Systematic Review and/or Meta-analysis

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Pharmacologic prevention and therapy of postoperative paralytic ileus after gastrointestinal cancer surgery: systematic review and meta-analysis

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Background: Postoperative paralytic ileus (POI) is a significant concern following gastrointestinal tumor surgery. Effective preventive and therapeutic strategies are crucial but remain elusive. Current evidence from randomized-controlled trials on pharmacological interventions for prevention or treatment of POI are systematically reviewed to guide clinical practice and future research.

Materials and methods: Literature was systematically searched for prospective randomized-controlled trials testing pharmacological interventions for prevention or treatment of POI after gastrointestinal tumor surgery. Meta-analysis was performed using a random effects model to determine risk ratios and mean differences with 95% CI. Risk of bias and evidence quality were assessed.

Results: Results from 55 studies, involving 5078 patients who received experimental interventions, indicate that approaches of opioid-sparing analgesia, peripheral opioid antagonism, reduction of sympathetic hyperreactivity, and early use of laxatives effectively prevent POI. Perioperative oral Alvimopan or intravenous administration of Lidocaine or Dexmedetomidine, while safe regarding cardio-pulmonary complications, demonstrated effectiveness concerning various aspects of postoperative bowel recovery [Lidocaine: – 5.97 (– 7.20 to – 4.74)h, $P < 0.0001$; Dexmedetomidine: – 13.00 (– 24.87 to – 1.14)h, $P = 0.03$ for time to first defecation; Alvimopan: – 15.33 (– 21.22 to – 9.44)h, $P < 0.0001$ for time to *GI-2*] and length of hospitalization [Lidocaine: – 0.67 (– 1.24 to – 0.09)d, $P = 0.02$; Dexmedetomidine: – 1.28 (– 1.96 to – 0.60)d, $P = 0.0002$; Alvimopan: – 0.58 (– 0.84 to – 0.32)d, $P < 0.0001$] across wide ranges of evidence quality. Perioperative nonopioid analgesic use showed efficacy concerning bowel recovery as well as length of hospitalization [– 1.29 (– 1.95 to – 0.62)d, $P = 0.0001$]. Laxatives showed efficacy regarding bowel movements, but not food tolerance and hospitalization. Evidence supporting pharmacological treatment for clinically evident POI is limited. Results from one single study suggest that Neostigmine reduces time to flatus and accelerates bowel movements [– 37.06 (– 40.26 to – 33.87)h, $P < 0.0001$ and – 42.97 (– 47.60 to – 38.35)h, $P < 0.0001$, respectively] with low evidence quality.

Conclusion: Current evidence concerning pharmacological prevention and treatment of POI following gastrointestinal tumor surgery is limited. Opioid-sparing concepts, reduction of sympathetic hyperreactivity, and laxatives should be implemented into multimodal perioperative approaches.

Keywords: alvimopan, bowel recovery, cancer surgery, dexmedetomidine, gastrointestinal atony, gastrointestinal surgery, lidocaine, postoperative Ileus, surgical oncology

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:4329–4341

Received 29 December 2023; Accepted 10 March 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery.

Published online 25 March 2024

http://dx.doi.org/10.1097/JS9.0000000000001393

Introduction

Gastrointestinal dysmotility following abdominal surgery is to certain extents a physiological response. Patients undergoing gastrointestinal tumor resections are particularly susceptible, with up to 30%, experiencing prolonged gastrointestinal dysmotility and postoperative (paralytic) ileus (POI)[1,2]. POI leads to significant discomfort, increased morbidity, and prolonged hospital stay[2]. Consecutively, it imposes substantial costs and thus is a financial burden on healthcare systems[1,2]. Given these factors, effective preventive measures and prompt initiation of suitable therapeutic interventions against clinically evident POI are essential to improve patient outcomes.

Beyond the transient physiological gastrointestinal paralysis that occurs shortly after major abdominal surgery, the development of prolonged postoperative gastrointestinal dysmotility is influenced by multiple factors[3–5]. Perioperative neurogenic dysregulation and inflammatory processes play pivotal roles in the pathogenesis of POI[2,6]. Additionally, medications administered in the perioperative phase, such as opioids, potentially exacerbate postoperative gastrointestinal atony[2,6]. Alongside technical considerations involving minimally invasive surgical techniques that mitigate the inflammatory response and postoperative opioid consumption by minimizing surgical trauma[2,4–6], pharmacological interventions gain importance in clinical practice for both primary prevention and secondary treatment of POI within, '*enhanced recovery after surgery*' concepts[6]. Due to the multifactorial pathogenesis, numerous pharmacological strategies have been explored in clinical trials resulting in a broad spectrum of perioperative pharmacological options[2,6,7]. Approximately 100 substances have been tested for either preventing or treating postoperative gastrointestinal dysmotility[6]. The scientific landscape is diverse due to inconsistent trial quality, inhomogeneous patient collectives, varying endpoints, absence of well-defined '*core outcome sets*' for POI, and the wide range of pharmaceuticals investigated as interventions[7,8]. Moreover, some drugs tested for prophylaxis or targeted therapy of POI bear the risk of potential serious side effects. These factors pose challenges in implementing focused pharmacological interventions in clinical practice and make the translation of extensive literature into practical application complex. Nonetheless, surgeons and treating physicians must be acquainted with potential agents amidst a myriad of tested drugs that hold promise for sufficiently preventing or effectively treating POI.

In order to address this, we have systematically reviewed current evidence from randomized-controlled trials (RCT), which tested substances for their potential in either the prevention or treatment of postoperative gastrointestinal dysmotility and POI. Our focus is on substances that are globally available and can be safely administered in clinical routine. Due to the limited availability of high-quality evidence supporting specific pharmacological interventions against postoperative gastrointestinal dysmotility and POI using widely accessible pharmaceuticals, results of the meta-analysis will be subsequently discussed in terms of their practical relevance in the perioperative setting and their implications for further research within the field.

HIGHLIGHTS

- Evidence for pharmacological prevention of postoperative paralytic ileus following gastrointestinal tumor surgery is limited.
- Postoperative opioid-sparing analgesia, perioperative peripheral opioid antagonism and perioperative reduction of sympathetic hyperreactivity are promising approaches for enhancing bowel recovery.
- Oral Alvimopan or intravenous Lidocaine or Dexmedetomidine, respectively, showed the highest effectiveness in various domains of postoperative bowel as well as overall recovery and prevention of postoperative ileus.
- Evidence for pharmacologic intervention for the therapy of clinically evident postoperative paralytic ileus is much worse; intravenous Neostigmine and oral Gastrografin have demonstrated some benefits regarding bowel movements, but the efficacy in other domains of bowel recovery remain elusive.
- Inadequate pharmacological preventive measures for postoperative paralytic ileus lead to increased morbidity and prolonged hospitalization.
- Further research is urgently needed for improvements in patient recovery.

Methods

The study was prospectively registered in the *International Prospective Register of Systematic Reviews* (PROSPERO; unique identifying number: PROSPERO 2022 CRD42022351799; hyperlink: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022351799). Systematic review and meta-analysis were performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplemental Digital Content 1, http://links.lww.com/JS9/C227) 2020 statement[9] and Assessing the methodological quality of systematic reviews (AMSTAR-2) guidelines[10]. The overall quality of this work has been rated as high by AMSTAR-2 (see AMSTAR-2 checklist in the Digital Supplement, Supplemental Digital Content 2, http://links.lww.com/JS9/C228).

Systematic literature search and data extraction

English or German literature was screened in MEDLINE, CENTRAL, as well as information were extracted from ClinicalTrials.gov. Prospective randomized-controlled trials investigating pharmacologic options for either the prevention or therapy of gastrointestinal dysmotility and POI after gastrointestinal tumor surgery were identified using a predefined search strategy (Supplement 1, Supplemental Digital Content 3, http://links.lww.com/JS9/C229). Final searches were performed on 15 August 2023.

Eligibility criteria for inclusion in the meta-analysis required that the study data be sourced from RCTs involving patients who had undergone gastrointestinal tumor resections, including resections of the esophagus, stomach, pancreas, liver, small and/or large bowel. Additionally, the drug under investigation must have been tested against placebo, standard therapy, or no therapy. Studies lacking suitable comparators– for example, comparison with another pharmacologic intervention, studies failing to include patients undergoing gastrointestinal tumor resections, or studies examining drugs not approved by German and / or U.S. American drug administration authorities, mainly due to safety

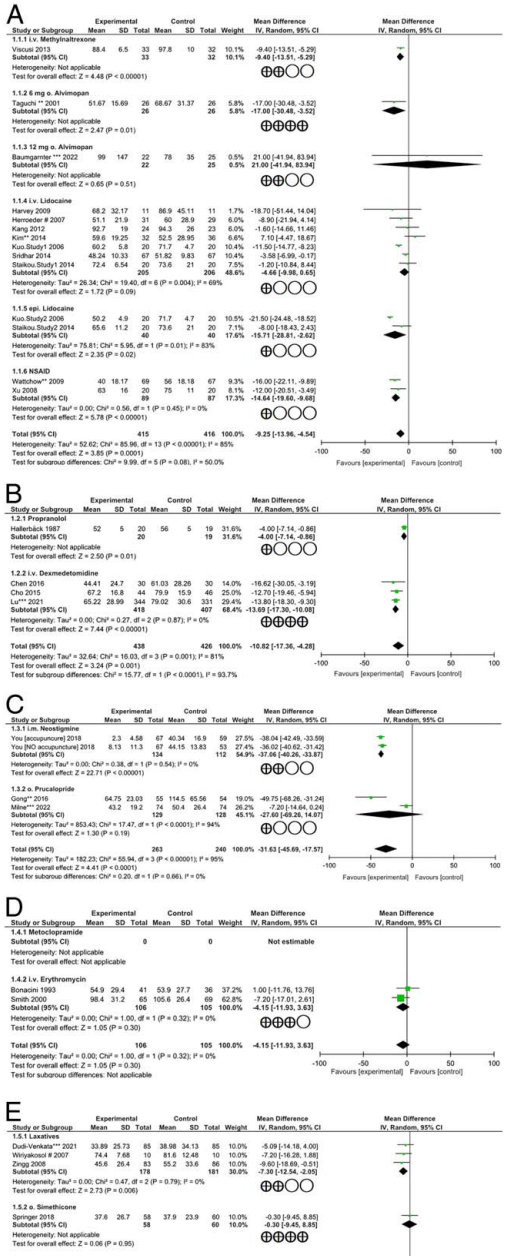

Figure 1. Duration until first flatus [h]. Effect of pharmacologic intervention on duration until first flatus versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. ** Estimation of mean ± SD using the method described by Wan *et al*.[12]. *** Data were obtained directly from the study authors. # data estimated from publication graphs. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural; i.m., intramuscular. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

concerns, were excluded from the meta-analysis. Administrative approval of pharmaceuticals by the German and/or U.S. American health care system served as the benchmark for assessing overall treatment efficacy and safety. The absence of such approval from these evidence-based health care systems indicates limited global accessibility and applicability, translating to a lack of relevance in the context of perioperative medicine.

The mean outcomes for gastrointestinal recovery were: time to first flatus and time to first bowel movement (TTF, TTM; Figs 1, 2). Other continuous outcome parameters were time to (solid) diet tolerance (TTD; Fig. 3), time to achieve the GI-2 composite outcome criterion (GI-2 combines TTM and TTD; Fig. 4) and length of hospital stay (LOS; Fig. 5). Secondary outcomes were: Nasogastric tube (re-) insertion rate, postoperative (total, cardiac, pulmonary, surgical, i.e. > grade II regarding the Clavien–Dindo classification of surgical complications[11]) complication rates (Tables 1, 2) and patient satisfaction.

Two reviewers independently screened the titles and abstracts of studies retrieved using the search strategies outlined above and those from additional sources for potential inclusion. Full texts of potentially eligible studies were retrieved and again independently assessed for final inclusion into the meta-analysis by two reviewers (see PRISMA flow diagram in Supplement 2, Supplemental Digital Content 4, http://links.lww.com/JS9/C230). Data for quality assessment and evidence synthesis were extracted from the studies and included into a standardized form by two reviewers. At any stage disagreements between the two primary reviewers were resolved by an independent third party.

If relevant data were missing from the published manuscript or other sources, these were requested from study authors. Other potential sources for obtaining comprehensive datasets were open registries for clinical studies. Otherwise, if only the median was provided or SD of means were lacking, conversion from median to mean and SD was carried out using the method by Wan *et al*.[12] or SD of means were estimated following the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4, 2023. www.training.cochrane.org/handbook) and using the RevMan Calculator (www.training.cochrane.org/resource/revman-calculator), respectively.

Data synthesis and statistical analysis

When comparable data from multiple RCTs were available, data synthesis and statistical analysis were performed using the Cochrane Collaboration's Review Manager (RevMan Version 5.4). Heterogeneity of included studies was tested using Cochran's Q statistic and I^2 test ($I^2 = 0$–40%: low; $I^2 = 41$–74%: moderate; $I^2 = 75$–100%: high).

For dichotomous outcomes, risk ratios (RR) were calculated. RR < 1 is in favor of the experimental pharmacologic intervention. For continuous parameters, mean differences (MD) between two groups were calculated. If studies report on time-to-event data, the logarithmically transformed hazard ratios were synthesized to obtain an overall estimate of the treatment effect. Random effects modeling was used for analysis due to considerable heterogeneity among studies concerning modalities of intervention and comparator, sample sizes, patient population, types of surgery, and results in I^2 tests. Results are reported in forest plots with 95% CI. Funnel Plots in Supplement 3 (Supplemental Digital Content 5, http://links.lww.com/JS9/C231) indicate

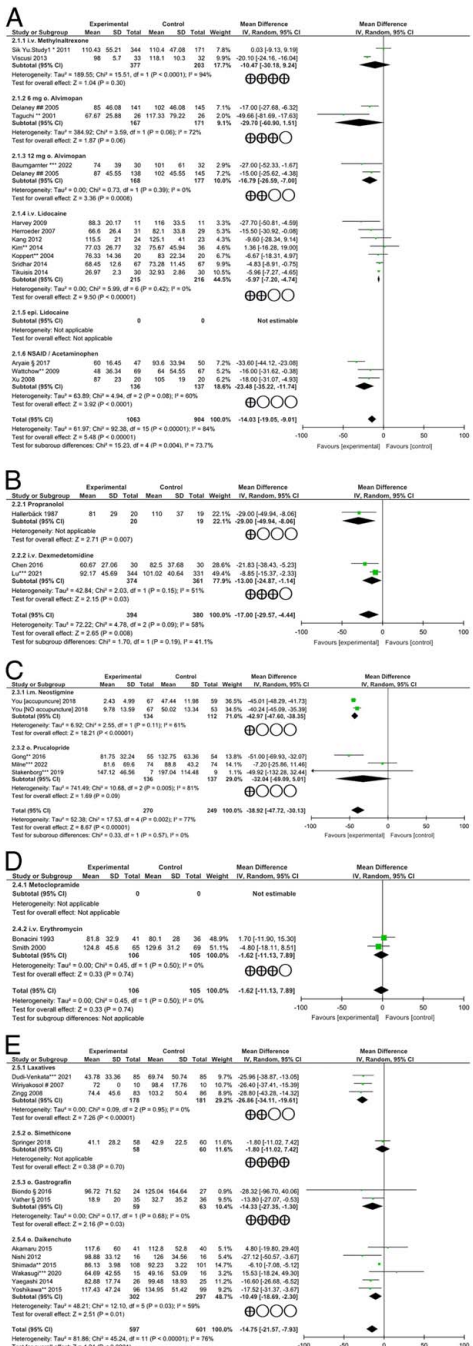

Figure 2. Duration until first defecation [h]. Effect of pharmacologic intervention on duration until first bowel movement versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. *data were extracted from clinical trial registries. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. # data estimated from publication graphs. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. § Studies did not isolate the variables 'time to first flatus' and 'time to first bowel movement' as separate variables but recorded the 'time to first flatus or bowel movement' as the outcome. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural; i.m., intramuscular. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

publication bias among different studies with various interventional pharmacologic treatment modalities regarding the continuous outcomes analyzed. If no meta-analysis could be calculated due to missing data or clinical or statistical heterogeneity, results of the individual studies are reported narratively.

Assessment of bias and quality of evidence

Risk of bias was assessed independently for each outcome of interest of each study included into the meta-analysis by two investigators and a third party, if necessary, using the Cochrane Collaboration's risk-of-bias tool-2 (available at: www.methods.cochrane.org; version from 22 August 2019; Supplement 4, Supplemental Digital Content 6, http://links.lww.com/JS9/C232 depicts results of risk of bias assessment). Quality of evidence was assessed using 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE software GRADEpro GDT; available at: www.gradepro.org). The respective certainty of evidence (CoE) is given at each calculation: very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

Results

Results from 55 RCTs with 5078 patients having undergone experimental intervention versus 3857 patients having undergone placebo, standard care (three studies) or no therapy (five studies), respectively, were included into the meta-analysis (Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233).

Reduction of peripheral opioid effects and opioid-sparing approaches

Three RCTs tested the selective μ-opioid receptor antagonist methylnaltrexone intravenously at different dosages against placebo for the prevention of POI in patients, who underwent oncologic colorectal resections with primary anastomosis[13,14]. Sik Yu *et al*. summarize the results of two RCTs with similar study designs in their publication[14]. Herein, 12 mg or 24 mg of methylnaltrexone was given repetitively after surgery until gastrointestinal recovery. Owing to an incompatible published data set and unavailability of source data, continuous data from the second RCT reported by Sik Yu *et al*. (NCT00387309) were excluded from the meta-analysis[14]. Nevertheless, findings regarding the effects of methylnaltrexone on gastrointestinal recovery from both studies summarized by Sik Yu *et al*. are basically consistent[14]. A similar study design with intravenous 0.3 mg/kg of methylnaltrexone was tested against placebo by Viscusi *et al*.[13]. Although some benefits of methylnaltrexone on gastrointestinal recovery were observed in the small RCT by Viscusi *et al*., these could not be confirmed in larger patient cohorts by Sik Yu *et al*.[13,14]. Even no significant differences in effectiveness were observed between the groups receiving different dosing strategies and the placebo group were described by Sik Yu *et al*.[14]. Thus, in the meta-analysis, methylnaltrexone failed to have an effect on LOS [MD −0.28 (−1.99–1.43]d, $P = 0.75$; Fig. 5A) or on the prevention of gastrointestinal dysmotility as indicated by both relevant outcome parameters, TTM [MD −10.47 (−30.18–9.24)h, $P = 0.30$; Fig. 2A] and achievement of the composite outcome GI-2 [MD −18.89 (−48.43–10.65)h, $P = 0.21$; Fig. 4A]. GI-2 combines TTM and TTD. The latter was

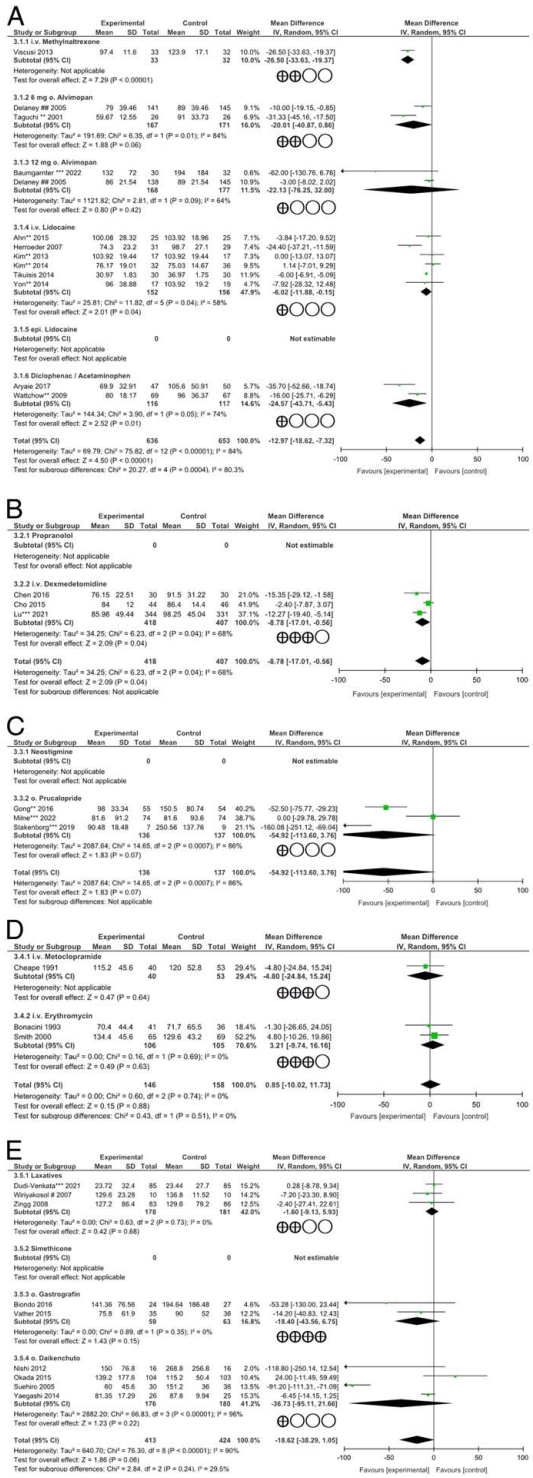

Figure 3. Duration until food tolerance [h]. Effect of pharmacologic intervention on duration until (solid) food tolerance versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. # data estimated from publication graphs. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

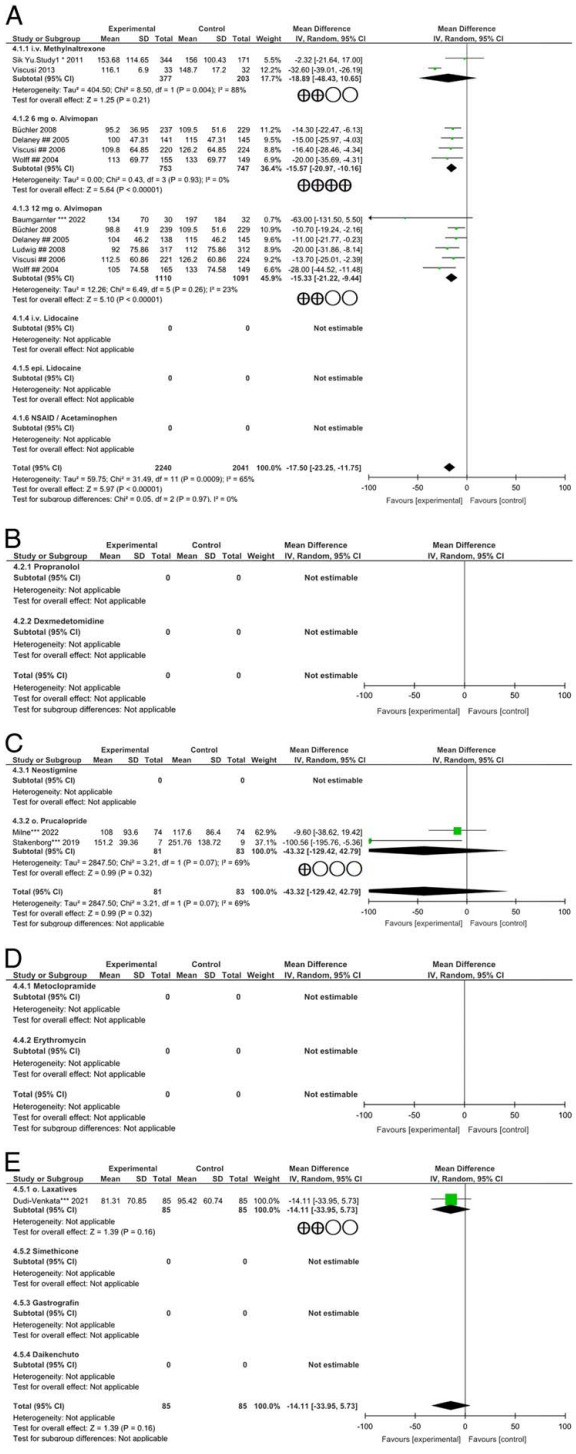

Figure 4. Duration until achievement of the composite outcome GI-2 [h]. Effect of pharmacologic intervention on duration until achievement of the composite outcome GI-2 versus comparator. GI-2 includes first bowel movement and oral intake tolerance. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants and adjuncts. *data were extracted from clinical trial registries. ***Data were obtained directly from the study authors. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; NSAID, non-steroidal anti-inflammatory drugs; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁.

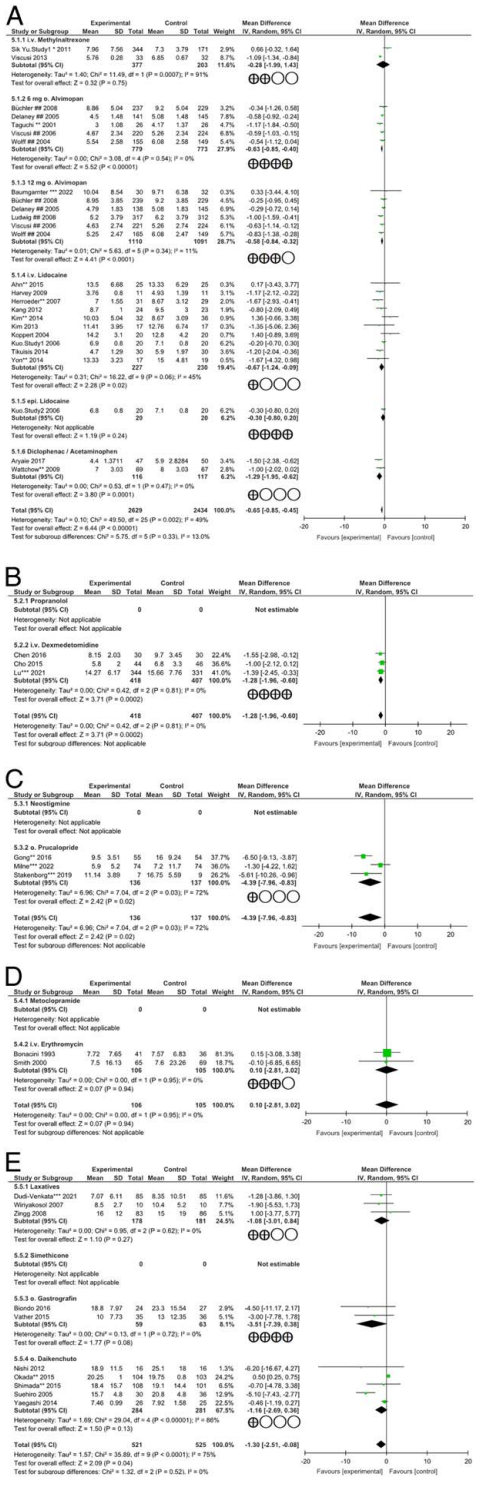

Figure 5. Length of hospital stay [d]. Effect of pharmacologic intervention on length of hospital stay versus comparator. Results are given as mean difference and 95% CI. A, Reduction of peripheral opioid effects and opioid-sparing approaches. B, Reduction of perioperative sympathetic hyperreaction. C, Parasympathomimetic agents. D, Prokinetic drugs. E, Laxatives, stimulants, and adjuncts. *data were extracted from clinical trial registries. **Estimation of mean ± SD using the method described by Wan *et al*.[12]. ***Data were obtained directly from the study authors. ## SD of means estimated using RevMan Calculator regarding the Cochrane Handbook. i.v., intravenous; o., per os; epi., epidural. Certainty of evidence is indicated for each calculation as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕.

reported as a single parameter only by Viscusi *et al*., thus potentially introducing bias regarding methylnaltrexone's efficacy in reducing the time to solid diet tolerance reported by Viscusi *et al*. Consequently, this leads to a low CoE. Seven RCTs investigated the efficacy of perioperative oral alvimopan, even a peripherally acting μ-opioid receptor antagonist, on postoperative bowel recovery. Alvimopan was administered once before surgery until postoperative day seven or reaching the endpoint of bowel recovery or discharge. The patient cohorts and administration protocols were reasonably homogeneous across studies. The four earliest studies included patients undergoing small or large bowel resection with primary anastomosis or hysterectomy[15–18], while Ludwig *et al*. and Büchler *et al*. focused on patients undergoing bowel resections with primary anastomosis[19,20]. Baumgartner *et al*. included patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy[21]. In the initial RCT by Taguchi *et al*., 1 mg or 6 mg of alvimopan versus placebo was evaluated[15], while more recent RCTs tested 12 mg against placebo[19,21]. Other studies investigated two dosing strategies, either 6 mg or 12 mg, against placebo[16–18,20] (Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233). As Taguchi *et al*. did not observe differences with 1mg alvimopan versus placebo[15] (Supplement 6, Supplemental Digital Content 8, http://links.lww.com/JS9/C234), a detailed presentation of these individual single study results in the respective figures is omitted. Regarding the dosage with 6 mg and 12 mg, the studies reported varying efficacy between individual dosing strategies, which were analyzed separately in the meta-analysis. The statistics of continuous outcomes primarily relied on time-to-event analyses reported in the included studies[16–20]. Means and SD were estimated according to the Cochrane Handbook and incorporated into the meta-analysis. Supplement 6 (Supplemental Digital Content 8, http://links.lww.com/JS9/C234) provides the synthesis of original hazard ratios for published continuous outcomes. The pooled data from various dosing strategies did not reveal differences in safety outcomes, exhibiting low CoE (Table 1). Although the analysis of individual outcomes did not show clear significance within different dosages of oral alvimopan, the meta-analysis highlights significant efficacy of higher-dose alvimopan (6 mg or 12 mg) on relevant outcomes for gastrointestinal and overall recovery, GI-2 and LOS (Figs 4A, 5A). These synthesized results of GI-2 and LOS were consistent with the meta-analysis of hazard ratios obtained from the primary published data, as presented in Supplement 6 (Supplemental Digital Content 8, http://links.lww.com/JS9/C234). Furthermore, the meta-analysis of results from four RCTs heterogeneously shows a reduced nasogastric tube (re-) insertion rate upon intervention with alvimopan [RR 0.58 (0.43–0.78), $P < 0.001$; Table 1].

Due to their opioid-sparing, analgesic and anti-inflammatory properties, NSAIDs, and selective cyclooxygenase-2 inhibitors have been tested regarding their effects on postoperative gastrointestinal dysmotility in several smaller RCTs. While the latter have some serious safety concerns and do not hold general approval, two RCTs testing twice perioperative applications of 1 mg/kg i.v. Flurbiprofen or perioperative 50 mg oral Diclofenac, twice daily for seven days, against placebo were identified[22,23]. One RCT evaluated the postoperative opioid-sparing effects of i.v. 1000 mg Acetaminophen administered perioperatively every 6 h for a maximum of five postoperative days following colorectal resections[24]. In the meta-analysis, these opioid-

sparing approaches had an effect on parameters indicating bowel recovery, including TTF [MD −14.64 (−19.60 to −9.68)h, $P<0.0001$; Fig. 1A], TTM [MD −23.48 (−35.22 to −11.74)h, $P<0.0001$; Fig. 2A] and TTD [MD −24.57 (−43.71 to −5.43)h, $P=0.01$; Fig. 3A] as well as on LOS [MD −1.29 (−1.95 to −0.62)d, $P=0.0001$; Fig. 5A]. However, the CoE is very low.

We identified 12 RCTs investigating effects of intravenous[25–36] or epidural[26,34] lidocaine with varying dosages and administration protocols (detailed information are given in Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233), and addressing their impact on gastrointestinal recovery following gastrointestinal tumor surgery as secondary endpoints. Meta-analysis of study data demonstrated positive effects of intravenous lidocaine on TTM [MD −5.97 [−7.20 to −4.74)h, $P<0.0001$; Fig. 2A], TTD [MD −6.02 (−11.88 to −0.15)h, $P=0.04$; Fig. 3A] and LOS [MD −0.67 (−1.24 to −0.09)d, $P=0.02$; Fig. 5A], as well as a trend towards shorter TTF [MD −4.66 (−9.98–0.65)h, $P=0.09$; Fig. 1A]. The meta-analysis of results from three studies[28,33,35] revealed higher patient satisfaction scores under intervention [MD 1.12 (0.60–1.64), $P<0.0001$; $I^2=0\%$]. Epidurally administered lidocaine had an effect on TTF [MD −15.71 (−28.81 to −2.62)h, $P=0.02$; Fig. 1A] but not on LOS. No further relevant outcomes were available in the epidural context.

No differences were observed concerning the risk of complications upon intervention with both selective μ-opioid receptor antagonists, NSAIDs, or Acetaminophen. Although one study explicitly reported one adverse event with intravenous lidocaine[28], the meta-analysis did not identify unfavorable complication rates upon administration of lidocaine. By contrast, the meta-analysis provides some evidence that relevant surgical complications occurred less frequently in the lidocaine groups [RR 0.35 (0.13–0.97), $P=0.04$; Table 1].

Reduction of perioperative sympathetic hyperreaction

Therapy with β-adrenoreceptor antagonists and α2-receptor agonists aims to downregulate perioperative sympathetic hyperactivity, thus disrupting the contribution of the enteric nervous system to postoperative gastrointestinal paralysis and POI[37,38]. Perioperative use of β-adrenoreceptor blockers for prophylaxis of postoperative ileus in patients undergoing colorectal resections was investigated in one RCT[37]. Either 4 mg or 10 mg of intravenous Propranolol were administered twice daily, and escalated to 40 mg or 80 mg per os after surgery. Both Propranolol regimens resulted in shorter TTF and TTM (Figs 1B, 2B). This effect was particularly evident in older patients (>60 years) and those who underwent left-sided colon resections. Propranolol led to a reduction in heart rate, but without notable cardiovascular side effects. However, the mixed patient cohort and unclear blinding results in very low CoE. Furthermore, this study does not include alternative readouts of gastrointestinal recovery after colorectal resections, such as diet tolerance or LOS.

Recent studies have focused on the α2-receptor agonist Dexmedetomidine, which has sympatholytic, sedative and analgesic effects, thereby promoting opioid-sparing benefits[38,39]. In three studies, Dexmedetomidine was administered perioperatively as an adjuvant to general anesthesia: loading doses (0.5 μg/kg–1μg/kg) before anesthesia induction and maintenance with 0.2 μg/kg/h–0.4 μg/kg/h during surgery[38,40,41]. In the study by Xin *et al.*, Dexmedetomidine was administered via *patient controlled analgesia* with 0.04 μg/h for 48 h in addition to postoperative opioid-based pain management[42]. Although Dexmedetomidine led to lower heart rates and blood pressures, it did not result in critical bradycardia, hypotension, or higher rates of clinically evident hemodynamic instability (Table 1). With a moderate to high CoE, the meta-analysis proves beneficial effects of perioperative i.v. Dexmedetomidine on TTF [MD −13.69 (−17.30 to −10.08)h, $P<0.0001$; Fig. 1B], TTM [MD −13.00 (−24.87 to −1.14)h, $P=0.03$; Fig. 2B], TTD [MD −8.78 (−17.01 to −0.56)h, $P=0.04$; Fig. 3B], and LOS [MD −1.28 (−1.96 to −0.60)d, $P=0.0002$; Fig. 5B]. Additionally, Xin *et al.* reported higher patient satisfaction, lower pain levels, subsequently reduced supplementary analgesic use, and lower incidence of nausea under *patient controlled analgesia* supplemented with dexmedetomidine[42].

Parasympathomimetic agents

Parasympathomimetics enhance intestinal smooth muscle tone. Two RCTs tested the efficacy of neostigmine in treatment of clinically evident POI following gastrointestinal tumor resections. Myrhoj *et al.*[43] defined paralysis as absence of flatus or stool on postoperative day two, with patients receiving either placebo or 0.5 mg Neostigmine intramuscularly in 3 h intervals. However, no significant effect of Neostigmine on gastrointestinal recovery was observed[43]. Because of inappropriate data format, these results were not suitable for inclusion into the meta-analysis. Similar inclusion criteria were employed by You *et al.*[44] in their four-arm RCT among patients after oncologic gastrectomy. Notably, bilateral injection of 0.5 mg Neostigmine at the ST36 acupuncture point was particularly effective and reduced TTF [MD −37.06 (−40.26 to −33.87)h, $P<0.0001$; Fig. 1C] and TTM [MD −42.97 (−47.60 to −38.35)h, $P<0.0001$; Fig. 2C]. Additionally, sole intramuscular injection of 1 mg Neostigmine outperformed both sole acupuncture and standard therapy[44]. However, CoE in this regard is low due to lack of blinding and heterogeneity of study results. Care has to be taken since complications, especially those of cardiovascular origin, are rarely reported.

Serotonin-5-hydroxytryptamine-4 receptor agonists unfold prokinetic activity through neuronal acetylcholine release in myenteric plexus, and exert local anti-inflammatory effects[6]. Three RCTs evaluated oral Prucalopride (2 mg, orally up to the 7th postoperative day)[45–47], which is approved in Germany for salvage therapy of chronic constipation[48]. Other drugs from this substance group including cisapride and mosapride are not generally approved, as described above, due to some severe cardiac side effects. The meta-analysis did not reveal any effects of oral Prucalopride on postoperative gastrointestinal recovery (Figs 1C–4C). Nevertheless, Prucalopride demonstrated some advantage in terms LOS [MD −4.39 (−7.96 to −0.83)d, $P=0.02$; Fig. 5C] with a very low CoE.

Prokinetic drugs

Two RCTs evaluated the effect of postoperative administration of 10 mg metoclopramide either intramuscularly or intravenously on prevention of postoperative gastrointestinal dysmotility[49,50]. Although some advantages regarding postoperative nausea and vomiting were observed in the small patient cohort reported by Davidson *et al.*, no relevant effects of metoclopramide were seen regarding TTD or rate of nasogastric tube reinsertion (Fig. 3D, Table 2).

Table 1

Summary of findings from dichotomous outcomes regarding opioid-sparing approaches and pharmacologic reduction of perioperative sympathetic hyperreaction.

Experimental pharmacologic intervention	Total complications	Cardiac complications	Pulmonary complications	Surgical complications > CD II°	Naso-gastric tube reinsertion
Reduction of peripheral opioid effects and opioid-sparing approaches					
i.v. Methylnaltrexone	↔ RR 1.0 95% CI 0.9–1.1 *P* = 0.93	↔ RR 1.25 95% CI 0.90–1.73 *P* = 0.18	↔ RR 0.79 95% CI 0.21–2.96 *P* = 0.73	—	—
CoE	⊕⊕⊕◯	⊕⊕⊕⊕	⊕⊕⊕◯	—	—
Number of RCTs	2 RCTs	3 RCTs	2 RCTs		
Heterogeneity	I^2 = 66%	I^2 = 0%	I^2 = 74%		
o. Alvimopan	↔ RR 0.97 95% CI 0.80–1.17 *P* = 0.73	↔ RR 0.81 95% CI 0.62–1.05 *P* = 0.11	↔ RR 3.00 95% CI 0.13–71.61 *P* = 0.50	↔ RR 0.79 95% CI 0.44–1.42 *P* = 0.43	↑ RR 0.58 95% CI 0.43–0.78 *P* < 0.001
CoE	⊕◯◯◯	⊕⊕◯◯	⊕⊕◯◯	⊕◯◯◯	⊕⊕⊕⊕
Number of RCTs	2 RCTs	5 RCTs	1 RCT	4 RCTs	4 RCTs
Heterogeneity	I^2 = 86%	I^2 = 0%	I^2 = n.a.	I^2 = 58%	I^2 = 0%
o. Diclophenac	—	↔ RR 0.49 95% CI 0.05–5.23 *P* = 0.55	—	—	—
CoE	—	⊕⊕◯◯	—	—	—
Number of RCTs		1 RCT			
Heterogeneity		I^2 = n.a.			
i.v. Lidocaine	↔ RR 0.71 95%CI 0.13–3.97 *P* = 0.69	↔ RR 7.00 95%CI 0.38–127.32 *P* = 0.19	—	↑ RR 0.35 95%CI 0.13–0.97 *P* = 0.04	↔ n.e.
CoE	⊕◯◯◯	⊕⊕⊕◯	—	⊕◯◯◯	⊕⊕◯◯
Number of RCTs	2 RCTs	4 RCTs		4 RCTs	1 RCT
Heterogeneity	I^2 = 82%	I^2 = n.a.		I^2 = 0%	I^2 = n.a.
epi. Lidocaine	—	↔ n.e.	—	—	↔ n.e.
CoE	—	⊕⊕⊕◯	—	—	⊕⊕◯◯
Nnumber of RCTs		2 RCT			1 RCT
Heterogeneity		I^2 = n.a.			I^2 = n.a.
Reduction of perioperative sympathetic hyperreaction					
i.v. / o. Propranolol	—	—	↔ n.e.	—	—
CoE	—	—	⊕⊕◯◯	—	—
Number of RCTs			1 RCT		
Heterogeneity			I^2 = n.a.		
i.v. Dexmedetomidine	—	↔ RR 0.86 95% CI 0.65–1.14 *P* = 0.29	—	↔ RR 0.42 95% CI 0.09–2.04 *P* = 0.28	—
CoE	—	⊕⊕⊕⊕	—	⊕⊕⊕⊕	—
Number of RCTs		2 RCTs		1 RCT	
Heterogeneity		I^2 = 0%		I^2 = n.a.	

Effect of experimental pharmacologic intervention on dichotomous outcomes versus comparator (no effect: ↔; ↑ = positive effect through experimental intervention, indicated by decreasing risk ratio; ↓ = negative effect through experimental intervention, indicated by increasing risk ratio). - = outcome not assessed in the respective studies. n.a., not applicable; n.e., not estimable; CD, Clavien–Dindo classification of surgical complications[11]. i.v., intravenous; o., oral; epi., epidural; CoE, certainty of evidence regarding GRADE (Grading of Recommendations, Assessment, Development and Evaluations, GRADE software GRADEpro GDT; available at: www.gradepro.org). Certainty of evidence is indicated for each calculation as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕. RCT, randomized-controlled trial; RR, risk ratio.

The macrolide antibiotic erythromycin, which acts as a prokinetic agent especially in the upper gastrointestinal tract through motilin receptors, was tested in two RCTs against placebo. 200 mg–250 mg erythromycin, administered repetitively intravenously after surgery showed no effect in the prevention of postoperative gastrointestinal dysmotility including TTF, TTM, or TTD (Figs 1D–3D) in the meta-analysis of two RCTs[51,52].

Table 2

Summary of findings from dichotomous outcomes regarding parasympathomimetics, prokinetics, laxatives, and stimulants.

Experimental pharmacologic intervention	Total complications	Cardiac complications	Pulmonary complications	Surgical complications > CD II°	Naso-gastric tube reinsertion
Parasympathomimetic agents					
i.m. Neostigmine	—	—	—	—	—
o. Prucalopride	↔ RR 1.15 95% CI 0.77–1.70 $P = 0.50$	↔ RR 0.95 95% CI 0.33–2.76 $P = 0.93$	↔ RR 2.0 95% CI 0.19–21.58 $P = 0.57$	↔ RR 1.05 95% CI 0.56–1.95 $P = 0.88$	↔ RR 0.75 95% CI 0.40–1.39 $P = 0.36$
CoE	⨁⨁⨁⨁	⨁⨁⨁◯	⨁⨁⨁⨁	⨁⨁⨁⨁	⨁⨁⨁⨁
Number of RCTs	1 RCT	2 RCTs	1 RCT	2 RCTs	2 RCTs
Heterogeneity	I^2 = n.a.	I^2 = 41%	I^2 = n.a.	I^2 = 0%	I^2 = 0%
Prokinetic drugs					
i.v. Metoclopramide	—	—	—	—	↔ RR 0.88 95%CI 0.27–2.92 $P = 0.84$
CoE	—	—	—	—	⨁⨁⨁◯
Number of RCTs					1 RCT
Heterogeneity					I^2 = n.a.
i.v. Erythromycin	↔ RR 0.82 95% CI 0.39–1.73 $P = 0.60$	↔ RR 0.10 95% CI 0.01–1.71 $P = 0.11$	↔ RR 1.76 95% CI 0.17–18.57 $P = 0.64$	—	↔ RR 1.27 95% CI 0.41–3.97 $P = 0.68$
CoE	⨁⨁⨁◯	⨁⨁⨁◯	⨁⨁⨁⨁	—	⨁⨁⨁◯
Number of RCTs	1 RCT	1 RCT	1 RCT		1 RCT
Heterogeneity	I^2 = n.a.	I^2 = n.a.	I^2 = n.a.		I^2 = n.a.
Laxatives, stimulants, and adjuncts					
Laxatives	↔ RR 0.86 95% CI 0.41–1.79 $P = 0.69$	↔ RR 1.26 95% CI 0.35–4.60 $P = 0.73$	↔ RR 2.39 95% CI 0.85–6.77 $P = 0.10$	↔ RR 1.52 95% CI 0.85–2.72 $P = 0.36$	↔ RR 0.94 95% CI 0.65–1.36 $P = 0.75$
CoE	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯	⨁⨁◯◯
Number of RCTs	2 RCTs	3 RCTs	3 RCTs	3 RCTs	2 RCTs
Heterogeneity	I^2 = 11%	I^2 = 0%	I^2 = 10%	I^2 = 1%	I^2 = 0%
o. Simethicone	↔ RR 1.10 95% CI 0.63–1.91 $P = 0.75$	—	—	↔ RR 0.52 95% CI 0.05–5.55 $P = 0.59$	—
CoE	⨁⨁⨁⨁	—	—	⨁⨁⨁⨁	—
Number of RCTs	1 RCT			1 RCT	
Heterogeneity	I^2 = n.a.			I^2 = n.a.	
o. Gastrografin	↔ RR 0.99 95% CI 0.82–1.19 $P = 0.93$	—	↔ RR 0.56 95% CI 0.05–5.82 $P = 0.63$	↔ RR 0.81 95% CI 0.06–10.37 $P = 0.87$	↔ RR 0.88 95% CI 0.70–1.10 $P = 0.26$
CoE	⨁⨁⨁⨁	—	⨁⨁⨁⨁	⨁⨁⨁◯	⨁⨁⨁⨁
Number of RCTs	2 RCTs		1 RCT	2 RCTs	2 RCTs
Heterogeneity	I^2 = 0%		I^2 = n.a.	I^2 = 73%	I^2 = 0%
o. Daikenchuto	↔ RR 0.93 95% CI 0.69–1.24 $P = 0.61$	—	↔ RR 0.37 95% CI 0.10–1.47 $P = 0.16$	↔ RR 0.81 95% CI 0.39–1.65 $P = 0.56$	↔ RR 0.99 95% CI 0.06–15.62 $P = 0.99$
CoE	⨁⨁◯◯	—	⨁⨁◯◯	⨁◯◯◯	⨁⨁◯◯
Number of RCTs	8 RCTs		5 RCTs	5 RCTs	1 RCT
Heterogeneity	I^2 = 15%		I^2 = 8%	I^2 = 45%	I^2 = n.a.

Effect of experimental pharmacologic intervention on dichotomous outcomes versus comparator (no effect: ↔; ↑ = positive effect through experimental intervention, indicated by decreasing risk ratio; ↓ = negative effect through experimental intervention, indicated by increasing risk ratio). - = outcome not assessed in the respective studies. n.a., not applicable; CD, Clavien–Dindo classification of surgical complications[11]. i.v., intravenous; o., oral; i.m., intramuscular; CoE, certainty of evidence regarding GRADE (Grading of Recommendations, Assessment, Development and Evaluations, GRADE software GRADEpro GDT; available at: www.gradepro.org). Certainty of evidence is indicated for each calculation as very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁. RCT, randomized-controlled trial; RR, risk ratio.

Laxatives, stimulants, and adjuncts

Beneath their osmotic effects, laxatives increase colonic motility. Two RCTs were identified in which colorectal cancer patients perioperatively received laxatives orally including 10 mg bisacodyl or a multimodal mixture versus placebo or standard therapy, respectively[53,54]. One further study assessed rectal application 10 mg bisacodyl once at postoperative day 3 for the treatment of clinically manifest POI[55]. Laxatives were administered repetitively until reaching the respective study endpoints (bowel movement or GI-2). The meta-analysis demonstrated beneficial effects of laxatives, both in the prevention of gastrointestinal dysmotility and treatment of POI following colorectal resections, with regard to TTF [MD – 7.30 (– 12.54 to – 2.05)h, $P = 0.006$; Fig. 1E] and TTM [MD – 26.86 (– 34.11 to – 19.61)h, $P < 0.0001$; Fig. 2E]. In the smaller study by Zingg *et al.*[53] bisacodyl shortened the time to reach the composite outcome GI-3, which combines TTD and TTM or TTF. In the report of their larger trial, Dudi-Venkata *et al.*[54] also noted a significantly shorter duration until achieving the composite criterion GI-2. However, this effect could not be replicated in the present analysis of the primary data provided by the authors [MD – 14.11 (– 33.95–5.73)h, $P = 0.16$; Fig. 4E]. Thereby perioperative therapy with laxatives is safe as complication rates did not differ between the investigated groups (Table 2). However, no effect was observed with regard to TTD or LOS (Figs 3E, 5E).

In contrast, simethicone (160 mg oral, four times daily) did not yield an effect on prevention of gastrointestinal dysmotility following colorectal resections in one RCT[56]. Concerning the osmotically active radiographic contrast agent Gastrografin (100 ml oral at diagnosis of POI) the meta-analysis of two RCTs revealed some advantages regarding TTF or TTM [MD – 14.33 (– 27.35 to – 1.30)h, $P = 0.03$; Fig. 2E] for therapy of clinically manifest POI[57,58]. Both RCTs summarized TTF or TTM into a single outcome measure, which is a relevant limitation. No other benefits were observed by Vather *et al.*[58], neither regarding time to resolution of POI, nor regarding any other parameters including nausea and vomiting. Even the meta-analysis of other surrogate parameters for resolution of POI, including TTD or LOS showed no further benefits of Gastrografin in the treatment of clinically manifest POI (Figs 3E, 5E).

Daikenchuto (DKC) is a phytotherapeutic formula derived from traditional Japanese medicine and consists of the herbal components Japanese pepper, dried ginger, ginseng root, and maltose powder[59]. DKC is attributed with stool-regulating and anti-inflammatory properties[60–62]. Eleven RCTs were identified, wherein the perioperative oral administration of DKC was tested with varying dosages and administration protocols (detailed information are given in Supplement 5, Supplemental Digital Content 7, http://links.lww.com/JS9/C233) against placebo or no treatment for its impact on postoperative gastrointestinal motility in the context of gastrointestinal tumor resections[59–69]. Although effects were observed in the meta-analysis for DKC concerning TTF [MD – 9.91 (– 19.15 to – 0.67)h, $P = 0.04$; Fig. 1E] and TTM [MD – 10.49 (– 18.69 to – 2.30]h, $P = 0.01$; Fig. 2E], DKC failed to demonstrate efficacy in relation to other parameters of gastrointestinal recovery, including the rate of nasogastric tube reinsertion, TTD and LOS (Figs 3E, 5E, Table 2). Four of the RCTs provide insight into quality of life and patient satisfaction across various dimensions, with all consistently reporting no differences between DKC and their control groups[60,61,64,65]. However, CoE regarding TTF and TTM remains very low due to the use of diverse comparators across various RCTs, high risk of bias among the studies and inconsistency in results.

Discussion

The presented meta-analysis evaluates evidence from RCTs that have focused on the pharmacological prophylaxis or treatment of POI following major oncologic gastrointestinal surgery. The systematic review with meta-analysis included data from 5078 patients in the intervention groups. Across the various RCTs reviewed here, a total of 17 substances were tested. These were categorized into five subgroups regarding their mechanisms of action. Single RCTs that evaluated choline citrate[70] and glutamin[71] were not included in the meta-analysis. These studies did not show any relevant effects on postoperative gastrointestinal dysmotility and bowel recovery in their reported results.

The selection of medications limited to those approved by German and/or U.S. American drug administration authorities underscores the stringent evidence-based criteria regarding efficacy and safety driving pharmaceutical authorization. However, it is crucial to note that this approach does not diminish the broader applicability of our findings beyond the German or U.S. American healthcare context, as the inclusion process of studies in the meta-analysis largely pertains to globally available medications. Furthermore, our deliberate focus on medications approved within these rigorously evidence-based healthcare systems does not imply restrictions on the general validity of our results. This selection process purposefully excludes therapeutic strategies relying on limited evidence, ensuring the comprehensive evaluation of treatments demonstrating both efficacy and safety within a well-established healthcare setting. Certain substances tested in RCTs for POI were excluded from the meta-analysis. This exclusion was attributed to significant safety concerns, coupled with a lack of general approval in both health care systems. Consequently, these substances exhibit limited global applicability in the perioperative setting. The excluded substances encompass selective cyclooxygenase-2 inhibitors, cholecystokinin-like acting drugs, ghrelin agonists, dihydroergotamine, and the serotonin-5-hydroxytryptamine-4 receptor agonists cisapride and mosapride. However, their benefit in preventing POI is uncertain and evidence for most of these substances does not substantially go beyond the results of the meta-analyses by Traut *et al.*[7] from 2008 and Milne *et al.*[1] from 2018.

The evidence for pharmacological treatment of clinically manifest POI is very limited, but the results from one single study suggest, that neostigmine is particularly effective[44]. In the prophylaxis of POI, especially opioid-sparing analgesic techniques, reduction of peripheral opioid effects and approaches that reduce sympathetic hyperreactivity, along with early use of laxatives, should be considered. In particular, the perioperative oral administration of alvimopan or intravenous administration of lidocaine or dexmedetomidine demonstrated effectiveness in various domains of postoperative bowel recovery and LOS, with dexmedetomidine showing the strongest effects regarding LOS as the surrogate parameter for postoperative overall recovery. However, it remains unclear which surgical cancer patients would benefit most from the perioperative administration of

dexmedetomidine. Furthermore, regarding the sympatholytic and analgesic effects of dexmedetomidine, it is unclear whether pharmacological therapy with dexmedetomidine is at least equivalent or more effective compared to the widely used practice of epidural anesthesia in abdominal surgery, or to what extent its effects can be potentiated by spinal analgesic techniques. However, when considering the indications and dosing of dexmedetomidine in the perioperative setting, it is important to take into account the adverse events reported by Beloeil *et al*. and Shehabi *et al*. These authors reported increasing cardiac complications and long-term mortality, albeit at substantially higher doses, longer duration of administration and in different settings and patient populations[72–74]. Even in the context of long-term use of alvimopan for chronic opioid-induced constipation, severe cardiac side effects have been observed[75]. Consequently, despite not being approved in Germany, the indication for alvimopan by the American Food and Drug Administration is strictly limited to the perioperative setting, specifically for patients who have undergone bowel resections with primary anastomosis[75]. Nevertheless, in contrast to Methylnaltrexone, another representative of the class of peripherally acting μ-opioid receptor antagonists, our meta-analysis demonstrated good effectiveness in the assessed domains of postoperative bowel and overall recovery after perioperative administration of 6 mg or 12 mg alvimopan versus placebo. No differences in the safety profile of perioperative alvimopan were observed in our meta-analysis. Vice versa, inadequate pharmacological preventive measures for POI lead to increased postoperative morbidity and longer LOS. This is demonstrated by the results of the present meta-analysis concerning lidocaine, dexmedetomidine, and alvimopan.

Despite these findings, our study has some limitations primarily rooted in the published data and heterogeneous study populations. The pathophysiology of POI is multifactorial, and beyond the pathways addressed by the proposed pharmacological treatment options, further factors contribute to an increased risk of POI. There is some evidence available for nonpharmacological, adjunctive interventions for patients after gastrointestinal surgery to prevent POI, such as early use of coffee or chewing gum and in general early mobilization[76–78]. Nevertheless, these were not the focus of our systematic review and meta-analysis. However, they can be applied as safe and cost-effective adjuvant interventions in clinical practice. Moreover, procedure-specific and surgical-technical aspects are relevant in the development of POI, such as surgical site, minimally invasiveness as well as factors like operation, and anesthesia duration or patient-specific characteristics such as general physical condition. However, these factors are inadequately addressed within the scope of the meta-analysis since the patient cohorts reported in the current literature exhibit heterogeneity. The absence of subgroup analyses in individual publications and the lack of available or published primary data impede the synthesis of data for secondary subgroup analyses. Consequently, meaningful identification of patient subgroups that particularly benefit from specific pharmacological interventions remains elusive based on the available data. This underscores the need for further clinical research, especially regarding the most promising pharmacological approaches for preventing POI identified in our meta-analysis. These include opioid-sparing approaches, peripheral opioid antagonism through perioperative administration of lidocaine or alvimopan and alpha-2 agonism through dexmedetomidine.

Conclusion

In summary, effective prevention as well as adequate therapeutic pharmacologic options against prolonged gastrointestinal dysmotility and POI is important to enhance outcome of patients after oncologic gastrointestinal surgery as well as to reduce healthcare resource utilization and length of hospital stays. However, considering the current state of research, evidence for pharmacological intervention for either prevention of postoperative gastrointestinal dysmotility or therapy of POI following gastrointestinal tumor resections is limited. The findings from our meta-analysis can be used to generate hypotheses for further studies in this field.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

M.R. was supported by the Justus-Liebig University Giessen Clinician Scientist Program in Biomedical Research (JLU-CAREER) funded by the German Research Foundation (DFG No. GU405/14-1).

T.O.V. was funded by the German Cancer Aid (Deutsche Krebshilfe) for the development of an S3 Guideline for 'Perioperative Treatment in gastrointestinal Cancer Surgery'.

Author contribution

All the authors have made a substantial contribution to the concept or design of the study, or the acquisition, analysis or interpretation of data, and to drafting the work or revising it critically for important intellectual content. S.P., T.V., and M.W.: study concept; M.R., T.V., M.W., and A.H.: data collection; M.R., M.W., and A.H.: data analysis; M.R., F.W., M.S., M.W., and A.H.: data interpretation; M.R., M.W., and A.H.: writing – first draft; F.W., S.P., M.S., and T.V.: writing – critical revision.

Conflicts of interest disclosure

No conflicts of interests to be declared concerning this article.

Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO registry.
2. Unique identifying number or registration ID: PROSPERO 2022 CRD42022351799.
3. Hyperlink to your specific registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022351799.

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Data availability statement

Any datasets generated during and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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