.31 [1.07, 1.60]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wolff 2004</td>
<td>165 149</td>
<td>0.3506 (0.1196)</td>
<td>9.7%</td>
<td>1.42 [1.12, 1.80]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>67.1%</td>
<td>1.31 [1.20, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.49, df = 4 (P = 0.48); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.00 (P &lt; 0.00001)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 6mg Alvimopan versus Placebo</td>
<td>Delaney 2005</td>
<td>141 145</td>
<td>0.4054 (0.1215)</td>
<td>9.4%</td>
<td>1.50 [1.18, 1.90]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taguchi 2001</td>
<td>26 26</td>
<td>0.8754 (0.3278)</td>
<td>1.3%</td>
<td>2.40 [1.26, 4.56]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viscusi 2006</td>
<td>220 224</td>
<td>0.2776 (0.1034)</td>
<td>12.9%</td>
<td>1.32 [1.08, 1.62]</td>
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<tr>
<td></td>
<td>Wolff 2004</td>
<td>155 149</td>
<td>0.2231 (0.1218)</td>
<td>9.3%</td>
<td>1.25 [0.98, 1.59]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td>32.9%</td>
<td>1.38 [1.22, 1.57]</td>
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<tr>
<td>Heterogeneity: Chi² = 4.16, df = 3 (P = 0.24); I² = 28%</td>
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<tr>
<td>Test for overall effect: Z = 4.97 (P &lt; 0.00001)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
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<td></td>
<td></td>
<td>100.0%</td>
<td>1.33 [1.24, 1.43]</td>
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<tr>
<td>Heterogeneity: Chi² = 8.06, df = 8 (P = 0.43); I² = 1%</td>
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<tr>
<td>Test for overall effect: Z = 7.76 (P &lt; 0.00001)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0.0%</td>
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</tr>
</tbody>
</table>

Favours control Favours treatment
Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: 1 Alvimopan versus Placebo
Outcome: 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
</tr>
<tr>
<td>1     12mg Alvimopan versus Placebo</td>
<td></td>
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</tr>
<tr>
<td>Delaney 2005</td>
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<td>1.18 [0.93, 1.50]</td>
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<tr>
<td>Herzog 2006</td>
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<td>102</td>
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<td>Ludwig 2006</td>
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<td>0.27 (0.1026)</td>
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<tr>
<td>Wolff 2004</td>
<td>165</td>
<td>149</td>
<td>0.3506 (0.1196)</td>
<td>1.42 [1.12, 1.80]</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**
- Heterogeneity: Chi$^2$ = 3.49, df = 4 (P = 0.48); I$^2$ = 0.0%
- Test for overall effect: Z = 6.00 (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>IV, Fixed, 95% CI</td>
<td>IV, Fixed, 95% CI</td>
<td></td>
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<tr>
<td>2     6mg Alvimopan versus Placebo</td>
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<td></td>
</tr>
<tr>
<td>Delaney 2005</td>
<td>141</td>
<td>145</td>
<td>0.4054 (0.1215)</td>
<td>1.50 [1.18, 1.90]</td>
<td></td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26</td>
<td>26</td>
<td>0.8754 (0.3278)</td>
<td>2.40 [1.26, 4.56]</td>
<td></td>
</tr>
<tr>
<td>Viscusi 2006</td>
<td>220</td>
<td>224</td>
<td>0.2776 (0.1034)</td>
<td>1.32 [1.08, 1.62]</td>
<td></td>
</tr>
<tr>
<td>Wolff 2004</td>
<td>155</td>
<td>149</td>
<td>0.2231 (0.1218)</td>
<td>1.25 [0.98, 1.59]</td>
<td></td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**
- Heterogeneity: Chi$^2$ = 4.16, df = 3 (P = 0.24); I$^2$ = 28%
- Test for overall effect: Z = 4.97 (P < 0.00001)
Analysis 1.6. Comparison 1 Alvimopan versus Placebo, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 1 Alvimopan versus Placebo

Outcome: 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Alvimopan</th>
<th>Placebo</th>
<th>log [Hazard Ratio]</th>
<th>Hazard Ratio</th>
<th>Weight</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (SE)</td>
<td>IV,Random,95% CI</td>
<td>N (SE)</td>
<td>IV,Random,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herzog 2006</td>
<td>408 (102)</td>
<td>0.2311 (0.1117)</td>
<td>58.8 %</td>
<td>1.26 [ 1.01, 1.57 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taguchi 2001</td>
<td>26 (26)</td>
<td>0.9162 (0.3089)</td>
<td>41.2 %</td>
<td>2.50 [ 1.36, 4.58 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>1.67 [ 0.86, 3.23 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.18; \chi^2 = 4.35, df = 1 (P = 0.04); I^2 = 77\%$

Test for overall effect: $Z = 1.52 (P = 0.13)$

<table>
<thead>
<tr>
<th>Favours control</th>
<th>Favours treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Analysis 2.3. Comparison 2 Cholecystokinin-like acting drugs versus Placebo or No treatment, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cerulein/Ceruleotide</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (SE)</td>
<td>IV,Random,95% CI</td>
<td>N (SE)</td>
<td>IV,Random,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez 1979</td>
<td>25 (25)</td>
<td>0.0359 (0.0602)</td>
<td>27.8 %</td>
<td>1.04 [ 0.92, 1.17 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreira 1980</td>
<td>29 (30)</td>
<td>-0.515 (0.115)</td>
<td>21.9 %</td>
<td>0.60 [ 0.48, 0.75 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frisse 1985</td>
<td>27 (30)</td>
<td>-0.1967 (0.1197)</td>
<td>21.4 %</td>
<td>0.82 [ 0.65, 1.04 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadek 1988</td>
<td>47 (44)</td>
<td>-0.031 (0.0496)</td>
<td>28.8 %</td>
<td>0.97 [ 0.88, 1.07 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.86 [ 0.71, 1.04 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.03; \chi^2 = 19.80, df = 3 (P = 0.000199); I^2 = 85\%$

Test for overall effect: $Z = 1.35 (P = 0.12)$

<table>
<thead>
<tr>
<th>Favours treatment</th>
<th>Favours control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
### Analysis 2.4. Comparison 2 Cholecystokinin-like acting drugs versus Placebo or No treatment, Outcome 4

**Time to tolerance of regular diet.**

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cerulein/ Ceruletide</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 1979</td>
<td>25</td>
<td>25</td>
<td>-0.059 (0.0241)</td>
<td></td>
<td>70.9 %</td>
<td>0.94 [ 0.90, 0.99 ]</td>
</tr>
<tr>
<td>Sadek 1988</td>
<td>47</td>
<td>44</td>
<td>-0.096 (0.0376)</td>
<td></td>
<td>29.1 %</td>
<td>0.91 [ 0.84, 0.98 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² =0.0%

Test for overall effect: Z = 3.44 (P = 0.00058)

### Analysis 2.5. Comparison 2 Cholecystokinin-like acting drugs versus Placebo or No treatment, Outcome 5

**Length of hospital stay.**

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cerulein/ Ceruletide</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 1979</td>
<td>25</td>
<td>25</td>
<td>-0.299 (0.146)</td>
<td></td>
<td>39.7 %</td>
<td>0.74 [ 0.56, 0.99 ]</td>
</tr>
<tr>
<td>Sadek 1988</td>
<td>47</td>
<td>44</td>
<td>-0.1541 (0.1185)</td>
<td></td>
<td>60.3 %</td>
<td>0.86 [ 0.68, 1.08 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: Chi² = 0.59, df = 1 (P = 0.44); I² =0.0%

Test for overall effect: Z = 2.30 (P = 0.021)
### Analysis 2.6. Comparison 2 Cholecystokinin-like acting drugs versus Placebo or No treatment, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cerulein/ Ceruletide</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frisell 1985</td>
<td>27</td>
<td>30</td>
<td>-0.1206 (0.1005)</td>
<td>62.0%</td>
<td>0.89</td>
<td>[0.73, 1.08]</td>
</tr>
<tr>
<td>Sadek 1988</td>
<td>47</td>
<td>44</td>
<td>-0.474 (0.2)</td>
<td>38.0%</td>
<td>0.62</td>
<td>[0.42, 0.92]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td>0.77</td>
<td>[0.55, 1.08]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 2.49$, df = 1 ($P = 0.11$); $I^2 = 60$

Test for overall effect: $Z = 1.49$ ($P = 0.14$)

---

### Analysis 3.3. Comparison 3 Cisapride versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 3 Cisapride versus Placebo

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cisapride</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1999</td>
<td>17</td>
<td>18</td>
<td>-0.2231 (0.0746)</td>
<td>27.9%</td>
<td>0.80</td>
<td>[0.69, 0.93]</td>
</tr>
<tr>
<td>Clevers 1991</td>
<td>17</td>
<td>20</td>
<td>0.0 (0.113)</td>
<td>25.6%</td>
<td>1.00</td>
<td>[0.80, 1.25]</td>
</tr>
<tr>
<td>Hallerbeck 1991</td>
<td>36</td>
<td>33</td>
<td>-0.6821 (0.1034)</td>
<td>26.3%</td>
<td>0.51</td>
<td>[0.41, 0.62]</td>
</tr>
<tr>
<td>Tallesson 1991(2)</td>
<td>20</td>
<td>20</td>
<td>-0.4182 (0.1914)</td>
<td>20.2%</td>
<td>0.66</td>
<td>[0.45, 0.96]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td>0.72</td>
<td>[0.54, 0.97]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 22.14$, df = 3 ($P = 0.00006$); $I^2 = 86$

Test for overall effect: $Z = 2.16$ ($P = 0.031$)
## Analysis 3.4. Comparison 3 Cisapride versus Placebo, Outcome 4 Time to tolerance of regular diet.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 3 Cisapride versus Placebo

**Outcome:** 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cisapride</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1999</td>
<td>17</td>
<td>18</td>
<td>-0.223 (0.0709)</td>
<td></td>
<td>53.4 %</td>
<td>0.80 [0.70, 0.92]</td>
</tr>
<tr>
<td>Clevers 1991</td>
<td>17</td>
<td>20</td>
<td>0.0 (0.0915)</td>
<td></td>
<td>46.6 %</td>
<td>1.00 [0.84, 1.20]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favours treatment</strong></td>
<td>100.0 %</td>
<td>0.89 [0.71, 1.10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau ^2 = 0.02; \) Chi² = 3.71, df = 1 (P = 0.05); \( I^2 = 73\% \)

Test for overall effect: \( Z = 1.07 \) (P = 0.28)

## Analysis 3.5. Comparison 3 Cisapride versus Placebo, Outcome 5 Length of hospital stay.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 3 Cisapride versus Placebo

**Outcome:** 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cisapride</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1999</td>
<td>17</td>
<td>18</td>
<td>-0.1973 (0.0962)</td>
<td></td>
<td>79.0 %</td>
<td>0.82 [0.68, 0.99]</td>
</tr>
<tr>
<td>Clevers 1991</td>
<td>17</td>
<td>20</td>
<td>0.0 (0.1866)</td>
<td></td>
<td>21.0 %</td>
<td>1.00 [0.69, 1.44]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>0.2</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favours treatment</strong></td>
<td>100.0 %</td>
<td>0.86 [0.72, 1.01]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); \( I^2 = 0.0\% \)

Test for overall effect: \( Z = 1.82 \) (P = 0.068)
Analysis 3.6.  Comparison 3 Cisapride versus Placebo, Outcome 6 Time to passage of first flatus.

Review:  Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison:  3 Cisapride versus Placebo

Outcome:  6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Cisapride N</th>
<th>Placebo N</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benson 1994</td>
<td>11</td>
<td>12</td>
<td>-0.307 (0.157)</td>
<td>15.6 %</td>
<td>0.74 [ 0.54, 1.00 ]</td>
</tr>
<tr>
<td>Clevers 1991</td>
<td>17</td>
<td>20</td>
<td>0.0 (0.1019)</td>
<td>37.0 %</td>
<td>1.00 [ 0.82, 1.22 ]</td>
</tr>
<tr>
<td>Roberts 1995</td>
<td>7</td>
<td>7</td>
<td>-0.1865 (0.1406)</td>
<td>19.4 %</td>
<td>0.83 [ 0.63, 1.09 ]</td>
</tr>
<tr>
<td>Tollesson 1991(2)</td>
<td>20</td>
<td>20</td>
<td>-0.0759 (0.1281)</td>
<td>23.4 %</td>
<td>0.93 [ 0.72, 1.19 ]</td>
</tr>
<tr>
<td>Von Ritter 1987</td>
<td>17</td>
<td>15</td>
<td>-0.227 (0.291)</td>
<td>4.5 %</td>
<td>0.80 [ 0.45, 1.41 ]</td>
</tr>
</tbody>
</table>

Total (95% CI)

Heterogeneity: Chi² = 3.27, df = 4 (P = 0.51); I² = 0.0%

Test for overall effect: Z = 1.81 (P = 0.070)

Analysis 4.3.  Comparison 4 Dihydroergotamine versus No treatment, Outcome 3 Time to passage of first stool.

Review:  Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison:  4 Dihydroergotamine versus No treatment

Outcome:  3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dihydroergotamine N</th>
<th>No treatment N</th>
<th>log [Ratio of the Medians] (SE)</th>
<th>Ratio of the Medians</th>
<th>Weight</th>
<th>Ratio of the Medians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altaparmakov 1984</td>
<td>23</td>
<td>23</td>
<td>-0.5819 (0.0803)</td>
<td>53.5 %</td>
<td>0.56 [ 0.48, 0.65 ]</td>
<td></td>
</tr>
<tr>
<td>Thorup 1983</td>
<td>43</td>
<td>34</td>
<td>-0.0659 (0.158)</td>
<td>46.5 %</td>
<td>0.94 [ 0.69, 1.28 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)

Heterogeneity: Tau² = 0.12; Chi² = 8.48, df = 1 (P = 0.004); I² = 88%

Test for overall effect: Z = 1.33 (P = 0.18)
### Analysis 5.3. Comparison 5 Dopaminantagonists versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 5 Dopaminantagonists versus Placebo

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Metoclopramide</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means (95% CI)</th>
<th>Weight</th>
<th>Ratio of the Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tollesson 1991(1)</td>
<td>10</td>
<td>10</td>
<td>-0.0392 (0.1792)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.96</td>
<td>[0.68, 1.37]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.22 (P = 0.83)

### Analysis 5.4. Comparison 5 Dopaminantagonists versus Placebo, Outcome 4 Time to tolerance of regular diet.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 5 Dopaminantagonists versus Placebo

Outcome: 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Metoclopramide</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means (95% CI)</th>
<th>Weight</th>
<th>Ratio of the Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheape 1991</td>
<td>40</td>
<td>53</td>
<td>-0.105 (0.063)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.90</td>
<td>[0.80, 1.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.67 (P = 0.096)
### Analysis 5.6. Comparison 5 Dopaminantagonists versus Placebo, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 5 Dopaminantagonists versus Placebo

Outcome: 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dopaminantagonist</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>(SE)</td>
<td>IV/Ratio,95% CI</td>
<td></td>
<td>IV/Ratio,95% CI</td>
</tr>
<tr>
<td>Conte 1983</td>
<td>84</td>
<td>80</td>
<td>-0.301 (0.0836)</td>
<td></td>
<td>46.7 %</td>
<td>0.74 [ 0.63, 0.87 ]</td>
</tr>
<tr>
<td>Jepsen 1986</td>
<td>30</td>
<td>25</td>
<td>0.2271 (0.2444)</td>
<td></td>
<td>26.6 %</td>
<td>1.25 [ 0.78, 2.02 ]</td>
</tr>
<tr>
<td>Tollesson 1991(1)</td>
<td>10</td>
<td>10</td>
<td>0.0571 (0.2427)</td>
<td></td>
<td>26.7 %</td>
<td>1.06 [ 0.66, 1.70 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: Tau² = 0.06; Chi² = 5.60, df = 2 (P = 0.06); I² =64%

Test for overall effect: Z = 0.36 (P = 0.72)

---

### Analysis 6.3. Comparison 6 Erythromycin versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 6 Erythromycin versus Placebo

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Erythromycin</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>(SE)</td>
<td>IV/Fixed,95% CI</td>
<td></td>
<td>IV/Fixed,95% CI</td>
</tr>
<tr>
<td>Bonacini 1993</td>
<td>41</td>
<td>36</td>
<td>0.021 (0.0856)</td>
<td></td>
<td>27.4 %</td>
<td>1.02 [ 0.86, 1.21 ]</td>
</tr>
<tr>
<td>Lightfoot 2007</td>
<td>11</td>
<td>11</td>
<td>0.1823 (0.255)</td>
<td></td>
<td>3.1 %</td>
<td>1.20 [ 0.73, 1.98 ]</td>
</tr>
<tr>
<td>Smith 2000</td>
<td>65</td>
<td>69</td>
<td>-0.0377 (0.0537)</td>
<td></td>
<td>69.5 %</td>
<td>0.96 [ 0.87, 1.07 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² =0.0%

Test for overall effect: Z = 0.33 (P = 0.74)
### Analysis 6.4. Comparison 6 Erythromycin versus Placebo, Outcome 4 Time to tolerance of regular diet.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 6 Erythromycin versus Placebo  
**Outcome:** 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Erythromycin</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means (IV, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Ratio of the Means (IV, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonacini 1993</td>
<td>41</td>
<td>36</td>
<td>-0.0183 (0.1813)</td>
<td></td>
<td>8.8%</td>
<td>0.98 [0.69, 1.40]</td>
</tr>
<tr>
<td>Lightfoot 2007</td>
<td>11</td>
<td>11</td>
<td>0.1177 (0.2382)</td>
<td></td>
<td>5.1%</td>
<td>1.12 [0.71, 1.79]</td>
</tr>
<tr>
<td>Smith 2000</td>
<td>65</td>
<td>69</td>
<td>0.0363 (0.0581)</td>
<td></td>
<td>86.0%</td>
<td>1.04 [0.93, 1.16]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Heterogeneity: $\chi^2 = 0.21$, df = 2 ($P = 0.90$); $I^2 = 0.0\%$  
Test for overall effect: $Z = 0.66$ ($P = 0.51$)

![Favours treatment vs Favours control](image)

### Analysis 6.5. Comparison 6 Erythromycin versus Placebo, Outcome 5 Length of hospital stay.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 6 Erythromycin versus Placebo  
**Outcome:** 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Erythromycin</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means (IV, Fixed, 95% CI)</th>
<th>Weight</th>
<th>Ratio of the Means (IV, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonacini 1993</td>
<td>41</td>
<td>36</td>
<td>0.0168 (0.2155)</td>
<td></td>
<td>5.7%</td>
<td>1.02 [0.67, 1.55]</td>
</tr>
<tr>
<td>Lightfoot 2007</td>
<td>11</td>
<td>11</td>
<td>0.1053 (0.2116)</td>
<td></td>
<td>5.9%</td>
<td>1.11 [0.73, 1.68]</td>
</tr>
<tr>
<td>Smith 2000</td>
<td>65</td>
<td>69</td>
<td>-0.0132 (0.0553)</td>
<td></td>
<td>86.2%</td>
<td>0.99 [0.89, 1.10]</td>
</tr>
<tr>
<td>Wilkinson 2002</td>
<td>11</td>
<td>10</td>
<td>0.1823 (0.3401)</td>
<td></td>
<td>2.3%</td>
<td>1.20 [0.62, 2.34]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Heterogeneity: $\chi^2 = 0.60$, df = 3 ($P = 0.90$); $I^2 = 0.0\%$  
Test for overall effect: $Z = 0.00$ ($P = 1.0$)

![Favours treatment vs Favours control](image)
Analysis 6.6. Comparison 6 Erythromycin versus Placebo, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 6 Erythromycin versus Placebo

Outcome: 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Erythromycin</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>(SE)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Bonacini 1993</td>
<td>41</td>
<td>36</td>
<td>0.0183 (0.1197)</td>
<td>11.7 %</td>
<td>1.02 [0.81, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Lightfoot 2007</td>
<td>11</td>
<td>11</td>
<td>0.0 (0.2337)</td>
<td>3.1 %</td>
<td>1.00 [0.63, 1.58]</td>
<td></td>
</tr>
<tr>
<td>Smith 2000</td>
<td>65</td>
<td>69</td>
<td>-0.0706 (0.0495)</td>
<td>68.6 %</td>
<td>0.93 [0.85, 1.03]</td>
<td></td>
</tr>
<tr>
<td>Wilkinson 2002</td>
<td>11</td>
<td>10</td>
<td>0.0 (0.1007)</td>
<td>16.6 %</td>
<td>1.00 [0.82, 1.22]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0 % 0.95 [0.88, 1.03]

Heterogeneity: Chi^2 = 0.78, df = 3 (P = 0.85); I^2 = 0.0%
Test for overall effect: Z = 1.13 (P = 0.26)

Analysis 7.3. Comparison 7 Lidocaine versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 7 Lidocaine versus Placebo

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lidocaine</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>(SE)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Groudine 1998</td>
<td>18</td>
<td>20</td>
<td>-0.1788 (0.0704)</td>
<td>85.8 %</td>
<td>0.84 [0.73, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Rimbck 1990</td>
<td>15</td>
<td>15</td>
<td>-0.2177 (0.1734)</td>
<td>14.2 %</td>
<td>0.80 [0.57, 1.13]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0 % 0.83 [0.73, 0.95]

Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 = 0.0%
Test for overall effect: Z = 2.83 (P = 0.0047)
Analysis 7.5. Comparison 7 Lidocaine versus Placebo, Outcome 5 Length of hospital stay.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: 7 Lidocaine versus Placebo
Outcome: 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lidocaine N</th>
<th>Placebo N</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV, Random, 95% CI</th>
<th>Weight %</th>
<th>Ratio of the Means IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groudine 1998</td>
<td>18</td>
<td>20</td>
<td>-0.2423 (0.1038)</td>
<td></td>
<td>39.6 %</td>
<td>0.78 [0.64, 0.96]</td>
</tr>
<tr>
<td>Kuo 2006</td>
<td>20</td>
<td>20</td>
<td>-0.0286 (0.0361)</td>
<td></td>
<td>60.4 %</td>
<td>0.97 [0.91, 1.04]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.89 [0.73, 1.10]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 3.78, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.08 (P = 0.28)

Analysis 7.6. Comparison 7 Lidocaine versus Placebo, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: 7 Lidocaine versus Placebo
Outcome: 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lidocaine N</th>
<th>Placebo N</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV, Fixed, 95% CI</th>
<th>Weight %</th>
<th>Ratio of the Means IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groudine 1998</td>
<td>18</td>
<td>20</td>
<td>-0.3901 (0.1373)</td>
<td></td>
<td>3.4 %</td>
<td>0.68 [0.52, 0.89]</td>
</tr>
<tr>
<td>Kuo 2006</td>
<td>20</td>
<td>20</td>
<td>-0.1748 (0.026)</td>
<td></td>
<td>94.6 %</td>
<td>0.84 [0.80, 0.88]</td>
</tr>
<tr>
<td>Rimbd: 1990</td>
<td>15</td>
<td>15</td>
<td>-0.1 (0.1774)</td>
<td></td>
<td>2.0 %</td>
<td>0.90 [0.64, 1.28]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.83 [0.79, 0.88]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.58, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 7.14 (P < 0.00001)
Analysis 8.3. Comparison 8 Neostigmine versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: Neostigmine versus Placebo
Outcome: Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Neostigmine</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (SE) IV ,Random,95% CI</td>
<td>IV ,Random,95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallerbeck 1987(1)</td>
<td>18</td>
<td>17</td>
<td>-0.2218 (0.1067)</td>
<td>100.0</td>
<td>0.80</td>
<td>[ 0.65, 0.99 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.80</td>
<td>[ 0.65, 0.99 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 2.08 (P = 0.038)

Analysis 8.6. Comparison 8 Neostigmine versus Placebo, Outcome 6 Time to passage of first flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults
Comparison: Neostigmine versus Placebo
Outcome: Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Neostigmine</th>
<th>Placebo</th>
<th>log [Ratio of the Means]</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (SE) IV ,Random,95% CI</td>
<td>IV ,Random,95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orlando 1994</td>
<td>19</td>
<td>20</td>
<td>-0.556 (0.288)</td>
<td>100.0</td>
<td>0.57</td>
<td>[ 0.33, 1.01 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.57</td>
<td>[ 0.33, 1.01 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.93 (P = 0.054)
### Analysis 9.3. Comparison 9 Propranolol versus Placebo, Outcome 3 Time to passage of first stool.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 9 Propranolol versus Placebo

Outcome: 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Propranolol</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallebeck 1987(2)</td>
<td>20</td>
<td>19</td>
<td>-1.006 (0.1132)</td>
<td></td>
<td>100.0%</td>
<td>0.37 [ 0.29, 0.46 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: not applicable

Test for overall effect: Z = 8.89 (P < 0.00001)

### Analysis 9.6. Comparison 9 Propranolol versus Placebo, Outcome 6 Time to first passage of flatus.

Review: Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

Comparison: 9 Propranolol versus Placebo

Outcome: 6 Time to first passage of flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Propranolol</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferraz 2001</td>
<td>12</td>
<td>15</td>
<td>-0.141 (0.169)</td>
<td></td>
<td>37.6%</td>
<td>0.87 [ 0.62, 1.21 ]</td>
</tr>
<tr>
<td>Hallebeck 1987(2)</td>
<td>20</td>
<td>19</td>
<td>-0.0741 (0.1312)</td>
<td></td>
<td>62.4%</td>
<td>0.93 [ 0.72, 1.20 ]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² =0.0%

Test for overall effect: Z = 0.96 (P = 0.34)
### Analysis 10.3. Comparison 10 Propranolol and Neostigmine versus Placebo, Outcome 3 Time to passage of first stool.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 10 Propranolol and Neostigmine versus Placebo  
**Outcome:** 3 Time to passage of first stool

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Propra/Neostigm N</th>
<th>Placebo N</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV/Random,95% CI</th>
<th>Weight</th>
<th>Ratio of the Means IV/Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia 1993</td>
<td>17</td>
<td>20</td>
<td>0.0 (0.1261)</td>
<td>49.0 %</td>
<td>1.00 [ 0.78, 1.28 ]</td>
<td></td>
</tr>
<tr>
<td>Hallerbeck 1987(1)</td>
<td>16</td>
<td>17</td>
<td>-0.3204 (0.1176)</td>
<td>51.0 %</td>
<td>0.73 [ 0.58, 0.91 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.85 [ 0.62, 1.16 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.04; \chi^2 = 3.45, df = 1 (P = 0.06); I^2 = 71\
Test for overall effect: $Z = 1.02 (P = 0.31)$

---

### Analysis 10.6. Comparison 10 Propranolol and Neostigmine versus Placebo, Outcome 6 Time to passage of first flatus.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 10 Propranolol and Neostigmine versus Placebo  
**Outcome:** 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Propra/Neostigm N</th>
<th>No treatment N</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV/Random,95% CI</th>
<th>Weight</th>
<th>Ratio of the Means IV/Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia 1993</td>
<td>17</td>
<td>20</td>
<td>-0.223 (0.1369)</td>
<td>100.0 %</td>
<td>0.80 [ 0.61, 1.05 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>0.80 [ 0.61, 1.05 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: $Z = 1.63 (P = 0.10)$
### Analysis 11.4. Comparison 11 Albumin versus No treatment, Outcome 4 Time to tolerance of regular diet.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 11 Albumin versus No treatment  
**Outcome:** 4 Time to tolerance of regular diet

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Albumin</th>
<th>No treatment</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV,Random,95% CI</th>
<th>Weight</th>
<th>Ratio of the Means IV,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woods 1993</td>
<td>37</td>
<td>32</td>
<td>0.1006 (0.0786)</td>
<td></td>
<td>100.0%</td>
<td>1.11 [0.95, 1.29]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Heterogeneity: not applicable  
Test for overall effect: Z = 1.28 (P = 0.20)

### Analysis 11.5. Comparison 11 Albumin versus No treatment, Outcome 5 Length of hospital stay.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults  
**Comparison:** 11 Albumin versus No treatment  
**Outcome:** 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Albumin</th>
<th>No treatment</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV,Random,95% CI</th>
<th>Weight</th>
<th>Ratio of the Means IV,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woods 1993</td>
<td>37</td>
<td>32</td>
<td>0.083 (0.107)</td>
<td></td>
<td>100.0%</td>
<td>1.09 [0.88, 1.34]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.78 (P = 0.44)
### Analysis 12.6. Comparison 12 Fructose 1,6 Disphosphate versus Fructose, Outcome 6 Time to passage of first flatus.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Fruc(1,6)diphosphat</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manani 1982</td>
<td>50</td>
<td>50</td>
<td>-0.171 (0.0774)</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td></td>
<td>0.84 [ 0.72, 0.98 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 2.21 (P = 0.027)

### Analysis 13.6. Comparison 13 Pantothen acid versus Placebo, Outcome 6 Time to passage of first flatus.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Pantothen Acid</th>
<th>Placebo</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means</th>
<th>Weight</th>
<th>Ratio of the Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mieny 1972</td>
<td>44</td>
<td>45</td>
<td>-0.0020 (0.0811)</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td></td>
<td>1.00 [ 0.85, 1.17 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.02 (P = 0.98)
### Analysis 14.5. Comparison 14 Vasopressin versus Placebo, Outcome 5 Length of hospital stay.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 14 Vasopressin versus Placebo

**Outcome:** 5 Length of hospital stay

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasopressin</th>
<th>No treatment</th>
<th>log [Ratio of the Means] (SE)</th>
<th>Ratio of the Means IV(Random,95% CI)</th>
<th>Weight</th>
<th>Ratio of the Means IV(Random,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakansson 1985</td>
<td>30</td>
<td>30</td>
<td>0.133 (0.1448)</td>
<td></td>
<td>100.0%</td>
<td>1.14 [ 0.86, 1.52 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.14 [ 0.86, 1.52 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 0.92 (P = 0.36)

### Analysis 14.6. Comparison 14 Vasopressin versus Placebo, Outcome 6 Time to passage of first flatus.

**Review:** Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults

**Comparison:** 14 Vasopressin versus Placebo

**Outcome:** 6 Time to passage of first flatus

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasopressin</th>
<th>No treatment</th>
<th>log [Ratio of the Medians] (SE)</th>
<th>Ratio of the Medians IV(Random,95% CI)</th>
<th>Weight</th>
<th>Ratio of the Medians IV(Random,95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakansson 1985</td>
<td>30</td>
<td>30</td>
<td>-0.327 (0.235)</td>
<td></td>
<td>100.0%</td>
<td>0.72 [ 0.45, 1.14 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.72 [ 0.45, 1.14 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.39 (P = 0.16)

### WHAT’S NEW

Last assessed as up-to-date: 22 September 2007

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 August 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
</tbody>
</table>
HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 1, 2008

Date | Event | Description
--- | --- | ---
23 September 2007 | New citation required and conclusions have changed | Substantive amendment

CONTRIBUTIONS OF AUTHORS

Four reviewers (UT, LB, RK, MKO) independently performed appraisal of the methodological quality and extracted the data of all included trials in duplicate. Differences in the assessment of quality or data extraction between two reviewers were resolved by consensus. If necessary and possible, additional information was sought from the authors of the trials. Prespecified data extraction forms were used to record all data.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)
Abdomen [*surgery]; Gastrointestinal Agents [classification; *therapeutic use]; Intestinal Pseudo-Obstruction [*drug therapy]; Peristalsis [drug effects]; Postoperative Complications [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words
Adult; Humans