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

Traut U, Brügger L, Kunz R, Pauli-Magnus C, Haug K, Bucher H, Koller MT

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[Intervention 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 Cisapride has been withdrawn from the market due to adverse cardiac events in many countries.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 can not be recommended due to lack of evidence or absence of effect.

PLAIN LANGUAGE SUMMARY

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 (Kalff 1998, Kalff 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, perioperative 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 systemically 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/ceruletide 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 decapeptid ceruletide 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 (Tonini 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 acetycholinesterase 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 (paresis) 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 (pantothenic 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
#22 ((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 (paresis) 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 (pantothenic 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) 373
#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 (paresis) or (ileus) or (aton*) or (peristalsis) or (motility) or (adynam*) or (paralytic) 100669
#18 (intestines)or (alvimopan) or (purgative*) or (laxative*) or (dexpanthenol) or (ceruletide) or (procinetic) or (prokinetic) or (selective gastrointestinal opioid antagonists) or (cathartics) or (pantothenic 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

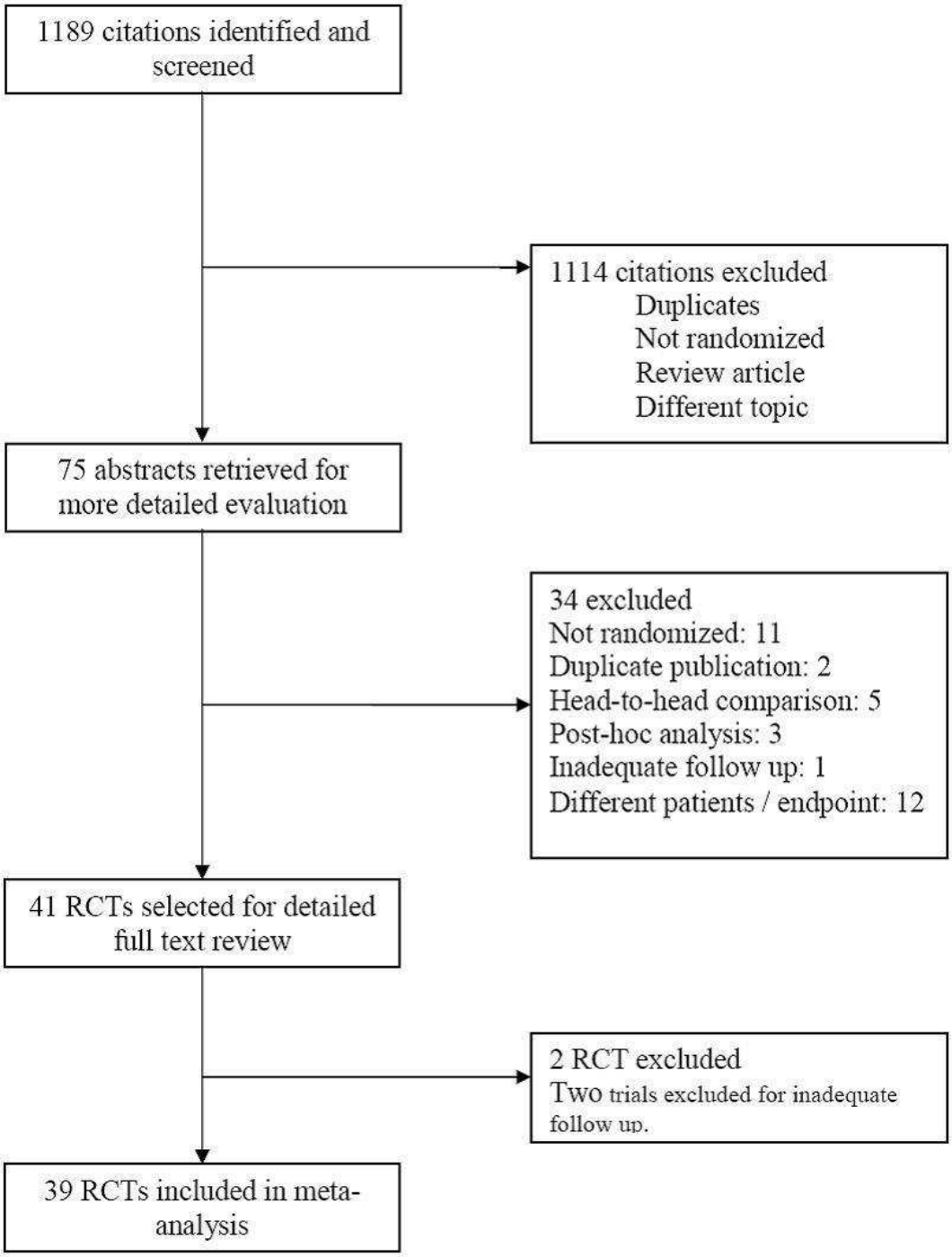
Searches and results below from saved search history from EMBASE SS for RCT/CCT are listed below
#17 #12 not #16 1665210
#16 #14 not #15 2675100
#15 #13 and #14 476674
#14 (ANIMAL or NONHUMAN) in DER 3151774
#13 HUMAN in DER 5823446
#12 #9 or #10 or #11 2665088
#11 (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB) 86449
#10 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB 471851
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 2452728
#8 "SINGLE-BLIND-PROCEDURE"/all subheadings 6660
#7 "DOUBLE-BLIND-PROCEDURE"/all subheadings 64218
#6 "PHASE-4-CLINICAL-TRIAL"/all subheadings 596
#5 "PHASE-3-CLINICAL-TRIAL"/all subheadings 7423
#4 "MULTICENTER-STUDY"/all subheadings 38817
#3 "CONTROLLED-STUDY"/all subheadings 2422081
#2 "RANDOMIZATION"/all subheadings 22563
#1 "RANDOMIZED-CONTROLLED-TRIAL"/all subheadings 119188
MEDLINE
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/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) 499842
#39 (colon*) or (gut) or (intestin*) or (bowel) 579621
#38 (paralysis) or (gastrointestinal motility) or (paresis) or (ileus) or (aton*) or (peristalsis)or (motility) or (adynam*) or (paralytic) 121965
#37 (intestines) or (alvimopan) or (purgative*) or (laxative*) or (dexpanthenol) or (ceruletide) or (procinetic) or (prokinetic) or (selective gastrointestinal opioid antagonists) or (cathartics) or (pantothenic acid) or (prostaglandins) or (anaesthetics) or (dihydroergotamine) or (erythromycin) or (adrenergic antagonists) or (cholecystokinin) or (vasopressins) or (caerulein) or (dopamine 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) 1746855
#36 #9 or #25 or #35 2255636
#35 #34 not (#9 or #25) 1495005
#34 #32 not #33 1963230
#33 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS)) 3981295
#32 #26 or #27 or #28 or #29 or #31 2636042
#31 (#30 in TI) or (#30 in AB) 1808238
#30 control* or prospectiv* or volunteer* 2549375
#29 PROSPECTIVE-STUDIES 219643
#28 FOLLOW-UP-STUDIES 336173
#27 explode EVALUATION-STUDIES/all subheadings 655695
#26 TG=COMPARATIVE-STUDY 0
#25 #24 not #9 404115
#24 #22 not #23 743777
#23 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS)) 3981295
#22 #10 or #11 or #12 or #13 or #15 or #16 or #17 or #18 or #19 or #20 or #21 844148
#21 RESEARCH-DESIGN 39763
#20 random* in AB 371259
#19 random* in TI 55674
#18 placebo* in AB 100158
#17 placebo* in TI 15711
#16 PLACEBOS 26294
#15 (#14 in TI) or (#14 in AB) 90239
#14 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*) 123962
#13 (clin* near trial*) in AB 107191
#12 (clin* near trial*) in TI 27408
#11 explode CLINICAL-TRIALS/all subheadings 187759
#10 CLINICAL-TRIAL in PT 431820
#9 #7 not #8 356516

#8 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS)) 3981295
#7 #1 or #2 or #3 or #4 or #5 or #6 389405
#6 SINGLE-BLIND-METHOD 10819
#5 DOUBLE-BLIND-METHOD 90364
#4 RANDOM-ALLOCATION 57287
#3 RANDOMIZED-CONTROLLED-TRIALS 41633
#2 CONTROLLED-CLINICAL-TRIAL in PT 74414
#1 RANDOMIZED-CONTROLLED-TRIAL in PT 232881
The Cochrane Central Register of Controlled Trials (CENTRAL): Searches and results from saved search history from the Cochrane Central of Clinical Trials database for RCT/CCT are listed below
#1 (intestines) or (alvimopan) or (purgative*) or (laxative*) or (dexpanthenol) or (ceruletide) or (procinetic) or (prokinetic) or (selective gastrointestinal opioid antagonists) or (cathartics) or (pantothenic acid) or (prostaglandins) or (anaesthetics) or (dihydroergotamine) or (erythromycin) or (adrenergic antagonists) or (cholecystokinin) or (vasopressins) or (caerulein) or (dopamine 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) in All Fields in all products 205562 edit delete
#2 (paralysis) or (gastrointestinal motility) or (paresis) or (ileus) or (aton*) or (peristalsis)or (motility) or (adynam*) or (paralytic) in All Fields in all products 2672 edit delete
#3 (laparo*) or (digestive surgery) or (abdom* surgery) or (aortic aneurysm/surgery) or (urologic surgical procedures) or (colorectal surgery) or (gynecologic surgical procedures) or (digestive system surgical procedures) or (obsteric surgical procedures) or (postoperative) or (postoperative) or (postoperative complications) or (postoperative care) or (postoperative period) in All Fields in all products 41563 edit delete
#4 (colon*) or (gut) or (intestin*) or (bowel) in All Fields in all products 21181 edit delete
#5 (#1 AND #2 AND #3 AND #4),

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 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.



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 and if 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(quartile3)-log(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 Furukuwa 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.

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 anaesthetic 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.

Nine trials reported outcomes directly for individual patients (Alvarez 1979, Benson 1994, Conte 1983, Ferraz 2001, Ferreira 1980, Hallerbäck 1987(2) , Orlando 1994, Sadek 1988, Von Ritter 1987). In this case the AFT model was used to compute summary estimates and standard errors (see 'Methods of the review'). For five trials, the summary POI restoration times had to be read off from figures according to treatment allocation (Benson 1994; Herzog 2006; Rimbäck 1990; Tollesson 1991(1); Von Ritter 1987). Five trials reported the mean or median restoration time according to treatment allocation but did not report dispersion parameters (Clevers 1991, Garcia 1993, Roberts 1995, Wilkinson 2002, Woods 1993). In these cases we used the imputation method to estimate the standard errors of the log ratio of the means (Furukawa 2006).

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, Frisell 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, Rimbäck 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 included 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 treatmen t

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 in treated 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

Seven trials investigated the effect of cisapride to shorten POI (Benson 1994, Brown 1999, Clevers 1991, Hallerbäck 1991, Roberts 1995, Tollesson 1991(2) , Von Ritter 1987). Methodological quality was acceptable in only one trial where all quality criteria but attrition were properly reported (Brown 1999). Of the remaining trials, no information on the randomization process was given and only two trials properly applied the intention to treat principle
(Tollesson 1991(2), Roberts 1995). Withdrawal of patients was stated, but often not in detail specified.

Time to passage of first stool

(Comparison 03, outcome 03)

Four trials reported on the effect of cisapride to reduce time to the passage of first stool (Clevers 1991, Hallerbäck 1991, Tollesson 1991(2) , Brown 1999). The pooled analysis encompassed a total of 181 patients allocated to cisapride or placebo. The mean time to passage of first stool was smaller in the cisapride group compared to the placebo group (pooled ratio of means 0.72 (95% CI 0.54, 0.97). Effect estimates across trials were heterogeneous and therefore the random effects model was used (I^2 = 86.5%). There was variation regarding duration of drug administration and the surgical interventions between the analysed trials. In two trials, the duration of drug administration was restricted to either 48 hours (Clevers 1991) or 56 hours (Hallerbäck 1991). These two trials did not show an effect on reduction of time to passage of first stool. Two other trials used longer durations of drug administration, namely 72 hours (Tollesson 1991(2)) and until hospital discharge (Brown 1999). These two trials showed a significant effect of cisapride on time to passage of first stool (Brown 1999, Tollesson 1991(2)).

Time to tolerance of regular diet and length of hospital stay

(Comparison 03, outcome 04 and outcome 05)

Two trials reported on time to tolerance of regular diet and on length of hospital stay (Clevers 1991, Brown 1999). The pooled analysis included a total of 72 patients in the cisapride and control group for both outcomes. Only the more recent trial of Brown et al showed a small effect on both outcomes. The random effects model showed a non-significant reduction in time to tolerance of regular diet with a pooled ratio of the means of 0.89 (95% CI 0.71, 1.10) in patients treated with cisapride compared to placebo. Similarly, the pooled ratio of the means of the fixed effects model for length of hospital stay was 0.86 (95% CI 0.72, 1.01) for cisapride compared to placebo.

*Time to passage of first flatus**

(Comparison 03, outcome 06)

Five trials investigated time to passage of first flatus or the combination of time to first flatus or first stool (Benson 1994, Clevers 1991, Roberts 1995, Tollesson 1991(2) , Von Ritter 1987). The pooled analysis of this comparison enrolled a total of 146 patients into the treatment and control groups. The effect was homogenous across all trials and showed a non-significant effect with a pooled ratio of the mean of time to passage of first flatus of 0.89 (95% CI 0.79, 1.01) in favour of cisapride compared to control.

* includes the combination of time to first flatus or stool

Summary of effect

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 trail 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 pa-

tients treated with metoclopramide compared to control (ratio of the means 0.96 (95% CI 0.68, 1.37).

One trail 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), Jepsen included patients with surgery of the aorta and iliac arteries (Jepsen 1986) 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, Rimbäck 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 (Rimbäck 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, Rimbäck 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, Rimbäck 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**

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 of 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 trail 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.

Table 1. Adverse drug reactions (Adr)

Study	Nr Treatment/ Control	Treatment	Control	Adr-Treatment	Adr-Control
Delaney 2005	296/153*	Alvimopan 6mg and 12mg	Placebo	Severe: Death 2/296 (0.7) Any of postoperative ileus, small bowel obstruction, anastomotic leakage, gastrointestinal disorders, infections 28/296 (9.4) Mild: Nausea 182/296 (61.5) Vomiting 60/296 (20.2) Abdominal distension 41/296 (13.8) Hypertension 37/296 (12.5)	Severe: Death 1 /153 (0.65) Any of postoperative ileus, small bowel obstruction, anastomotic leakage, gastrointestinal disorders, infections 28/153 (18.3) Mild: Nausea 104/153 (67.9) Vomiting 49/153 (32) Abdominal distension 24/153 (15.7) Hypertension 14/153 (9.2)

Table 1. Adverse drug reactions (Adr) (*Continued*)

				Headache 41/296 (13.8) Tachycardia 31/296 (10.5) Postoperative ileus 26/296 (8.8)	Headache 18/153 (11.8) Tachycardia 15/153 (9.8) Postoperative ileus 11/153 (7.2)
Herzog 2006	413/106*	Alvimopan, 12mg	Placebo	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)	Serious adverse events (life-threatening) 7/106 (6.6) Mild: Nausea 67/106 (65.7) Vomiting 27/106 (25.5) Abdominal distension 11/106 (10.4) Hypertension 6/106 (5.7) Headache 12/106 (11.3) Tachycardia 3/106 (2.8) Constipation 33/106 (31.1)
Ludwig 2006	329/325*	Alvimopan 12mg	Placebo	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)	Serious adverse events not reported Mild: Nausea 67/325 (66.2) Vomiting 80/325 (24.6) Abdominal pain 11/325 (3.4) Hypertension 34/325 (10.5) Tachycardia 35/325 (10.8) Postoperative Ileus 51/325 (15.7)
Taguchi 2001	52/26	ADL 8-2689 (Alvimopan), 1mg and 6mg	Placebo	Mild: Nausea 27% in 6mg- and 67% in 1mg in	Mild: Nausea 63% Vomiting 23%

Table 1. Adverse drug reactions (Adr) (*Continued*)

				alvimopan group Vomiting 0% in 6mg- and 26% in 1mg in alvimopan group	
Viscusi 2006	441/224*	Alvimopan, 6mg and 12mg	Placebo	Severe: Serious adverse events (requiring a prolonged hospital stay) 30/441 (6.8) (5.9 in 6mg group) Mild: Nausea 216/441 (48.9) Vomiting: 90/441 (20.4) Abdominal distension: 48/441 (10.9) Hypertension: 35/441 (7.9) Headache: 35/441 (7.9) Tachycardia: 17/441 (3.9) Postoperative ileus: 26/441 (5.9)	Severe: Serious adverse events (requiring a prolonged hospital stay) 26/224 (11.6) Mild: Nausea 121/224 (9.4) Vomiting: 56/224 (25) Abdominal distension: 29/224 (12.9) Hypertension: 23/224 (10.3) Headache: 18/224 (8.0) Tachycardia: 15/224 (6.7) Postoperative ileus: 23/224 (10.3)
Wolff 2004	345/165*	Alvimopan, 6mg and 12mg	Placebo	Serious adverse events 17/345 (5) (no details reported) Mild: Nausea 199/345 (57.7) Vomiting 76/345 (22.1) Abdominal distension 39/345 (11.3) Hypertension 42/345 (12.2) Tachycardia 41/345 (11.9) Postoperative ileus 25/345 (7.3)	Serious adverse events 2/165 (1.2) (no details reported) Mild: Nausea 106/165 (64.2) Vomiting 42/165 (25.5) Abdominal distension 25/165 (15.2) Hypertension 18/165 (10.9) Tachycardia 23/165 (13.9) Postoperative ileus 26/165 (15.8)

Table 1. Adverse drug reactions (Adr) (*Continued*)

Alvarez 1979	25/25	Cerulein 0.3mcg/kg	No Treatment	Mild: Not reported according to treatment arm Nausea 1/25 (4) Colic pain 1/25 (4) Tachycardia 3/25 (12) Diaforesis 3/25 (12)	Not reported for control group patients
Ferreira 1980	30/30	Cerulein 2ng/kg/min	No Treatment	Mild: Nausea 1/30 (3.3) Vomiting 1/30 (3.3) Colic pain 1/30 (3.3) Tachycardia 1/30 (3.3)	Not reported for control group patients
Frisell 1985	27/30	Cholecystokinin 75 IU	Placebo	Mild: Nausea 15/27 (55.5)	Mild: Nausea 5/30 (16.6)
Sadek 1988	47/44	Ceruletide 2.5ng/kg/min	Placebo	Severe: Pulmonary embolism 2/47 (4.3) "Intra-abdominal sepsis" 1/47 (2.1) (unclear) Mild: Nausea 31/47 (65.9) (encountered during first hour after infusion) Vomiting 11/47 (23.4) (encountered during first hour after infusion)	Mild: Nausea 11/44 (25) (encountered during first hour after infusion)
Benson 1994	11/12	Cisapride 30mg	Placebo	Mild: Hypokalemia 2/11 (18.2) (3.0-3.5mmol/l)	Mild: Hypokalemia 3/12 (25) (3.0-3.5mmol/l) Anastomotic

Table 1. Adverse drug reactions (Adr) (*Continued*)

					leakage 1/12 (8.3)
Brown 1999	17/18	Cisapride 20mg	Placebo	Severe: Transient ischemic attack 1/17 (5.9) Mild: Wound infection 3/17 (17.6)	Mild: Wound infection 2/18 (11.1) Azotemia 1/18 (5.5)
Clevers 1991	17/20	Cisapride 30mg	Placebo	Severe nausea 17/17 (100) Repeated vomiting 10/17 (58.8) Reinsertion of nasogastric tube 5/17 (29.4)	Severe nausea 18/20 (90) Repeated vomiting 10/20 (50) Reinsertion of nasogastric tube 2/20 (10)
Hallerbäck 1991	36/33	Cisapride 30mg	Placebo	Severe: Prolonged ileus 1/36 (2.7)	Severe: Prolonged ileus 0/33 (0)
Roberts 1995	7/7	Cisapride 20mg and 30mg	Placebo	Not reported	Not reported
Tollesson 1991(2)	20/20	Cisapride 10mg	Placebo	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Von Ritter 1987	17/15	Cisapride 10mg	Placebo	Not reported	Not reported
Altaparmakov 1984	23/23	Dihydroergotamine	No Treatment	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Thorup 1983	43/34	Dihydroergotamine	No Treatment	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Cheape 1991	40/53	Metoclopramide 10mg	Placebo	Severe: Death 1/40 (2.5) Reoperation 1/40 (2.5) Prolonged Ileus 7/40 (17.5)	Reoperation 1/53 (1.9) Prolonged Ileus 8/53 (15.1)

Table 1. Adverse drug reactions (Adr) (*Continued*)

Jepsen 1986	30/25	Metoclopramide 20mg	Placebo	Severe: Renal failure 1/30 (3.3)	Severe: Ischaemic colitis 2/25 (8) Intraperitoneal bleeding 2/25 (8) Abdominal wound rupture 1/25 (4)
Tollesson 1991(1)	10/10	Metoclopramide 20mg	Placebo	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Conte 1983	84/80	Bromopride 20mg	No Treatment	Mild: Nausea 36/84 (42.9) Abdominal pain 41/84 (48.8)	Mild: Nausea 51/80 (63.8) Abdominal pain 55/80 (68.8)
Bonancini 1993	41/36	Erythromycin 250mg	Placebo	Severe: Gastrointestinal bleeding 1/41 (2.4) Mild: Vomiting 3/41 (7.3) Abdominal pain 2/41 (4.9) Skin rash 3/41 (7.3)	Severe: Gastrointestinal bleeding 1/36 (2.7) Mild: Vomiting 2/36 (5.5) Abdominal pain 2/36 (5.5) Skin rash 1/36 (2.7)
Lightfoot 2006	11/11	Erythromycin 125mg	Placebo	Mild: Nausea (=2days) 4 (36) Vomiting (=2days) 3 (27) Abdominal pain (=2days) 2 (18) QTc prolongation(=2days) 1 (9)	Mild: Nausea (=2days) 2 (18) Vomiting (=2days) 1 (9) Abdominal pain (=2days) 0 (0) QTc prolongation (=2days) 1 (9)
Smith 2000	65/69	Erythromycin 200mg	Placebo	Mild: Severe Nausea 17/65 (26.1) Vomiting 11/65 (16.9) Skin rash 1/65 (1.5) Cardiac arrhythmia 0/65 (0)	Mild: Severe Nausea 18/69 (26.1) Vomiting 11/69 (15.9) Skin rash 0/69 (0) Cardiac arrhythmia 11/69 (15.9)

Table 1. Adverse drug reactions (Adr) (*Continued*)

Wilkinson 2002	11/10	Erythromycin 250mg	Placebo	Severe: Venous thrombosis 0/11 (0) Mild: Nausea 1/11 (0.91) Wound infection Superficial 1/11 (0.91)	Severe: Venous thrombosis 1/10 (1) Mild: Nausea 1/10 (1) Wound infection Superficial 1/10 (1)
Groudine 1998	18/20	Lidocaine 1.5 mg/kg Bolus, Infusion 3mg/min >70kg, 2mg/min <70kg	Placebo	Mild: Fever 1/18 (5.6)	Mild: Fever 2/20 (10)
Rimbäck 1990	15/15	Lidocaine 100 mg Bolus, 3mg/min	Placebo	Mild: Nausea 9/15 (60) Vomiting 7/15 (46.6) Sedation 2/15 (13.3)	Mild: Nausea 6/15 (40) Vomiting 8/15 (53.3)
Kuo 2006	20/20	Lidocaine 2mg/kg Bolus, Infusion 3mg/kg/h	Placebo	Mild: Bradycardia 3/20 (15) Nausea or vomiting 5/20 (25)	Mild: Nausea or vomiting 9/20 (45)
Orlando 1994	19/20	Neostigmine 2x 5.4mg	Placebo	Mild: Asthenia in all patients Fasciculations 0/19 (0) (no details reported) Miosis in combination with sweating and secretion 1/19 (5.2)	Mild: Asthenia in all patients Fasciculations 2/20 (10) (no details reported) Miosis in combination with sweating and secretion 0/20 (0)
Hallerbäck 1987(1)	I(Pro/Neo):21 II(N): 22 III(P): 19	Propranolol 10 mg and 80mg Neostigmine 0,5mg	Placebo	Mild: Nausea 1/21 (4.8) Pulmonary obstruction and itching 1/22 (4.5)	Not reported

Table 1. Adverse drug reactions (Adr) (*Continued*)

Ferraz 2001	12/15	Propranolol 40mg	No Treatment	Severe: Primary peritonitis 1/12 (8.3) Arrhythmia 1/12 (8.3)	Severe: Reoperation 2/15 (13.3)
Garcia 1993	17/20	Propranolol 7.5mg iv or 80mg Neostigmine 0.5mg	No Treatment	Not reported	Not reported
Hallerbäck 1987(2)	20/19	Propranolol 4mg and 10mg	Placebo	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Woods 1993	37/32	Albumin	No Treatment	Severe: Death 1/37 (2.7) Mild: Respiratory insufficiency and Bronchitis 5/37 (13.5) Total complication rate (35.1)	Total complication rate (31.3)
Manani 1982	50/50	Fructose-1,6 diphosphate 5g	Placebo (Fructose)	Mild: Nausea and/or Vomiting reported to resolve earlier in treatment group	Mild: Nausea and/or Vomiting reported to resolve earlier in treatment group
Mieny 1972	44/45	Panthothenic Acid	Placebo	Trial reported: Treatment was without adverse drug reactions	Trial reported: Treatment was without adverse drug reactions
Hakansson 1985	30/30	Vasopressin, 10IE	No Treatment	Trial reported: Treatment was without serious adverse drug reactions	Trial reported: Treatment was without serious adverse drug reactions
* 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 indicate 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 alvimoan 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. Cholecystokinin-like prokinetic drugs like cerulein/ceruletide 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 form 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 postoperative 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-methylnaltrexone (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, Methylnaltrexone).

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, dopamine-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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Altaparmakov 1984

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: Yes, details not reported Reporting of patient baseline characteristics: Yes Withdrawals: Not stated Sample size calculation: Not used
Participants	Setting: Unclear, Bulgaria, Germany Number eligible: Not stated Number enrolled: 46 Number in intervention group: 23 Number in control group: 23 Number of withdrawals: Not reported Inclusion criteria: Not reported Exclusion criteria: Not reported Type of surgery: Elective cholecystectomy
Interventions	Study drug: Dihydroergotamine with Heparin Dose: 0.5mg and 5000IE 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
Outcomes	Electromyographic analysis Time to passage of first bowel movement Occurrence of Bowel Sounds Adverse effects
Notes	POI defined as postoperative gut motility depressed

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Alvarez 1979

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, pylorolplasty, 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 Contious manometric recording Time to passage of first flatus Occurrence of bowel sounds Adverse effects
Notes	Data extracted from figures

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Brown 1999

Methods	Design: Parallel group RCT Randomisation: Sealed opaque envelopes, numbered medication kits distributed by pharmacy 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 hemicolectomy
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 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 stool/bowel movement Time to regular diet intake Length of hospital stay Hospital cost analysis Adverse effects
Notes	Military population

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Cheape 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: 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, stricturoplasty, 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 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, 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 post-operative 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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, cholecystojejunostomy, laparocele, hemicolectomy, 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Delaney 2005

Methods	Design: Parallel group RCT Randomisation: Stratified by type of surgery, (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 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 18-80years 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

Delaney 2005 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	Authors' judgement	Description

Ferraz 2001 (*Continued*)

Allocation concealment?	Unclear	D - Not used

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Frisell 1985

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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Garcia 1993

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, 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	

Garcia 1993 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Groudine 1998

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
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 anesthesia: 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

Groudine 1998 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Hakansson 1985

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: Not reported Exclusion criteria: Uremia, cardial, 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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

Item	Authors' judgement	Description

Hallerbäck 1987(1) (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Hallerbäck 1987(2)

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: Not reported Exclusion 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

Hallerbäck 1987(2) (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
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; Dextropropoxyohene 32.5mg, tablets; Paracetamol 0.325g, tablets

Hallerbäck 1991 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Herzog 2006 (*Continued*)

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 toleration of solid food. Data extracted from figures

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Jepsen 1986 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Kuo 2006 (*Continued*)

	- 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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:

Lightfoot 2007 (*Continued*)

	- Route: 8 hour interval, intravenous administration - Start: 1. POD - Duration: Until maximum of 21 doses (=7days) 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Ludwig 2006

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

Ludwig 2006 (*Continued*)

	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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Manani 1982 (*Continued*)

	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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mieny 1972

Methods	Design: Parallel group RCT Randomisation: Random number tables 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: Not reported Withdrawals: Not stated Sample size calculation: Not used
Participants	Setting: Single centre trial, South Africa Number eligible: Not stated Number enrolled: 89

Mieny 1972 (*Continued*)

	Number in intervention group: 44 Number in control group: 45 Number of withdrawals (intervention/placebo): Not reported Inclusion criteria: Not reported Exclusion criteria: Exploration of the common bile duct, other intraabdominal procedures Type of surgery: Elective cholecystectomy
Interventions	Study drug: Panthothenic Acid Dose: 500mg Administration: - Route: 24 hour interval, intravenous administration - Start: Immediately after surgery - Duration: Maximum 3 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 return of mixing sounds and propulsive sounds
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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)

Orlando 1994 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Rimbäck 1990

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: 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

Rimbäck 1990 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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,

Roberts 1995 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sadek 1988

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

Sadek 1988 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Smith 2000

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)

Smith 2000 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Taguchi 2001

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 immunsuppressive 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

Taguchi 2001 (*Continued*)

Item	Authors' judgement	Description
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

Item	Authors' judgement	Description

Thorup 1983 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Tollesson 1991(1)

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

Item	**Authors' judgement**	**Description**

Tollesson 1991(1) (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Tollesson 1991(2)

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

Item	**Authors' judgement**	**Description**

Tollesson 1991(2) (*Continued*)

Allocation concealment?	Unclear	B - Unclear

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

Viscusi 2006 (*Continued*)

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)

Risk of bias

Item	Authors' judgement	Description
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

Von Ritter 1987 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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	

Risk of bias

Wilkinson 2002 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wolff 2004

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: 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

Wolff 2004 (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Woods 1993 (*Continued*)

	Albumin, hemoglobin, potassium, chloride, sodium levels Adverse effects
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Data in parentheses are numbers analysed unless otherwise indicated
RCT = Randomised controlled trail, 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]*

Aloisio 1976	Not randomised trial.
Baig 2004	Duplicate Publication.
Boghaert 1987	Inadequate follow-up duration (maximum 2 hours).
Chan 2005	Effect of metoclopramide on intra-peritoneal chemotherapy (IPC) induced ileus.
Chen JH 2005	Effect of water soluble contrast medium on POI*. Intervention not systemic pharmacologic treatment directed to treat POI*.
Chen JY 2005	Indirect effect of ketorolac on POI* indirect via opiate dose reduction.
Clevers 1988	Not randomised trial.
Costa 1994	Study population cesearean section.
Cyba 1985	Head to head comparison of ceruletide and neostigmine.
Davidson 1979	Effect of metoclopramide on postoperative ileus. Outcome not according to protocol: number of doses of metoclopramide or placebo until resolution of ileus.
Delaney 2006	Post hoc analysis of original trials (Delaney 2005, Viscusi 2006, Wolff 2004).
Delaney 2007	Post hoc analysis of original trials (Delaney 2005, Viscusi 2006, Wolff 2004).
Fanning 1999	Not randomised trial.

(*Continued*)

Ferraz 1995	Not randomised trial.
Gales 1999	Not randomised trial.
Garcia-Caballero1993	Duplicate publication.
Jensen 1990	Study population inguinal hernia repair.
Kasparek 2007	Not randomised trial.
Kawaguchi 1985	Not randomised trial.
Kivalo 1970	Not randomised trial.
Kreis 2001	Not randomised trial.
Lykkegaard-Nielsen	Head to head comparison of ceruletide and metoclopramide.
Madsen 1983	Inadequate follow-up duration (maximum 24 hours).
Madsen 1986	Head to head comparison between ceruletide and neostigmine.
Myrhöj 1988	Inadequate follow-up duration (maximum 9 hours).
Nio 1980	Head-to-head comparison of prostaglandin F and panthothenic acid. Not randomised trial.
Noblett 2006	Food intervention. No pharmacological treatment.
Olesen 1985	Head-to-head comparison of morphine and pethidine.
Olsen 1985	Intervention not systemic pharmacologic treatment directed to treat POI*.
Ruppin 1976	Effect of 13- Nle- Motilin in patients with postoperative ileus. Outcome: intensity of bowel sounds not according to protocol.
Schmidt 2001	Review article on alvimopan. Not randomised trial.
Seta 2001	Not randomised trial.
Sinatra 2006	Effect of Rofecoxib on POI* indirect via opioid dosage reduction.
Thunedborg 1993	Not randomised trial.
van Berge 1997	Study on healthy volunteers.
Wolff 2007	Post hoc analysis of original trials (Delaney 2005, Viscusi 2006, Wolff 2004).

*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
Notes	ClinicalTrials.gov identifier: NCT00443040 Study ID numbers: ASMP2004

Lidocaine

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)

Lidocaine (*Continued*)

	- 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: NCT00382499 Study ID numbers: #2006512-01H

Lidocaine/Ketamin

Trial name or title	A randomised controlled trial of lidocaine infusion plus ketamine injection versus placebo to decrease post-operative ileus
Methods	
Participants	Patients undergoing elective or urgent colon surgery with an anastomotic procedure
Interventions	Drug: Lidocaine infusion plus ketamine injection or placebo
Outcomes	Primary outcomes: Mean time after surgery to completion of the following postoperative markers: - Drinking and retaining 500ml clear fluids - Presence of bowel sounds - Passage of flatus - Passage of stool Secondary outcomes: - Outcome pain after cough by VAS - Narcotic usage

Lidocaine/Ketamin (*Continued*)

	- Nausea - Vomiting - Infection, dehiscence and other surgical complications - Time to readiness for discharge from hospital
Starting date	September 2005
Contact information	William PS McKay MD Principal Investigator Saskatoon Health Region University of Saskatchewan 410 22nd Street East Saskatoon Saskatchewan, Canada S7K 5T6
Notes	ClinicalTrials.gov identifier: NCT00229567 Study ID numbers: Bio-REB 03-1316

Methylnaltrexone

Trial name or title	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)
Methods	
Participants	Patients must be scheduled for a segmental colectomy
Interventions	Drug: Methylnaltrexone
Outcomes	No details available
Starting date	Not available
Contact information	David Jacobs MD tel: 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

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

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

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

Comparison 3. Cisapride versus Placebo

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

Comparison 4. Dihydroergotamine versus No treatment

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

Comparison 5. Dopaminantagonists versus Placebo

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

Comparison 6. Erythromycin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Time to passage of first stool	3	233	Ratio of the Means (Fixed, 95% CI)	0.99 [0.90, 1.08]
4 Time to tolerance of regular diet	3	233	Ratio of the Means (Fixed, 95% CI)	1.04 [0.93, 1.15]
5 Length of hospital stay	4	254	Ratio of the Means (Fixed, 95% CI)	1.00 [0.90, 1.11]
6 Time to passage of first flatus	4	254	Ratio of the Means (Fixed, 95% CI)	0.95 [0.88, 1.03]

Comparison 7. Lidocaine versus Placebo

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

Comparison 8. Neostigmine versus Placebo

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

Comparison 9. Propranolol versus Placebo

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

Comparison 10. Propranolol and Neostigmine versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Time to passage of first stool	2	70	Ratio of the Means (Random, 95% CI)	0.85 [0.62, 1.16]
6 Time to passage of first flatus	1	37	Ratio of the Means (Random, 95% CI)	0.80 [0.61, 1.05]

Comparison 11. Albumin versus No treatment

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

Comparison 12. Fructose 1,6 Disphosphate versus Fructose

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

Comparison 13. Pantothen acid versus Placebo

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

Comparison 14. Vasopressin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Length of hospital stay	1	60	Ratio of the Means (Random, 95% CI)	1.14 [0.86, 1.52]
6 Time to passage of first flatus	1	60	Ratio of the Medians (Random, 95% CI)	0.72 [0.45, 1.14]

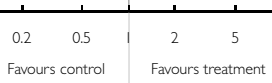
Analysis 1.1. Comparison 1 Alvimopan versus Placebo, Outcome 1 GI-2.

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

Comparison: 1 Alvimopan versus Placebo

Outcome: 1 GI-2

Study or subgroup	Alvimopan N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 12mg Alvimopan versus Placebo						
Delaney 2005	138	145	0.27 (0.1423)		10.5 %	1.31 [0.99, 1.73]
Herzog 2006	408	102	0.802 (0.1198)		12.7 %	2.23 [1.76, 2.82]
Ludwig 2006	317	312	0.4054 (0.083)		17.3 %	1.50 [1.27, 1.76]
Viscusi 2006	221	224	0.3074 (0.121)		12.6 %	1.36 [1.07, 1.72]
Wolff 2004	165	149	0.5128 (0.1283)		11.8 %	1.67 [1.30, 2.15]
Subtotal (95% CI)					**64.9 %**	**1.59 [1.33, 1.90]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.12$, df = 4 (P = 0.02); $I^2 = 67\%$						
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: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 2 (P = 0.96); $I^2 = 0.0\%$						
Test for overall effect: Z = 4.62 (P < 0.00001)						
Total (95% CI)					**100.0 %**	**1.52 [1.35, 1.71]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.85$, df = 7 (P = 0.05); $I^2 = 49\%$						
Test for overall effect: Z = 7.01 (P < 0.00001)						



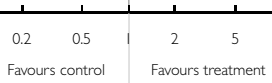
Analysis 1.2. Comparison 1 Alvimopan versus Placebo, Outcome 2 GI-3.

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

Comparison: 1 Alvimopan versus Placebo

Outcome: 2 GI-3

Study or subgroup	Alvimopan N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 12mg Alvimopan versus Placebo						
Delaney 2005	138	145	0.2468 (0.1287)		12.0 %	1.28 [0.99, 1.65]
Herzog 2006	408	102	0.1484 (0.1216)		13.4 %	1.16 [0.91, 1.47]
Viscusi 2006	221	224	0.2311 (0.1026)		18.8 %	1.26 [1.03, 1.54]
Wolff 2004	165	149	0.4317 (0.123)		13.1 %	1.54 [1.21, 1.96]
Subtotal (95% CI)					**57.3 %**	**1.30 [1.16, 1.46]**
Heterogeneity: Chi^2 = 2.88, df = 3 (P = 0.41); I^2 =0.0%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
2 6mg Alvimopan versus Placebo						
Delaney 2005	141	145	0.3715 (0.1257)		12.5 %	1.45 [1.13, 1.85]
Viscusi 2006	220	224	0.2151 (0.1059)		17.7 %	1.24 [1.01, 1.53]
Wolff 2004	155	149	0.2468 (0.1261)		12.5 %	1.28 [1.00, 1.64]
Subtotal (95% CI)					**42.7 %**	**1.31 [1.15, 1.50]**
Heterogeneity: Chi^2 = 0.95, df = 2 (P = 0.62); I^2 =0.0%						
Test for overall effect: Z = 3.97 (P = 0.000073)						
Total (95% CI)					**100.0 %**	**1.30 [1.19, 1.42]**
Heterogeneity: Chi^2 = 3.85, df = 6 (P = 0.70); I^2 =0.0%						
Test for overall effect: Z = 5.95 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.92), I^2 =0.0%						



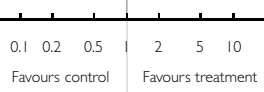
Analysis 1.3. Comparison 1 Alvimopan versus Placebo, Outcome 3 Time to passage of first stool.

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

Study or subgroup	Alvimopan N	Placebo N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 12mg Alvimopan versus Placebo						
Delaney 2005	138	145	0.3852 (0.1401)		17.7 %	1.47 [1.12, 1.93]
Herzog 2006	408	102	0.8458 (0.1216)		19.8 %	2.33 [1.84, 2.96]
Viscusi 2006	221	224	0.4187 (0.1185)		20.2 %	1.52 [1.20, 1.92]
Subtotal (95% CI)					**57.7 %**	**1.74 [1.29, 2.34]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.50$, df = 2 (P = 0.01); $I^2 = 76\%$						
Test for overall effect: Z = 3.68 (P = 0.00024)						
2 6mg Alvimopan versus Placebo						
Delaney 2005	141	145	0.4382 (0.1383)		17.9 %	1.55 [1.18, 2.03]
Taguchi 2001	26	26	1.0647 (0.4144)		4.0 %	2.90 [1.29, 6.53]
Viscusi 2006	220	224	0.4317 (0.1162)		20.5 %	1.54 [1.23, 1.93]
Subtotal (95% CI)					**42.3 %**	**1.60 [1.32, 1.92]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.21$, df = 2 (P = 0.33); $I^2 = 10\%$						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Total (95% CI)					**100.0 %**	**1.70 [1.43, 2.02]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 11.49$, df = 5 (P = 0.04); $I^2 = 56\%$						
Test for overall effect: Z = 5.95 (P < 0.00001)						

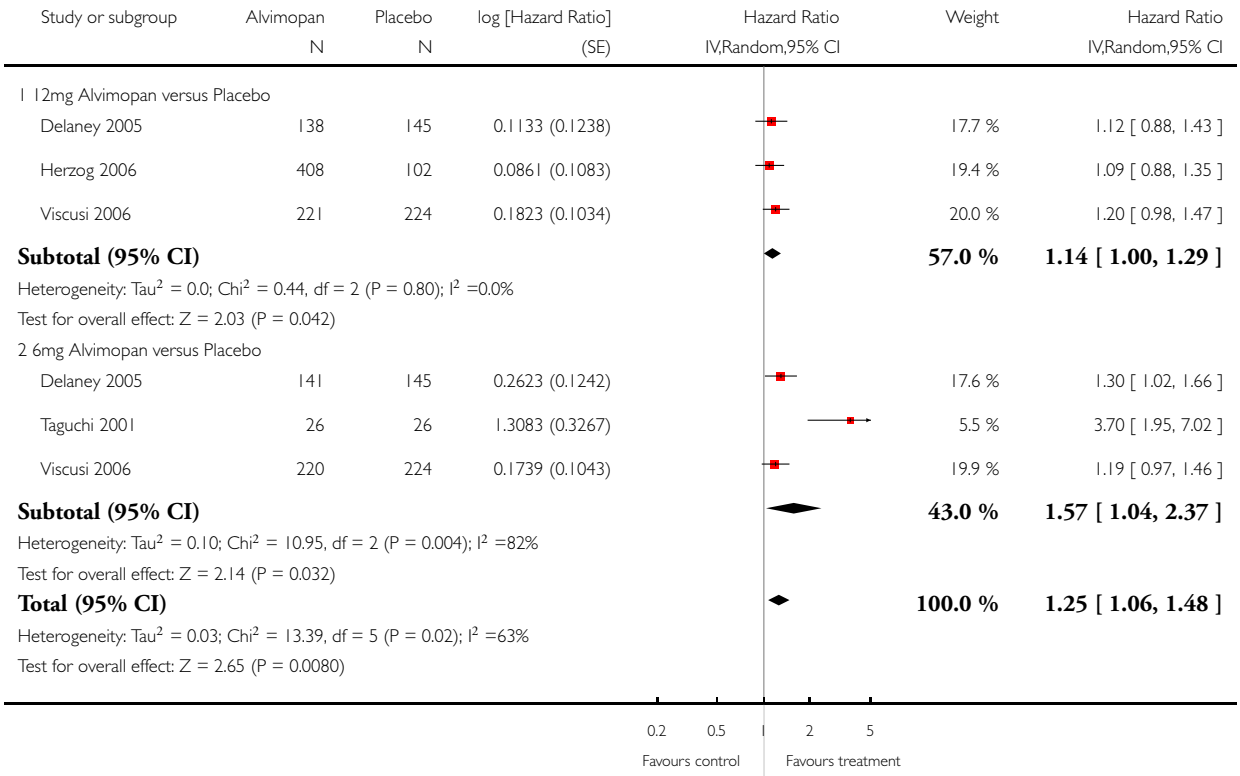


Analysis 1.4. Comparison 1 Alvimopan versus Placebo, Outcome 4 Time to tolerance of regular diet.

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



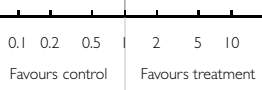
Analysis 1.5. Comparison 1 Alvimopan versus Placebo, Outcome 5 Length of hospital stay.

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

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



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

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

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)

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

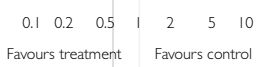
Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 3 Time to passage of first stool

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

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 19.80$, df = 3 (P = 0.00019); $I^2 = 85\%$

Test for overall effect: Z = 1.55 (P = 0.12)



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

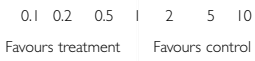
Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 4 Time to tolerance of regular diet

Study or subgroup	Cerulein/ Ceruletide N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Alvarez 1979	25	25	-0.059 (0.0241)		70.9 %	0.94 [0.90, 0.99]
Sadek 1988	47	44	-0.096 (0.0376)		29.1 %	0.91 [0.84, 0.98]
Total (95% CI)					**100.0 %**	**0.93 [0.90, 0.97]**

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

Study or subgroup	Cerulein/ Ceruletide N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Alvarez 1979	25	25	-0.299 (0.146)		39.7 %	0.74 [0.56, 0.99]
Sadek 1988	47	44	-0.1541 (0.1185)		60.3 %	0.86 [0.68, 1.08]
Total (95% CI)					**100.0 %**	**0.81 [0.68, 0.97]**

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

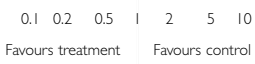
Comparison: 2 Cholecystokinin-like acting drugs versus Placebo or No treatment

Outcome: 6 Time to passage of first flatus

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

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

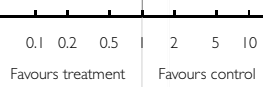
Comparison: 3 Cisapride versus Placebo

Outcome: 3 Time to passage of first stool

Study or subgroup	Cisapride N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Brown 1999	17	18	-0.2231 (0.0746)		27.9 %	0.80 [0.69, 0.93]
Clevers 1991	17	20	0 (0.113)		25.6 %	1.00 [0.80, 1.25]
Hallerbck 1991	36	33	-0.6821 (0.1034)		26.3 %	0.51 [0.41, 0.62]
Tollesson 1991(2)	20	20	-0.4182 (0.1914)		20.2 %	0.66 [0.45, 0.96]
Total (95% CI)					**100.0 %**	**0.72 [0.54, 0.97]**

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

Study or subgroup	Cisapride N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Brown 1999	17	18	-0.2231 (0.0709)		53.4 %	0.80 [0.70, 0.92]
Clevers 1991	17	20	0 (0.0915)		46.6 %	1.00 [0.84, 1.20]
Total (95% CI)					**100.0 %**	**0.89 [0.71, 1.10]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.71$, 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

Study or subgroup	Cisapride N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Brown 1999	17	18	-0.1973 (0.0962)		79.0 %	0.82 [0.68, 0.99]
Clevers 1991	17	20	0 (0.1866)		21.0 %	1.00 [0.69, 1.44]
Total (95% CI)					**100.0 %**	**0.86 [0.72, 1.01]**

Heterogeneity: $Chi^2 = 0.88$, 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

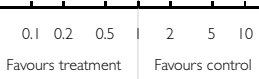
Comparison: 3 Cisapride versus Placebo

Outcome: 6 Time to passage of first flatus

Study or subgroup	Cisapride N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Benson 1994	11	12	-0.307 (0.157)		15.6 %	0.74 [0.54, 1.00]
Clevers 1991	17	20	0 (0.1019)		37.0 %	1.00 [0.82, 1.22]
Roberts 1995	7	7	-0.1865 (0.1406)		19.4 %	0.83 [0.63, 1.09]
Tollesson 1991(2)	20	20	-0.0759 (0.1281)		23.4 %	0.93 [0.72, 1.19]
Von Ritter 1987	17	15	-0.227 (0.291)		4.5 %	0.80 [0.45, 1.41]
Total (95% CI)					**100.0 %**	**0.89 [0.79, 1.01]**

Heterogeneity: Chi^2 = 3.27, df = 4 (P = 0.51); I^2 =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

Study or subgroup	Dihydroergotamine N	No treatment N	log [Ratio of the Medians] (SE)	Ratio of the Medians IV,Random,95% CI	Weight	Ratio of the Medians IV,Random,95% CI
Altaparmakov 1984	23	23	-0.5819 (0.0803)		53.5 %	0.56 [0.48, 0.65]
Thorup 1983	43	34	-0.0659 (0.158)		46.5 %	0.94 [0.69, 1.28]
Total (95% CI)					**100.0 %**	**0.71 [0.43, 1.18]**

Heterogeneity: Tau^2 = 0.12; Chi^2 = 8.48, df = 1 (P = 0.004); I^2 =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

Study or subgroup	Metoclopramide N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Tollesson 1991(1)	10	10	-0.0392 (0.1792)		100.0 %	0.96 [0.68, 1.37]
Total (95% CI)					**100.0 %**	**0.96 [0.68, 1.37]**

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

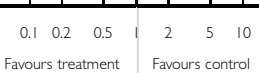
Comparison: 5 Dopaminantagonists versus Placebo

Outcome: 4 Time to tolerance of regular diet

Study or subgroup	Metoclopramide N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Cheape 1991	40	53	-0.105 (0.063)		100.0 %	0.90 [0.80, 1.02]
Total (95% CI)					**100.0 %**	**0.90 [0.80, 1.02]**

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

Study or subgroup	Dopaminantagonist N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Conte 1983	84	80	-0.301 (0.0836)		46.7 %	0.74 [0.63, 0.87]
Jepsen 1986	30	25	0.2271 (0.244)		26.6 %	1.25 [0.78, 2.02]
Tollesson 1991(1)	10	10	0.0571 (0.2427)		26.7 %	1.06 [0.66, 1.70]
Total (95% CI)					**100.0 %**	**0.94 [0.66, 1.33]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.60$, df = 2 (P = 0.06); $I^2 = 64\%$

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

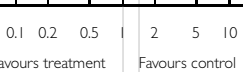
Comparison: 6 Erythromycin versus Placebo

Outcome: 3 Time to passage of first stool

Study or subgroup	Erythromycin N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Bonacini 1993	41	36	0.021 (0.0856)		27.4 %	1.02 [0.86, 1.21]
Lightfoot 2007	11	11	0.1823 (0.255)		3.1 %	1.20 [0.73, 1.98]
Smith 2000	65	69	-0.0377 (0.0537)		69.5 %	0.96 [0.87, 1.07]
Total (95% CI)					**100.0 %**	**0.99 [0.90, 1.08]**

Heterogeneity: $Chi^2 = 0.95$, df = 2 (P = 0.62); $I^2 = 0.0\%$

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

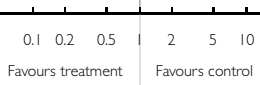
Comparison: 6 Erythromycin versus Placebo

Outcome: 4 Time to tolerance of regular diet

Study or subgroup	Erythromycin N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Bonacini 1993	41	36	-0.0183 (0.1813)		8.8 %	0.98 [0.69, 1.40]
Lightfoot 2007	11	11	0.1177 (0.2382)		5.1 %	1.12 [0.71, 1.79]
Smith 2000	65	69	0.0363 (0.0581)		86.0 %	1.04 [0.93, 1.16]
Total (95% CI)					**100.0 %**	**1.04 [0.93, 1.15]**

Heterogeneity: $Chi^2 = 0.21$, df = 2 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.66 (P = 0.51)



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

Study or subgroup	Erythromycin N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Bonacini 1993	41	36	0.0168 (0.2155)		5.7 %	1.02 [0.67, 1.55]
Lightfoot 2007	11	11	0.1053 (0.2116)		5.9 %	1.11 [0.73, 1.68]
Smith 2000	65	69	-0.0132 (0.0553)		86.2 %	0.99 [0.89, 1.10]
Wilkinson 2002	11	10	0.1823 (0.3401)		2.3 %	1.20 [0.62, 2.34]
Total (95% CI)					**100.0 %**	**1.00 [0.90, 1.11]**

Heterogeneity: $Chi^2 = 0.60$, df = 3 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.00 (P = 1.0)

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

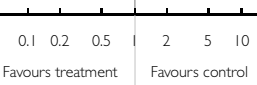
Comparison: 6 Erythromycin versus Placebo

Outcome: 6 Time to passage of first flatus

Study or subgroup	Erythromycin N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Bonacini 1993	41	36	0.0183 (0.1197)		11.7 %	1.02 [0.81, 1.29]
Lightfoot 2007	11	11	0 (0.2337)		3.1 %	1.00 [0.63, 1.58]
Smith 2000	65	69	-0.0706 (0.0495)		68.6 %	0.93 [0.85, 1.03]
Wilkinson 2002	11	10	0 (0.1007)		16.6 %	1.00 [0.82, 1.22]
Total (95% CI)					**100.0 %**	**0.95 [0.88, 1.03]**

Heterogeneity: Chi² = 0.78, df = 3 (P = 0.85); I² =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

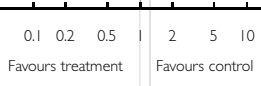
Comparison: 7 Lidocaine versus Placebo

Outcome: 3 Time to passage of first stool

Study or subgroup	Lidocaine N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Groudine 1998	18	20	-0.1788 (0.0704)		85.8 %	0.84 [0.73, 0.96]
Rimbck 1990	15	15	-0.2177 (0.1734)		14.2 %	0.80 [0.57, 1.13]
Total (95% CI)					**100.0 %**	**0.83 [0.73, 0.95]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² =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

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

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.78$, df = 1 (P = 0.05); $I^2 = 74\%$

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

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

Heterogeneity: $Chi^2 = 2.58$, df = 2 (P = 0.27); $I^2 = 23\%$

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

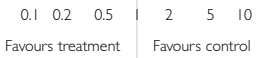
Comparison: 8 Neostigmine versus Placebo

Outcome: 3 Time to passage of first stool

Study or subgroup	Neostigmine N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Hallerbck 1987(1)	18	17	-0.2218 (0.1067)		100.0 %	0.80 [0.65, 0.99]
Total (95% CI)					**100.0 %**	**0.80 [0.65, 0.99]**

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: 8 Neostigmine versus Placebo

Outcome: 6 Time to passage of first flatus

Study or subgroup	Neostigmine N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Orlando 1994	19	20	-0.556 (0.288)		100.0 %	0.57 [0.33, 1.01]
Total (95% CI)					**100.0 %**	**0.57 [0.33, 1.01]**

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

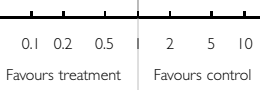
Comparison: 9 Propranolol versus Placebo

Outcome: 3 Time to passage of first stool

Study or subgroup	Propranolol N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Hallerbck 1987(2)	20	19	-1.006 (0.1132)		100.0 %	0.37 [0.29, 0.46]
Total (95% CI)					**100.0 %**	**0.37 [0.29, 0.46]**

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

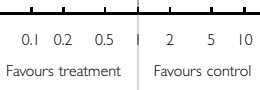
Comparison: 9 Propranolol versus Placebo

Outcome: 6 Time to first passage of flatus

Study or subgroup	Propranolol N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Fixed,95% CI	Weight	Ratio of the Means IV,Fixed,95% CI
Ferraz 2001	12	15	-0.141 (0.169)		37.6 %	0.87 [0.62, 1.21]
Hallerbck 1987(2)	20	19	-0.0741 (0.1312)		62.4 %	0.93 [0.72, 1.20]
Total (95% CI)					**100.0 %**	**0.91 [0.74, 1.11]**

Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =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

Study or subgroup	Propra/Neostigm N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Garcia 1993	17	20	0 (0.1261)		49.0 %	1.00 [0.78, 1.28]
Hallerbck 1987(1)	16	17	-0.3204 (0.1176)		51.0 %	0.73 [0.58, 0.91]
Total (95% CI)					**100.0 %**	**0.85 [0.62, 1.16]**

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

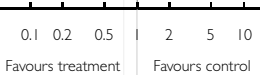
Comparison: 10 Propranolol and Neostigmine versus Placebo

Outcome: 6 Time to passage of first flatus

Study or subgroup	Propra/Neostigm N	No treatment N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Garcia 1993	17	20	-0.223 (0.1369)		100.0 %	0.80 [0.61, 1.05]
Total (95% CI)					**100.0 %**	**0.80 [0.61, 1.05]**

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

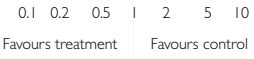
Comparison: 11 Albumin versus No treatment

Outcome: 4 Time to tolerance of regular diet

Study or subgroup	Albumin N	No treatment N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Woods 1993	37	32	0.1006 (0.0786)		100.0 %	1.11 [0.95, 1.29]
Total (95% CI)					**100.0 %**	**1.11 [0.95, 1.29]**

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

Study or subgroup	Albumin N	No treatment N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Woods 1993	37	32	0.083 (0.107)		100.0 %	1.09 [0.88, 1.34]
Total (95% CI)					**100.0 %**	**1.09 [0.88, 1.34]**

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.

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

Comparison: 12 Fructose 1,6 Disphosphate versus Fructose

Outcome: 6 Time to passage of first flatus

Study or subgroup	Fruc(1.6)diphosphat N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Manani 1982	50	50	-0.171 (0.0774)		100.0 %	0.84 [0.72, 0.98]
Total (95% CI)					**100.0 %**	**0.84 [0.72, 0.98]**
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.

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

Comparison: 13 Pantothen acid versus Placebo

Outcome: 6 Time to passage of first flatus

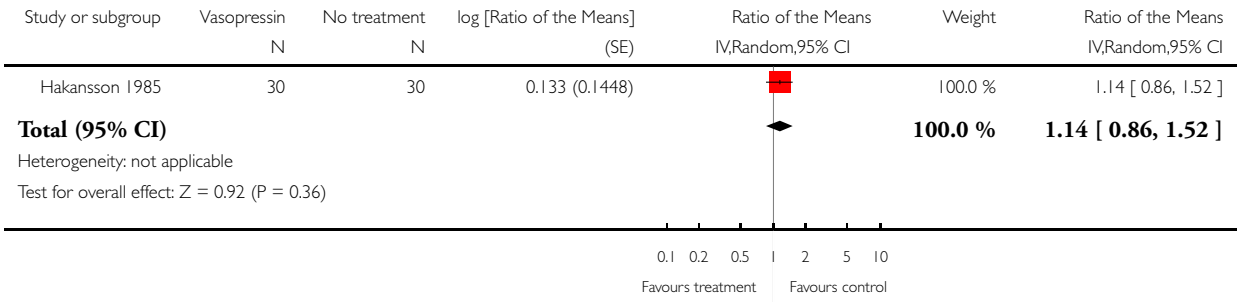
Study or subgroup	Pantothen Acid N	Placebo N	log [Ratio of the Means] (SE)	Ratio of the Means IV,Random,95% CI	Weight	Ratio of the Means IV,Random,95% CI
Mieny 1972	44	45	-0.002 (0.0811)		100.0 %	1.00 [0.85, 1.17]
Total (95% CI)					**100.0 %**	**1.00 [0.85, 1.17]**
Heterogeneity: not applicable						
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

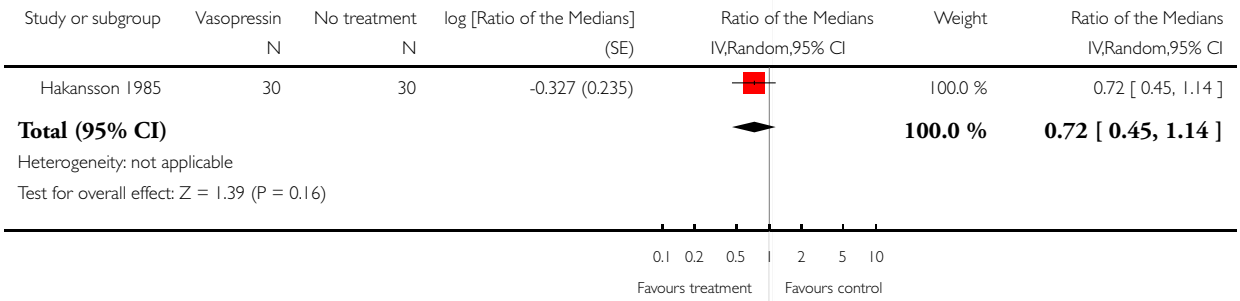


Analysis 14.6. Comparison 14 Vasopressin versus Placebo, Outcome 6 Time to passage of first flatus.

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



F E E D B A C K

Some information on evaluating clinical trials for the drug alvimopan (Entereg®) requires clarification, 10 August 2009

Summary

Thank you for the opportunity to present our feedback regarding the Cochrane review "Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus after abdominal surgery in adults" by Traut et al. in the forthcoming Cochrane Library. In this review, a considerable amount of text is devoted to evaluating clinical trials for the drug alvimopan (Entereg®); however, some of this information requires clarification.

1. The alvimopan phase III clinical trials have been evaluated by the FDA, and the drug is now approved (May, 2008) for the acceleration of gastrointestinal recovery after partial large- or small-bowel resection (BR) with primary anastomosis.

2. High methodological standards were implemented in all alvimopan clinical trials. All phase III trials were randomized, double-blind, placebo-controlled studies.[1−7] However, not all details of randomization and blinding were reported in the literature because of dissimilar journal guidelines. Additional details for each trial include

- In all trials (except for Herzog 2006[8]) patients were randomized 1:1 as evidenced by the "n" values in the treatment and placebo arms

- For all alvimopan phase III trials, an eligible patient was assigned to the first available randomization number for the stratum using the predetermined randomization schedules generated by the Adolor Biometrics Department before the start of the study. The study blind was to be broken only in situations where the safety of the patient was in jeopardy, and the treatment plan was dependent on the results of blind breaking.

- ○ In Delaney et al, 2005[2] (Study 14CL302), 2 predetermined randomization schedules were generated by the Adolor Biometrics Department, one for each surgery type (BR vs rTAH/sTAH) at each site. Eligible patients were assigned the first available randomization number for the surgery type to which they were stratified.

- ○ In Ludwig et al, 2008[5] (Study 14CL314), at the time informed consent was obtained, the investigator or designee contacted an Interactive Voice Response System to obtain blister card assignment of either alvimopan or matching placebo. Sites received operation and instruction manuals for the Interactive Voice Response System.

3. The modified intent-to-treat (ITT) population in alvimopan phase III clinical trials was defined to exclude patients who did not receive the protocol specified surgery, had no surgical intervention due to cancellation, or received no study drug; thus, we feel this population is a reliable measure of the efficacy of alvimopan (a drug indicated for BR surgery) in the phase III trials. Moreover, prespecified ITT analyses yielded similar results for primary and key secondary endpoints. Additionally, the statistical analyses used in the alvimopan phase III trials were examined by an external, statistics and scientific advisory board, through which experts met, agreed, and supported the choice of using the Cox proportional hazards model as the primary means of statistical analysis.
4. These protocols were posted on ClinicalTrials.gov and the results were published in peer-reviewed journals and full disclosure of involvement (financial or otherwise) was disclosed per journal guidelines. Moreover, whereas concern has been raised that industry-sponsored clinical trials are more likely to be positive compared with non-sponsored studies, a recent meta-analysis of high-quality industry-sponsored trials for acute pain and migraine using an analytical method based on potential conflict of interest within industry-sponsored trials indicated no evidence of bias.[9] Because the alvimopan trials were conducted with the highest methodological standards and all industry involvement was disclosed, this assumption is certainly not warranted in this case.
5. Additional points of clarification:

- Alvimopan is not a prokinetic agent.

- "Sigma-opioid" receptors should be delta-opioid receptors (page 3).

- Alvimopan acts as an antagonist of the inhibitory effects of endogenous and exogenous opioids on gastrointestinal motility (page 3).

- In the review it was stated that, "Physicians were allowed to administer comedication to treat postoperative ileus in 5 trials (Delaney 2005; Hallerback 1987(2); Herzog 2006; Sadek 1988; Smith 2000)" (page 7).

- ○ However, in all alvimopan trials, if medically necessary, any drug was permitted to treat an adverse event and prophylactic use of laxatives or prokinetic agents was prohibited.

- Six trials reported on the effect of alvimopan (Delaney 2005; Herzog 2006; Ludwig 2006; Taguchi 2001; Viscusi 2006; Wolff 2004) (page 8).

- ○ The Results section (pages 8-9) describing the 6 alvimopan clinical trials makes no distinction between surgical subpopulations (ie, BR vs TAH) when comparing clinical outcomes.

- The Ludwig poster presented at ACS in 2006 presented GI-2 as the primary endpoint.[10] GI-3 was a supportive endpoint.[10] Furthermore, this trial has now been published as a manuscript in 2008,[5] making the poster reference out of date (page 8).

- Alvimopan has been approved by the US FDA for the acceleration of upper and lower GI recovery following large or small BR with primary anastomosis (May, 2008).[11] Moreover, the clinical hold because of safety concerns regarding the long-term use of alvimopan in patients with chronic pain and opioid-induced bowel dysfunction was recently lifted (July, 2008)[12] (page 14).

- The article for Delaney 2005 states that the age range of patients was 29-93, not "18-80" (page 28).

- Exclusion criteria listed for Delaney 2005 is incomplete. Additional exclusions were also included in Delaney 2005: patients scheduled to receive total colectomy, colostomy, or ileostomy, or expected to receive epidural opioids, local anaesthetics, or nonsteroidal anti-inflammatory drugs for postoperative pain management (page 28).

- Outcomes section for Delaney 2005 (page 28), Herzog 2006 (page 36), Viscusi 2006 (page 49), and Wolff 2004 (page 51) lists length of hospital stay. The articles indicated that time of discharge order (DCO) written was an endpoint, not length of stay per se.

- Start of drug treatment for Herzog 2006 is listed as: "Start 1. POD" (page 36). However, the drug was administered at least 2 hours before surgery, then twice daily postoperatively.

- Outcomes section for Herzog 2006 does not list safety and tolerability of alvimopan (page 36).

- ○ Safety and tolerability were the primary endpoints of Herzog 2006, and these are reported in the manuscript on page 448

- Methods section for Ludwig 2006 states: Randomization: No details available and Blinding: Double blind, no details given (page 39).

- ○ This study has been published; therefore, information used from the poster presentation in 2006 is outdated.[5,10] The Ludwig manuscript states that after informed consent was obtained, an Interactive Voice Response System was used to obtain blister card assignment of alvimopan or placebo.[5] Blister cards contained identically packaged alvimopan or placebo with labels blackened for blinding.[5]

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WHAT'S NEW

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

10 August 2008	Feedback has been incorporated	Comments

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2008

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