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Pharmacological prevention and treatment of opioid-induced constipation in cancer patients: A systematic review and meta-analysis

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ABSTRACT

Background: Cancer-related pain often requires opioid treatment with opioid-induced constipation (OIC) as its most frequent gastrointestinal side-effect. Both for prevention and treatment of OIC osmotic (e.g. polyethylene glycol) and stimulant (e.g. bisacodyl) laxatives are widely used. Newer drugs such as the peripherally acting μ-opioid receptor antagonists (PAMORAs) and naloxone in a fixed combination with oxycodone have become available for the management of OIC.

This systematic review and meta-analysis aims to give an overview of the scientific evidence on pharmacological strategies for the prevention and treatment of OIC in cancer patients.

Methods: A systematic search in PubMed, Embase, Web of Science and the Cochrane Library was completed from inception up to 22 October 2022. Randomized and non-randomized studies were systematically selected. Bowel function and adverse drug events were assessed.

Results: Twenty trials (prevention: five RCTs and three cohort studies; treatment: ten RCTs and two comparative cohort studies) were included in the review.

Regarding the prevention of OIC, three RCTs compared laxatives with other laxatives, finding no clear differences in effectivity of the laxatives used. One cohort study showed a significant benefit of magnesium oxide compared with no laxative. One RCT found a significant benefit for the PAMORA naldemedine compared with magnesium oxide. Preventive use of oxycodone/naloxone did not show a significant difference in two out of three other studies compared to oxycodone or fentanyl. A meta-analysis was not possible.

Regarding the treatment of OIC, two RCTs compared laxatives, of which one RCT found that polyethylene glycol was significantly more effective than sennosides. Seven studies compared an opioid antagonist (naloxone, methylnaltrexone or naldemedine) with placebo and three studies compared different dosages of opioid antagonists. These studies with opioid antagonists were used for the meta-analysis.

Oxycodone/naloxone showed a significant improvement in Bowel Function Index compared to oxycodone with laxatives (MD −13.68; 95 % CI −18.38 to −8.98; $I^2 = 58$ %). Adverse drug event rates were similar amongst both groups, except for nausea in favour of oxycodone/naloxone (RR 0.51; 95 % CI 0.31–0.83; $I^2 = 0$ %). Naldemedine (NAL) and methylnaltrexone (MNTX) demonstrated significantly higher response rates compared to placebo (NAL: RR 2.07, 95 % CI 1.64–2.61, $I^2 = 0$ %; MNTX: RR 3.83, 95 % CI 2.81–5.22, $I^2 = 0$ %). With regard to adverse events, abdominal pain was more present in treatment with methylnaltrexone and diarrhea was significantly more present in treatment with naldemedine. Different dosages of methylnaltrexone were not significantly different with regard to both efficacy and adverse drug event rates.

Conclusions: Magnesium oxide and naldemedine are most likely effective for prevention of OIC in cancer patients. Naloxone in a fixed combination with oxycodone, naldemedine and methylnaltrexone effectively treat OIC in

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cancer patients with acceptable adverse events. However, their effect has not been compared to standard (osmotic and stimulant) laxatives. More studies comparing standard laxatives with each other and with opioid antagonists are necessary before recommendations for clinical practice can be made.

Introduction

Cancer-related pain is common, with an overall prevalence of 44.5 % and is experienced by 30.6 % of the patients as moderate to severe [1]. It diminishes quality of life by causing distress and affecting quality of sleep and physical, psychological, social and spiritual functioning [2,3]. Treatment of cancer-related pain can be challenging. It often consists of opioid-based pharmacotherapy [4–6]. Opioids have several gastrointestinal adverse effects, of which opioid-induced constipation (OIC) is the most common side effect with a reported prevalence ranging between 22 % and 81 % [7].

OIC significantly impairs the quality of life due to physical, psychological and social problems [8–12]. Additionally, the constipation may be so severe that patients prefer to reduce or discontinue opioids in order to improve their bowel function [13,14]. This can result in worsening of pain and even more reduction of quality of life [15]. Thus, OIC is a side effect with several important implications.

OIC can be diagnosed using the Rome IV criteria (Supplementary Table 1). Several assessment tools have been developed to evaluate OIC, of which the Bowel Function Index (BFI) is the commonly used tool in clinical trials. The BFI is a validated, clinician-administered, patient-reported questionnaire that has been recommended as the assessment tool of choice for OIC [16–20]. It contains three questions assessing ease of defecation, feeling of incomplete bowel evacuation and the patient's judgment of constipation over the last seven days. Each question has a score range from 0 (best possible outcome) to 100 (worst possible outcome), with a mean total score of $\geq$ 30 indicating clinically significant constipation. Another tool is the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire. This questionnaire contains twelve items measuring stool symptoms, rectal symptoms and abdominal symptoms. It has been validated for the assessment of OIC in patients with lower back pain [21]. The PAC-SYM is more time-consuming than the BFI and correlates moderately with it, making the BFI more practical for assessing OIC [17,19].

Management of OIC in cancer patients can be more challenging than in non-cancer patients, due to additional factors contributing to constipation. Firstly, cancer patients are mostly elderly, who already have decreased colonic motility caused by aging [22]. Secondly, they may show decreased mobility, inadequate oral intake of fluids and dietary fibers, tumor growth in the gastrointestinal tract and/or peritoneum and neuropathy of the autonomic nervous system, and may use other constipation-inducing drugs (e.g. anticholinergics and antiemetics) [23–25]. Hence, the prevalence of OIC is higher in cancer patients than in non-cancer patients and OIC may be less responsive to opioid antagonists in cancer patients [16].

Non-pharmacological management alone, e.g. increasing fluid and fiber intake and mobility, is often insufficient for the management of OIC [26]. Moreover, these lifestyle interventions may not be feasible for patients with advanced illness, due to cancer-related symptoms. Therefore, pharmacological treatment of OIC is often needed in cancer patients.

For pharmacological treatment different types of laxatives are available. Both for prevention and treatment of OIC standard laxatives such as osmotic laxatives (e.g. polyethylene glycol (PEG), magnesium (hydr)oxide) and stimulant laxatives (e.g. sodium picosulphate, sennosides) are recommended as first-line agents since they are safe, inexpensive and widely accessible [26–28]. Osmotic laxatives act by drawing water into the intestinal tract, hereby softening the stool. Stimulant laxatives irritate the sensory nerve endings of the myenteric plexus, which increases peristaltic contractions and reduces the absorption of water from the gut [26,29]. In chronic constipation psyllium (a bulk-forming agent), lactulose, polyethylene glycol (osmotic laxatives), bisacodyl and sodium picosulfate (stimulant laxatives) have been shown to be effective in placebo-controlled randomized clinical trials [29,30].

A relatively new class of drugs are the peripherally acting μ-opioid receptor antagonists (PAMORAs). These drugs (e.g. methylnaltrexone, naldemedine) are the best mechanism based treatment of OIC, but currently are only registered for second line treatment [27]. PAMORAs block the μ-opioid receptor peripherally in the gastrointestinal tract, do not cross the blood–brain barrier and therefore do not counteract the analgesic effect of opioids [31]. This is in contrast to naloxone, a centrally acting opioid antagonist which counteracts opioids if given parenterally. A fixed combination of naloxone and prolonged-release oxycodone has been developed for oral administration. Orally administered naloxone and naloxegol (a polyethylene glycol derivative of naloxol, derived from naloxone [32]) act mainly directly on the opioid receptors in the gut and do not counter the effect of opioids, because they undergo a substantial hepatic first-pass effect, resulting in a systemic bioavailability of less than three percent [27,33,34].

Until now, most systematic reviews focused mainly on the treatment of OIC in non-cancer patients [35,36]. Therefore, this systematic review and meta-analysis investigates the evidence of pharmacological strategies on the prevention and treatment of OIC in cancer patients.

Methods

This systematic review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [37] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [38]. The study protocol was registered in the PROSPERO database (registration number CRD42022362096).

Literature search

A systematic search was performed in the following databases: PubMed, Embase, Clarivate Analytics/Web of Science Core Collection and the Wiley/Cochrane Library. The timeframe within the databases was from inception to 12 October 2022 and the search was conducted by a medical information specialist (GLB). The search included keywords and free text terms for (synonyms of) 'opioids' combined with (synonyms of) 'constipation' combined with (synonyms of) 'cancer'. A full overview of the search terms per database can be found in the Appendix A (see Supplementary Table 2.1 to 2.4). Duplicate articles were excluded and the remaining articles were screened for eligibility. Articles that were not available in digital form were retrieved from national university libraries or from the original author.

Selection process

Studies eligible for inclusion were randomized controlled trials or non-randomized comparative cohort studies investigating any pharmacological intervention for prevention or treatment of OIC in adult cancer patients.

We excluded studies that examined non-cancer patients, pediatric patients, healthy volunteers, non-pharmacological interventions or constipation not caused by opioids. Animal studies, in vitro studies, articles written in languages other than English or Dutch, qualitative studies, non-original studies (i.e. reviews, conference abstracts,

editorials), case reports and study protocols were also excluded. Reasons for exclusion were documented (Fig. 1).

It was anticipated that some studies might have examined a mixed group of cancer and non-cancer patients. In order to get meaningful results, studies that consisted of a majority (≥50 %) of cancer patients or reported a subgroup analysis for cancer patients were included.

Two reviewers (FS and KK) independently screened all titles, abstracts and full-texts based on the eligibility criteria. Discrepancies were resolved by a third reviewer (DB). Reference lists of included articles were also screened for relevant studies.

Data extraction

One reviewer (KK) performed the data extraction using a data-extraction form and was checked by a second reviewer (DB). Any errors were resolved with the consensus of the two reviewers after checking with the original source. The data extraction form included information on publication year, journal, study design, study duration, funding, inclusion/exclusion criteria, trial medication, dose, route of administration of laxatives and PAMORA, sociodemographic and clinical data and outcomes (bowel function and most common adverse events (overall, abdominal pain, diarrhea and vomiting)). Data were extracted from the original article or from graphs using a graph digitizer.

Risk of bias assessment

The risk of bias of the included studies was assessed independently by two reviewers (KK and FS or DB). We used the assessment the Cochrane Collaboration's risk of bias tool for randomized clinical trials [37] for RCTs and the Risk Of Bias In Non-randomized Studies- of Interventions (ROBINS-I) tool for cohort studies [39]. Disagreements were resolved by discussion.

The certainty of the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

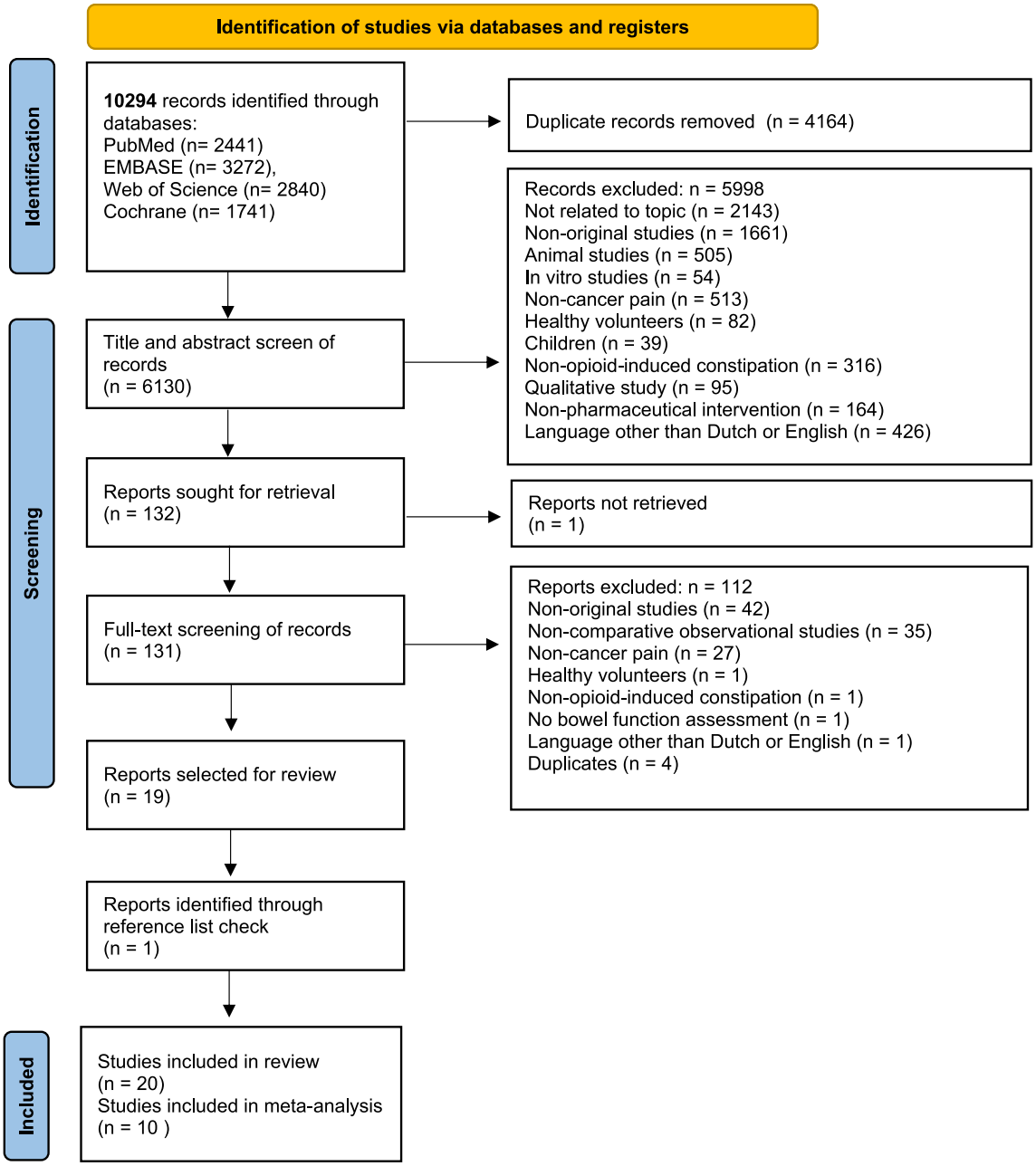

Fig. 1. PRISMA flow diagram of included studies.

approach [40]. This tool assesses five domains: methodological limitation (risk of bias), imprecision, inconsistency (heterogeneity), indirectness and publication bias. Each outcome is graded as high, moderate, low or very low certainty of evidence.

Statistical analysis

When possible, outcome data were analyzed quantitatively by calculating a pooled effect of different studies. In case it was not possible to pool quantitative data for meta-analysis, outcomes were presented narratively. For the meta-analysis, the Mantel-Haenszel random-effects model was used to estimate the overall effect size and 95 % confidence intervals (95 % CIs).

Dichotomous variables were analyzed dividing the number of events in the treatment arm by the number of events in the comparator arm. The pooled analysis was presented as a risk ratio (RR).

Continuous variables were analyzed using the mean and 95 % CI. The pooled analysis was presented as the mean difference with 95 % CI.

We conducted subgroup analyses for treatment with naldemedine and treatment with methylnaltrexone. For methylnaltrexone, we performed an additional analysis evaluating low dosage versus high dosage of methylnaltrexone.

Heterogeneity between studies was determined by using the Chi^2- and I^2-statistic. The Chi^2-test computed a p-value, with a p value of < 0.10 suggesting heterogeneity. The degree of heterogeneity was represented by the I^2 statistic where values 30–60 %, 50–90 % and 75 %–100 % suggested moderate, substantial and high heterogeneity, respectively [37]. Heterogeneity was reported in the forest plots.

All analyses were performed with Review Manager®, version 5.3.5.

Results

Study selection

The literature search identified 10.294 articles. The flowchart of the search, selection and review process is presented in Fig. 1. In total, 20 studies were included in the review [41–60] of which 10 were eligible for the meta-analysis [42–44,48–51,53,56,58]. The characteristics and main outcomes of the included studies are summarized in Table 1. Eight trials (five RCTs and three cohort studies) investigated prevention of OIC and twelve studies (ten RCTs and two cohort studies) investigated treatment of OIC. A total of 3095 participants was included, with 1473 participants in the meta-analyses. The most common reported bowel function outcomes were change in (complete) spontaneous bowel movements per week, spontaneous bowel movement response rate, response rate of rescue-free bowel movements < 4 h or < 24 h after the first dose, the total score of the BFI or Rome IV criteria.

Prevention of OIC in cancer patients

Standard laxatives. One RCT investigated sennosides versus lactulose in 91 cancer patients commencing opioid therapy [41]. It did not find significant differences in defecation-free periods, mean number of defecation days or the general state of health after 27 days of treatment. Another RCT compared polyethylene glycol (PEG), sodium picosulphate (SPS), lactulose and no laxative use (NL) in 358 ambulatory cancer patients [60]. After 7 days, there were no significant differences in number of patients with a stool-free interval > 72 h, mean defecation frequency per 5 days or quality of life. SPS, PEG and NL showed a lower numerical rating scale (NRS) of constipation than lactulose ($p = 0.01$, see Table 1). In contradiction to what the authors state, this study does not allow a conclusion about the effectivity of the laxatives used.

Another RCT compared sennosides with Misrakasneham, an old Ayurvedic liquid medicine with different kinds of herbs, castor oil, ghee and milk (not available in Western countries) in 50 cancer patients starting on oral morphine [54]. No significant differences in satisfactory bowel movements were found after 14 days.

A prospective, observational cohort study compared the incidence of OIC 14 days after initiation of opioid therapy in 220 patients treated with laxatives or without laxatives [59]. Patients receiving laxatives were mainly treated with magnesium oxide (89 %). After two weeks of treatment, the incidence of OIC based on the Rome IV criteria was 48 % (95 % CI 38.1–57.5 %) in the group treated with laxatives and 65 % (95 % CI 55.0–74.2 %) in the group who did not receive any laxatives.

Naloxone. Three studies evaluated the use of orally administered naloxone (in a fixed combination with prolonged-release oxycodone) for prevention of OIC [50,51,55]. Constipation was a secondary endpoint in all studies. Two studies compared the drug with oxycodone prolonged release (PR) and standard laxatives [50,51]. One RCT found that bowel habit changes (scored by the patient as worsened, no change or improved) did not differ significantly after four weeks between the two groups ($p = 0.264$) [51]. The changes in the QLQ-C30 constipation score were also similar between treatment groups. A cohort study showed a significantly improved BFI score from baseline in patients treated with oxycodone/naloxone ($n = 73$) compared to patients treated with oxycodone PR and laxatives ($n = 73$) at both 30 days ($p < 0.0001$) and at 60 days ($p = 0.02$) [50]. Another cohort study compared oxycodone/naloxone with transdermal fentanyl without laxatives in 336 patients [55]. The constipation rates (for both any degree and severe constipation) were comparable in both groups.

PAMORAs. A recent trial from 2022 compared magnesium oxide with naldemedine in 120 cancer patients starting on opioid therapy [52]. Compared with magnesium oxide, naldemedine resulted in less constipation based on Rome IV criteria and better stool consistency both at 2 weeks and at 12 weeks. It also showed significantly better constipation-related quality of life, measured with two different quality of life questionnaires. No significant differences were found in the number of spontaneous bowel movements per week and in quality of life as measured with the short form-36.

A meta-analysis of studies for prevention of OIC was not possible due to high heterogeneity.

Treatment of OIC in cancer patients

Standard laxatives. One RCT compared PEG with sennosides for treatment of OIC in 70 cancer patients, using the revised Victoria Bowel Performance Scale [46]. The overall effectiveness of PEG was 1.21 times (95 % CI 0.96–1.55) higher than sennosides. In contradiction to their conclusion, it cannot be concluded that PEG is more effective than sennosides. The same author also conducted a cohort study in 60 hospitalized cancer patients with OIC, comparing sennosides with sennosides and docusate [47]. No statistical significance was found between the two treatment groups.

Naloxone. One RCT studied naloxone orally versus placebo in the treatment of OIC in 27 cancer patients in a dose-ranging study [57]. Naloxone at doses of 10 % or less of the morphine dose did not lead to a clinically significant difference in small bowel transit time, but when administered at a dose of 20 % or more, there was a clinically significant effect. Two patients experienced symptoms of opioid withdrawal, one of whom also had return of pain.

A non-randomized study compared oxycodone/naloxone, itopride (an acetylcholine esterase enzyme inhibitor), oxycodone/naloxone plus itopride and standard laxatives only [45]. All patients used strong opioids and standard laxatives. They found similar number of days with bowel movements in all groups. Yet, the use of itopride decreased the use of laxatives.

Two RCTs investigated oxycodone/naloxone with laxatives versus oxycodone PR with laxatives [42,44]. Overall, oxycodone/naloxone resulted in a higher decrease in BFI than oxycodone PR (mean difference (MD) −13.79; 95 % CI −18.50 to −9.08, see Fig. 2). The heterogeneity between the studies was moderate ($I^2 = 34$ %, $p = 0.22$), as was the overall quality of evidence, because of a small sample size (see

Table 1
Characteristics and main outcomes of included studies.

Author	Study design	Setting	Prevention/ treatment	Intervention	Total patients (% cancer patients)	Main outcomes regarding constipation
Agra et al. (1998) [41]	RCT	Single center	Prevention	Sennosides 12 mg/day with increments of 12 mg every 3 days according to clinical response Lactulose,10 g/day with increments of 10 g every 3 days according to clinical response	91 (100 %)	No significant differences in defecation-free periods, mean number of defecation days or the general state of health.
Wirz et al. (2012) [60]	RCT	Single center	Prevention	Polyethylene glycol (PEG) one sachet/day Sodium picosulphate (S) 10 mg/ day Lactulose (L) 10 g/day No laxative (NL)	358 (100 %)	No significant difference in number of patients with a stool-free interval > 72 h, mean defecation frequency per 5 days or quality of life. Significant difference in NRS of constipation: PEG: 2.2 ± 2.3; SPS: 2.7 ± 2.7; L: 3.8 ± 3.3; NL 2 ± 2.6; p = 0.01).
Ramesh et al. (1998) [54]	RCT	Single center	Prevention	Misrakasneham 2.5–10 ml per day according to protocol Sennosides 24 mg-72 mg/day according to protocol	50 (100 %)	Percentage of patients with satisfactory bowel movement: 85 % vs. 69 % in Misrakasneham and sennosides, resp., p > 0.2.
Tokoro et al. (2019) [59]	Cohort study	Multicenter	Prevention	Magnesium oxide (MgO) No laxative	220 (100 %)	Incidence of constipation in magnesium oxide vs. no laxative: 48 % (95 % CI 38.1–57.5 %) vs. 65 % (95 % CI 55.0–74.2 %).
Ozaki et al. (2022) [52]	RCT	Single center	Prevention	Naldemedine 0.2 mg once MgO 500 mg t.i.d.	120 (100 %)	Incidence of constipation based on ROME IV criteria for naldemedine vs. magnesium oxide: 33 % vs. 55 % at two weeks, p = 0.02 and 40 % vs. 68 % at 12 weeks, p = 0.002.
Lazzari et al. (2015) * [50]	Cohort study	Single center	Prevention	Oxycodone/naloxone daily + standard laxatives, different dose ranges Oxycodone PR daily + standard laxatives, different dose ranges	146 (100 %)	30 days: (−13.4; 95 % CI −3.3–30.1 vs. 13.2; 95 % CI −4.7 – 31.1, p < 0.01) 60 days: (−16.0 ± 19.2; 95 % CI −35.2–3.2 vs. 13.8 ± 19.7; 95 % CI −5.9–33.5, resp., p < 0.001).
Lee et al. (2017)* [51]	RCT	Multicenter	Prevention	Oxycodone/naloxone + MgO rescue medication, start dose 20 mg/10 mg per day Oxycodone PR daily + MgO rescue medication, start dose 20 mg/day	128 (100 %)	No significant differences in change in bowel habits or in change in EORTC QLQ-30 constipation.
Roberto et al. (2017) [55]	Cohort study	Multicenter	Prevention	Oxycodone/naloxone daily, different dose ranges Transdermal fentanyl every 3 days, different dose ranges	336 (100 %)	Any degree of constipation: (76 (63.9 %) vs. 115 (60.2 %), p = 0.51)Severe constipation: (36 (30.2 %) vs 50 (26.2 %), p = 0.43).
Hawley et al. (2020) [46]	RCT	Multicenter	Treatment	Polyethylene glycol, different dosages according to bowel protocol Sennosides, different dosages according to bowel protocol	70 (100 %)	Overall effectiveness of PEG was 1.21 times (95 % CI 0.96–1.55) higher than sennosides.
Hawley et al. (2008) [47]	Cohort study	Single center	Treatment	Sennosides + ducosate, according to bowel protocol Sennosides, according to bowel protocol	60 (100 %)	Patients treated with sennosides and ducosate had at least 1 bowel movement/day in 49 % of the days and patients treated with sennosides only had at least 1 bowel movement/day in 50 % of the days with (p = 0.86).
Sykes (1996) [57]	RCT	Single center	Treatment	Naloxone daily + laxatives, different dose ranges Placebo + laxatives daily	27 (100 %)	No clinically significant difference in SBTT in naloxone at doses of ≤ 10 % of morphine dose. Clinically significant effect in SBTT in naloxone at doses of ≥ 20 % of morphine dose.
Dzierzanowski et al. (2022) [45]	Cohort study	Multicenter	Treatment	Oxycodone/naloxone daily + laxatives, different dose ranges Oxycodone/naloxone + itopride daily + laxatives, different dose ranges Itopride daily + laxatives, different dose ranges Standard laxatives, different dose ranges	93 (100 %)	No statistical significant difference in number of days with BMs in all groups.
Ahmedzai et al. (2012)* [42]	RCT	Multicenter	Treatment	Oxycodone/naloxone daily + laxatives, different dose ranges Oxycodone PR/placebo daily + laxatives, different dose ranges	185 (100 %)	Difference in change of BFI score between groups: ΔBFI: −11.14 (95 % CI −19.03 to −3.24; p < 0.01).
Dupoiron et al. (2017)* [44]	RCT	Multicenter	Treatment	Oxycodone/naloxone daily + laxatives, different dose ranges Oxycodone PR daily + laxatives, different dose ranges	46 (100 %)**	Difference in change of BFI score between groups: ΔBFI: −14.0 (95 % CI −22.1 to −5.9; p = 0.047).
Bull et al. (2015)* [43]	RCT	Multicenter	Treatment	Methylnaltrexone 8 mg (38–62 kg) or 12 mg (≥62 kg) every other day + laxatives	230 (66.1 %)	RR RFBM < 4 h after first dose: 69.8 % vs. 17.5 %; p < 0.0001. RR RFBM < 4 h after 4 or more of 7 doses:62.9 % vs. 9.6 %; p < 0.0001.

(*continued on next page*)

Table 1 (*continued*)

Author	Study design	Setting	Prevention/ treatment	Intervention	Total patients (% cancer patients)	Main outcomes regarding constipation
				Placebo every other day + laxatives		
Katakami, Oda et al. (2017)* [49]	RCT	Multicenter	Treatment	Naldemedine 0.1 mg once daily + laxatives Naldemedine 0.2 mg once daily + laxatives Naldemedine 0.4 mg once daily + laxatives Placebo once daily + laxatives	225 (100 %)	SBM RR:56.4 %, 77.6 %, and 82.1 % for naldemedine 0.1, 0.2, and 0.4 mg, resp., all statistically significant compared to placebo ($p = 0.0464$, $p < 0.001$, and $p < 0.001$, resp.).
Katakami, Harada et al. (2017)* [48]	RCT	Multicenter	Treatment	Naldemedine 0.2 mg once + laxatives if necessary Placebo once daily + laxatives if necessary	193 (100 %)	SBM RR: 71.1 % and 34.4 % for naldemedine 0.2 mg and placebo, resp. $p < 0.0001$.
Thomas et al. (2008)* [58]	RCT	Multicenter	Treatment	Methylnaltrexone 0.15 mg/kg every other day + laxatives Placebo every other day + laxatives	133 (58.5 %)	RR RFBM < 4 h after first dose: 48 % and 15 % for methylnaltrexone and placebo, resp. $p < 0.0001$. RR RFBM < 4 h after 4 or more of 7 doses:39 % vs. 6 %; $p < 0.001$.
Portenoy et al. (2008)* [53]	RCT	Multicenter	Treatment	Methylnaltrexone 1 mg every other day + laxatives Methylnaltrexone 5 mg every other day + laxatives Methylnaltrexone 12.5 mg every other day + laxatives Methylnaltrexone 20 mg every other day + laxatives	33 (85 %)	RR RFBM < 4 h after first dose: 10 %, 43 %,60 % and 33 % for methylnaltrexone 1 mg, 5 mg, 12.5 mg and 20 mg, resp. Statistical comparisons between 1 mg and higher doses were $p = 0.05$, $p = 0.06$ and $p = 0.52$.
Slatkin et al. (2009)* [56]	RCT	Multicenter	Treatment	Methylnaltrexone 0.15 mg/kg once + laxatives Methylnaltrexone 0.3 mg/kg once + laxatives Placebo once + laxatives	154 (82.2 %)	RR RFBM < 4 h after first dose: 61.7 %, 58.2 % and 13.5 % for methylnaltrexone 0.15 mg/kg, 0.3 mg/kg and placebo, resp. All statistically significant compared to placebo (both $p < 0.0001$).

* Included in meta-analysis.

** Subgroup analysis of cancer patients were performed. These data were included in the meta-analysis.

Abbreviations: RCT: randomized controlled trial; BM: bowel movement; SBM: spontaneous bowel movement; CSBM: complete spontaneous bowel movement; RFBM: rescue-free bowel movement; RR: responders rate; AE: adverse event; JPAC-QOL: Japanese Patient Assessment of Constipation-Quality of Life; BSFS: Bristol stool form scale; PAC-SYM: Patient Assessment of Constipation-Symptoms; CSS: constipation scoring system; BFI: Bowel Function Index; PR: prolonged release; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NRS: numeric rating scale; SBTT: small bowel transit time.

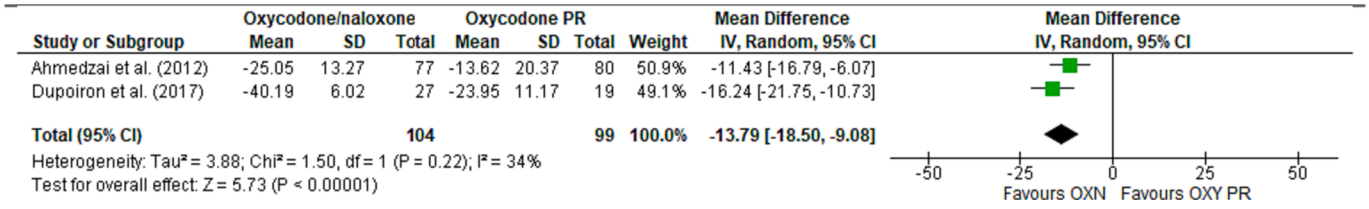

Fig. 2. Forest plot of the differences of the change in Bowel Function Index between oxycodone/naloxone and oxycodone prolonged release (PR). Abbreviations: OXN: oxycodone/naloxone; OXY PR: oxycodone prolonged release.

supplementary Table 3). Despite the small sample size, the confidence interval is small and the effect size is clinically meaningful (MD −13.79, with a change of ≥ 12 indicating a clinical meaningful change [16]). Since these findings are consistent with other studies [61], it increases the reliability of the effect size found.

PAMORAs. Five trials examined the efficacy of PAMORAs

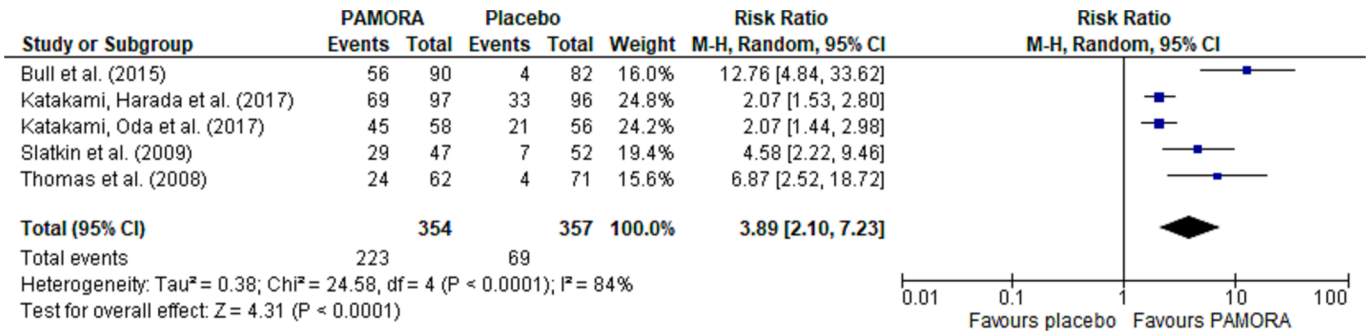

Fig. 3. Forest plot of the response rate of PAMORAs compared to placebo.

(naldemedine (2) and methylnaltrexone (3)) versus placebo after two weeks of treatment of OIC in cancer patients [43,48,49,56,58]. Treatment with PAMORAs showed a significant higher response rate (defined as a patient with an SBM per week frequency of at least three and an average increase in frequency of SBMs per week from baseline by at least one) than placebo (RR 3.89; 95 % CI 2.10–7.23, see Fig. 3), with a high heterogeneity ($I^2 = 84$ %, $p < 0.0001$). The certainty of evidence was graded very low. This was due to the high heterogeneity, indirectness and imprecision (see supplementary Table 4).

Subgroup and additional analyses

We performed subgroup analyses for treatment with naldemedine and treatment with methylnaltrexone. We analysed 2 RCTs comparing naldemedine 0.2 mg with placebo in 307 patients and found a significant higher response rate in patients treated with naldemedine (RR 2.07; 95 % CI 1.64–2.61) [48,49]. Furthermore, analyses showed a significant difference in changes from baseline in both spontaneous bowel movements (SBMs) per week (MD 3.47; 95 % CI 2.30–4.64) and complete spontaneous bowel movements (CSBMs) per week compared to baseline (MD 2.31, 95 % CI 1.45–2.31) in favour of naldemedine (see supplementary Fig. 1). Heterogeneity was low for all outcomes, due to the fact that both studies were conducted by the same research group. The certainty of evidence was high for the SBM responders rate, whereas it was moderate for the change in (C)SBMs, because of a high risk of bias of one of the studies (see supplementary Table 5).

The analysis of methylnaltrexone included 3 RCTs with 327 participants [43,56,58]. Methylnaltrexone showed a significant higher response rate in the first 4 h after first administration than treatment with placebo (RR 3.83; 95 % CI 2.81–5.22, see supplementary Fig. 2). This response rate increased even more after four out of seven doses (RR 9.46; 95 % CI 4.71–18.99). Heterogeneity between studies was low ($I^2 =$ 0 %). The quality of evidence was high and moderate, respectively (see supplementary Table 6).

Two studies investigated the dose–response of methylnaltrexone [53,56]. We created a low and high dose group based on dose equivalents evaluating short term response and medium term response (see supplementary Fig. 3). There were no significant differences between low and high dose treatment in both short and medium term response. Heterogeneity was low with a low certainty of evidence due to small sample sizes and indirectness (see supplementary Table 7).

Adverse events

Standard laxatives. Two RCTs reported the incidence of diarrhea, nausea and vomiting of treatment with polyethylene glycol, sodium picosulphate, lactulose and sennosides [46,60]. Treatment with polyethylene glycol or sennosides shows a trend towards a higher incidence of nausea and vomiting compared to the other laxatives (see supplementary Table 8). The incidence of diarrhea was similar in all groups.

Naloxone. The risk for nausea was lower in the oxycodone/naloxone group compared to oxycodone PR (RR 0.51; 95 % CI 0.31–0.83; $I^2 = 0$ %, see supplementary Fig. 4). The risks of overall adverse events and of other side effects were similar. The certainty of evidence for all adverse events was graded low to very low (see supplementary Table 3).

PAMORAs. The overall risk of adverse events for PAMORAs was slightly higher compared with placebo (RR 1.23; 95 % CI 1.03–1.47, see supplementary Fig. 5). With regard to specific adverse events, only the risk of abdominal pain was significantly higher (RR 2.19; 95 % CI 1.13–4.25; $I^2 = 49$ %). The certainty of evidence was low to very low due to heterogeneity, wide confidence intervals and indirectness (see supplementary Table 4).

Subgroup analysis with naldemedine compared to placebo showed non-significant risk ratios, except for a higher risk of diarrhea (RR 1.89; 95 % CI 1.15–3.10; $I^2 = 11$ %, see supplementary Fig. 6). The certainty of evidence was rated as moderate (see supplementary Table 5).

Between methylnaltrexone and placebo there was only a significant difference in adverse events risk ratios for nausea (RR 2.19; 95 % CI 1.13–4.25; $I^2 = 49$, see supplementary Fig. 7). However, all adverse events had a low to very low certainty of evidence, see supplementary Table 6. There was no significant difference in adverse events between a low dose and high dose of methylnaltrexone, again with a low to very low certainty of evidence (see supplementary Fig. 8 and supplementary Table 7).

Risk of bias

The included trials predominantly had a moderate to high risk of bias (see Fig. 4). Most RCTs raised concerns in the selection of the reported results because there was no pre-specified analysis plan available to compare the selected results with. Only one study did publish its protocol with pre-specified analysis plan, but several of the listed secondary outcomes were eventually not reported in the final article [48]. Another study reported mostly post-hoc analyses [52]. All cohort studies had a serious or critical risk of bias due to confounding or because intervention groups were not clearly defined in the articles.

Publication bias

We did not assess for publication bias due to a low number of studies included in the meta-analysis. This would make the assessment unreliable. However, we searched for study protocols of trials on prevention or treatment of OIC in cancer patients. We found twelve trials that were completed, but whose results were not available in peer-reviewed publications. An overview of these studies can be found in supplementary Table 9. All studies were focused on treatment of OIC. From nine studies the results remain unknown. Two RCTs found no significant difference between alvimopan (a PAMORA that is not registered for the treatment of OIC [31]) versus placebo and oxycodone/naloxone versus oxycodone PR, resp. [62,63]. One RCT found a significant improvement of bowel movement in patients treated with hydromorphone/naloxone compared to placebo [64]. We did not include these studies in our review, since the results have not been peer-reviewed and published. We identified three ongoing trials that have started, but results are not available yet (see supplementary Table 10).

Discussion

This systematic review assessed the evidence of pharmacological strategies for the prevention and treatment of OIC in cancer patients.

Regarding the *prevention* of OIC, our results show that magnesium oxide and naldemedine are most likely to be effective, but the studies included have a low quality, high heterogeneity and high risk of bias. Naldemedine seems to be more effective in preventing OIC [52]. However, while magnesium oxide is inexpensive (€0.18 euros per day [65]), naldemedine costs on average $376.74 USD for a 30-day supply [66]. Even though PEG is one of the most prescribed laxatives for both prevention and treatment of OIC, evidence of the effectivity of PEG remains limited. The studies investigating this laxative were either inconclusive or too small to draw conclusions. Apart from the studies in this systematic review, one study of Freedman et al. (1997) is often referred to as evidence for the effectivity of PEG for treatment of OIC, even though this RCT included only 57 participants [67]. Moreover, the participants were opioid-dependent patients on methadone maintenance, decreasing the generalizability. Hence, more research with higher quality RCTs is needed to prove the effectivity of PEG and other standard laxatives in cancer patients.

Regarding the *treatment* of OIC, there is hardly any evidence to prefer one laxative over another. Naloxone (in a fixed combination with oxycodone) and the PAMORAs methylnaltrexone and naldemedine are more effective compared to placebo in cancer patients with a moderate to high quality of evidence. We also found that there was no difference in

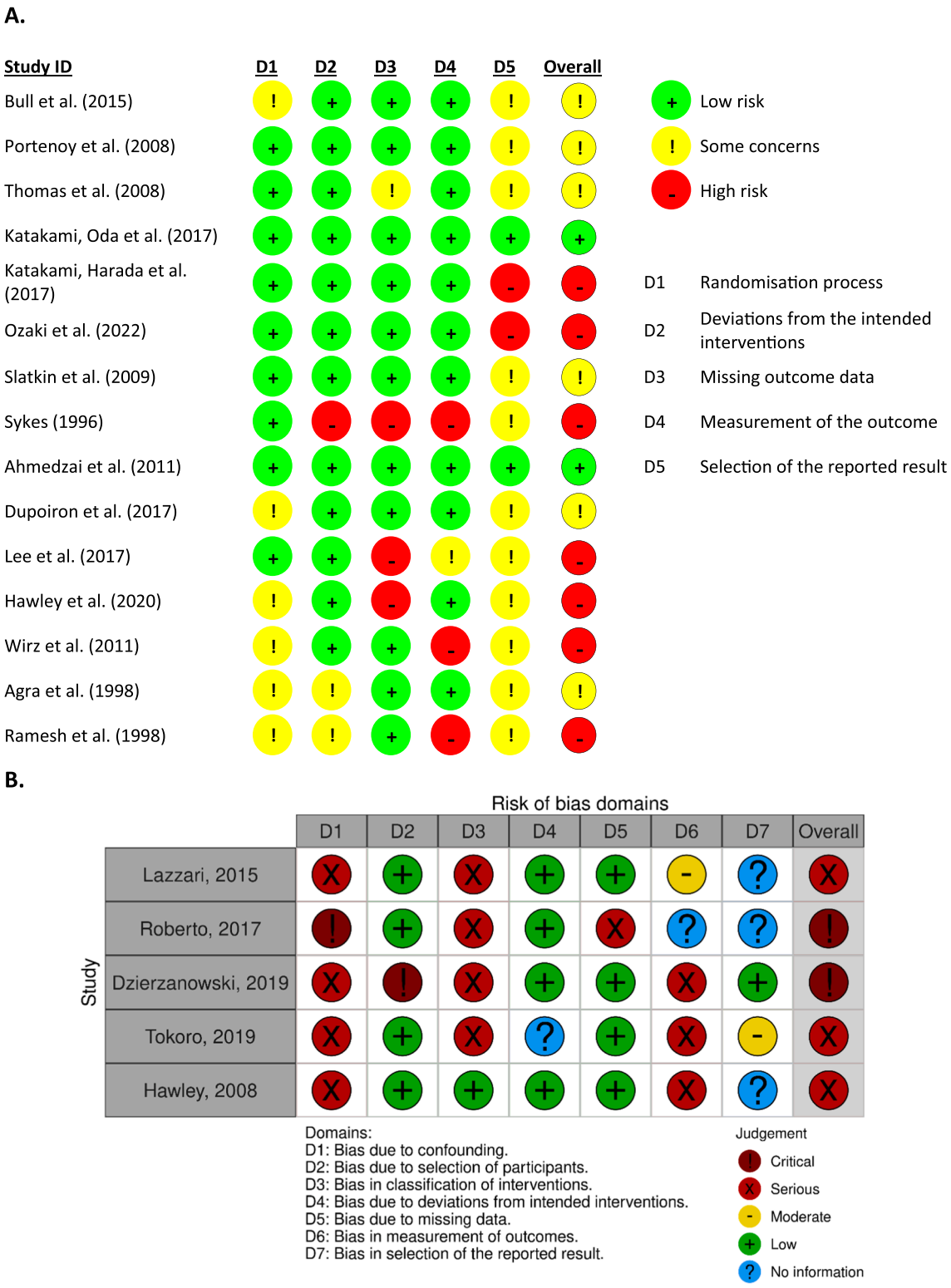

Fig. 4. Risk of bias evaluation of all included studies in the systematic review. A: risk of bias of all included RCTs. B: risk of bias of all included non-randomized cohort studies.

bowel function and adverse events in low dose (0.15 mg/kg) and high dose (0.30 mg/kg) methylnaltrexone, with a low to very low quality of evidence. The internationally approved dosages of 8–12 mg or 0.15 mg/kg methylnaltrexone are in line with these results [68,69]. As PAMORAs and oral naloxone have not been compared to standard laxatives in the treatment of OIC, are expensive and only registered for treatment of OIC not responding to laxatives, they currently are second-line treatment for OIC.

Overall, there were few differences in *adverse events* rates for standard laxatives compared with other laxatives, or for naloxone, naldemedine and methylnaltrexone compared with treatment with placebo or no laxative, making them safe to use. For methylnaltrexone there was a slightly increased risk of overall adverse events and of abdominal pain.

Previous systematic reviews found results similar to our review and

meta-analysis. One systematic review and meta-analysis focused on the efficacy of μ-opioid receptor antagonists for treatment of OIC in cancer patients and palliative care patients [70]. This review included the same RCTs with opioid antagonists as we did (with the exception of the study of Ozaki [52], which was published in 2022), but not the cohort studies. Their conclusions with regard to methylnaltrexone, naldemedine and naloxone align well with our results. Although the same three studies comparing oxycodone/naloxone with oxycodone PR (consisting of one prevention study and two treatment studies [42,44,51]) were included in their review, only two studies are mentioned in the evaluation of laxation response [42,51], one of which was a prevention study [51]. No meta-analysis was performed of these two studies, because the authors from both trials did not provide full data. In contrast, our meta-analysis analyzed the two treatment studies [42,44] and excluded the prevention study [51] for the evaluation of laxation response. This provides more insight into the evidence for the use of oxycodone/naloxone.

Interestingly, oxycodone/naloxone showed no benefit when administered for the prevention of OIC, while it did show benefit for the treatment of OIC. A possible explanation could be that in the prophylaxis studies oxycodone/naloxone alone was compared to standard laxatives, while in the treatment studies patients with OIC used standard laxatives before start of the trial and could continue them during the trial. Therefore the comparison was oxycodone/naloxone with standard laxatives compared to placebo with standard laxatives. It could be speculated that standard laxatives and oxycodone/naloxone together improve bowel function in OIC.

Two other systematic reviews also compared PAMORAs with placebo for treatment of OIC with similar results as ours, but mainly evaluated trials in non-cancer patients [35,36]. Another systematic review and meta-analysis reviewed lifestyle and pharmacological therapy options for prevention and treatment of opioid-induced and non-opioid-induced constipation both in patients with cancer and in non-cancer patients [71]. They found a moderate benefit for osmotic or stimulant laxatives and a small benefit for methylnaltrexone, naldemedine and electroacupuncture for the prevention and treatment of OIC in cancer patients, but did not separate cancer and non-cancer patients in their analysis. Furthermore, in some of the included studies a different form of constipation was assessed instead of OIC (e.g. functional idiopathic constipation).

Only two PAMORAs were evaluated in this systematic review, even though more agents are available on the market, such as naloxegol. Naloxegol has been recommended in guidelines for treatment of refractory OIC, yet has so far only been investigated in non-cancer patients [26,27,36]. Research in cancer patients is needed to evaluate its efficacy and safety. Moreover, the cost-effectiveness of PAMORAs compared to standard laxatives should be evaluated as well, since the costs of PAMORAs are generally much higher than the cost of standard laxatives [66,72]. Furthermore, more research into the preventive use of PAMORAs in cancer patients starting opioid treatment should be conducted.

Publication bias may play a role. We found twelve completed studies that have not been published in a peer-reviewed journal. Two out of three studies that had results available, did not find a statistical significant difference. This can be a sign of publication bias. Most studies with PAMORAs and oxycodone/naloxone were funded or assisted by pharmaceutical companies [42–44,50,51,53,56,58,59]. Even though this is not a part of the assessment of risk of bias, there should be awareness for potential bias due to the conflict of interest of the pharmaceutical companies [73,74].

Cancer patients often have other factors contributing to constipation and PAMORAS and naloxone may only be effective if opioids are the main cause of the constipation [23,24]. Unfortunately, most studies did not report other contributing factors (e.g. use of serotonin antagonists or anticholinergics and tumor growth in gastrointestinal tract). Therefore, it remains unclear if this influenced the results of the studies.

The mean daily opioid dosages varied widely between the included studies from 13 mg to 404 mg morphine equivalents per day. A higher opioid dose may increase the risk of developing constipation and may also increase the severity of constipation [75]. This may have affected the efficacy of the laxatives. However, OIC is not necessarily dose-dependent, but depends also on the clinical history of the patient and pharmacogenetic variation [76].

The strength of our systematic review and meta-analysis lies in its limitation to OIC in cancer patients, and its robust methodology, based on a broad literature search and the use of pre-defined inclusion and exclusion criteria. A limitation of this study is that it is restricted by our inclusion criteria, which only includes articles published in English and Dutch.

Conclusion

Scientific evidence on the prevention of OIC in cancer patients remains limited. There is very little evidence to prefer one laxative over another to prevent or treat OIC. Magnesium oxide and naldemedine are likely to be effective for prevention of OIC in cancer patients. Nalmedine seems to be more effective (based on one study), but is much more expensive. Naloxone (in a fixed combination with oxycodone) and the PAMORAs naldemedine and methylnaltrexone have proven to be effective in the treatment of OIC in cancer patients with acceptable adverse events. However, their effect has not been compared yet with standard laxatives. As PAMORAs are not registered as first-line prevention or treatment of OIC and their costs are significantly higher than the cost of standard laxatives, the latter are still more preferable for the prevention and treatment of OIC until further research is available. More comparative studies within and between laxatives and PAMORAs are necessary before recommendations for clinical practice can be made.

CRediT authorship contribution statement

K.R.J. Kistemaker: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **F. Sijani:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing. **D.J. Brinkman:** Conceptualization, Methodology, Validation, Writing – review & editing. **A. de Graeff:** Writing – review & editing, Supervision. **G.L. Burchell:** Investigation, Writing – review & editing. **M.A.H. Steegers:** Writing – review & editing, Supervision. **L. van Zuylen:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2024.102704.

References

[1] Snijders RAH, Brom L, Theunissen M, Van den Beuken -van Everdingen MHJ. Update on prevalence of pain in patients with cancer 2022. A System Literature Rev Meta-Anal Cancers 2023;15(3):591. https://doi.org/10.3390/cancers15030591.

[2] Tavoli A, Montazeri A, Roshan R, Tavoli Z, Melyani M. Depression and quality of life in cancer patients with and without pain: the role of pain beliefs. BMC Cancer 2008;8:177. https://doi.org/10.1186/1471-2407-8-177.

[3] Rodriguez C, Ji M, Wang HL, Padhya T, McMillan SC. Cancer pain and quality of life. J Hosp Palliat Nurs 2019;21(2):116–23. https://doi.org/10.1097/NJH.0000000000000507.

[4] WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

[5] Portenoy RK. Treatment of cancer pain. Lancet 2011;377(9784):2236–47. https://doi.org/10.1016/S0140-6736(11)60236-5.

[6] Fallon M, Giusti R, Aielli F, Hoskin P, Rolke R, Sharma M, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29(Suppl 4): iv166-iv91. 10.1093/annonc/mdy152.

[7] Hanson B, Siddique SM, Scarlett Y, Sultan S. American Gastroenterological Association Institute clinical guidelines C. American gastroenterological association institute technical review on the medical management of opioid-induced constipation. Gastroenterology 2019;156(1):229–53 e5. https://doi.org/10.1053/j.gastro.2018.08.018.

[8] Davies A, Leach C, Butler C, Gregory A, Henshaw S, Minton O, et al. Opioid-induced constipation in patients with cancer: a "real-world," multicentre, observational study of diagnostic criteria and clinical features. Pain 2021;162(1):309–18. https://doi.org/10.1097/j.pain.0000000000002024.

[9] Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and wellness survey. J Opioid Manag 2009;5(3):137–44. https://doi.org/10.5055/jom.2009.0014.

[10] Christensen HN, Olsson U, From J, Breivik H. Opioid-induced constipation, use of laxatives, and health-related quality of life. Scand J Pain 2016;11:104–10. https://doi.org/10.1016/j.sjpain.2015.12.007.

[11] Dhingra L, Shuk E, Grossman B, Strada A, Wald E, Portenoy A, et al. A qualitative study to explore psychological distress and illness burden associated with opioid-induced constipation in cancer patients with advanced disease. Palliat Med 2013;27(5):447–56. https://doi.org/10.1177/0269216312450358.

[12] Penning-van Beest FJ, van den Haak P, Klok RM, Prevoo YF, van der Peet DL, Herings RM. Quality of life in relation to constipation among opioid users. J Med Econ 2010;13(1):129–35. https://doi.org/10.3111/13696990903584436.

[13] Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 2003;63(7):649–71. https://doi.org/10.2165/00003495-200363070-00003.

[14] Tamayo AC, Diaz-Zuluaga PA. Management of opioid-induced bowel dysfunction in cancer patients. Support Care Cancer 2004;12(9):613–8. https://doi.org/10.1007/s00520-004-0649-7.

[15] Mesia R, Virizuela Echaburu JA, Gomez J, Sauri T, Serrano G, Pujol E. Opioid-induced constipation in oncological patients: new strategies of management. Curr Treat Options Oncol 2019;20(12):91. https://doi.org/10.1007/s11864-019-0686-6.

[16] Farmer AD, Drewes AM, Chiarioni G, De Giorgio R, O'Brien T, Morlion B, et al. Pathophysiology and management of opioid-induced constipation: European expert consensus statement. United Eur Gastroenterol J 2019;7(1):7–20. https://doi.org/10.1177/2050640618818305.

[17] Argoff CE, Brennan MJ, Camilleri M, Davies A, Fudin J, Galluzzi KE, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. Pain Med 2015;16(12):2324–37. https://doi.org/10.1111/pme.12937.

[18] Abramowitz L, Beziaud N, Causse C, Chuberre B, Allaert FA, Perrot S. Further validation of the psychometric properties of the bowel function index for evaluating opioid-induced constipation (OIC). J Med Econ 2013;16(12):1434–41. https://doi.org/10.3111/13696998.2013.851083.

[19] Rentz AM, van Hanswijck de Jonge P, Leyendecker P, Hopp M. Observational, nonintervention, multicenter study for validation of the bowel function index for constipation in European countries. Curr Med Res Opin 2011;27(1):35–44. https://doi.org/10.1185/03007995.2010.535270.

[20] Rentz AM, Yu R, Muller-Lissner S, Leyendecker P. Validation of the bowel function index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12(4):371–83. https://doi.org/10.3111/13696990903430481.

[21] Slappendel R, Simpson K, Dubois D, Keininger DL. Validation of the PAC-SYM questionnaire for opioid-induced constipation in patients with chronic low back pain. Eur J Pain 2006;10(3):209–17. https://doi.org/10.1016/j.ejpain.2005.03.008.

[22] Rumman A, Gallinger ZR, Liu LWC. Opioid induced constipation in cancer patients: pathophysiology, diagnosis and treatment. Expert Rev Quality Life Cancer Care 2016;1(1):25–35. https://doi.org/10.1080/23809000.2016.1131595.

[23] Varrassi G, Banerji V, Gianni W, Marinangeli F, Pinto C. Impact and consequences of opioid-induced constipation: a survey of patients. Pain Ther 2021;10(2):1139–53. https://doi.org/10.1007/s40122-021-00271-y.

[24] Clemens KE, Klaschik E. Management of constipation in palliative care patients. Curr Opin Support Palliat Care 2008;2(1):22–7. https://doi.org/10.1097/SPC.0b013e3282f53146.

[25] McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and diarrhea: pathophysiology. Curr Emerging Treatments Front Pharmacol 2016;7:414. https://doi.org/10.3389/fphar.2016.00414.

[26] Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American gastroenterological association institute clinical guidelines C. American gastroenterological association institute guideline on the medical management of opioid-induced constipation. Gastroenterology 2019;156(1):218–26. https://doi.org/10.1053/j.gastro.2018.07.016.

[27] Larkin PJ, Cherny NI, La Carpia D, Guglielmo M, Ostgathe C, Scotte F, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018; 29(Suppl 4): iv111-iv25. 10.1093/annonc/mdy148.

[28] Palliaweb. Guideline Constipation in the palliative phase. [Available from: https://palliaweb.nl/richtlijnen-palliatieve-zorg/richtlijn/obstipatie/preventie/opioid geinduceerde-obsitapatie. Accessed 16 Nov 2022.

[29] Leung L, Riutta T, Kotecha J, Rosser W. Chronic constipation: an evidence-based review. J Am Board Fam Med 2011;24(4):436–51. https://doi.org/10.3122/jabfm.2011.04.100272.

[30] Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60(2):209–18. https://doi.org/10.1136/gut.2010.227132.

[31] Rekatsina M, Paladini A, Drewes AM, Ayob F, Viswanath O, Urits I, et al. Efficacy and safety of peripherally acting mu-opioid receptor antagonist (PAMORAs) for the Management of Patients with Opioid-Induced Constipation: a systematic review. Cureus 2021;13(7):e16201.

[32] Floettmann E, Bui K, Sostek M, Payza K, Eldon M. Pharmacologic profile of naloxegol, a peripherally acting micro-opioid receptor antagonist, for the treatment of opioid-induced constipation. J Pharmacol Exp Ther 2017;361(2):280–91. https://doi.org/10.1124/jpet.116.239061.

[33] De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. Neurogastroenterol Motil 2004;16(4):383–94. https://doi.org/10.1111/j.1365-2982.2004.00513.x.

[34] Mueller-Lissner S. Fixed combination of oxycodone with naloxone: a new way to prevent and treat opioid-induced constipation. Adv Ther 2010;27(9):581–90. https://doi.org/10.1007/s12325-010-0057-y.

[35] Nee J, Zakari M, Sugarman MA, Whelan J, Hirsch W, Sultan S, et al. Efficacy of treatments for opioid-induced constipation: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16(10):1569–84 e2. https://doi.org/10.1016/j.cgh.2018.01.021.

[36] Vijayvargiya P, Camilleri M, Vijayvargiya P, Erwin P, Murad MH. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. Aliment Pharmacol Ther 2020;52(1):37–53. https://doi.org/10.1111/apt.15791.

[37] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

[38] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7):e1000100.

[39] Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.

[40] Guyatt G, Zhao Y, Mayer M, Briel M, Mustafa R, Izcovich A, et al. GRADE guidance 36: updates to GRADE's approach to addressing inconsistency. J Clin Epidemiol 2023. https://doi.org/10.1016/j.jclinepi.2023.03.003.

[41] Agra Y, Sacristan A, Gonzalez M, Ferrari M, Portugues A, Calvo MJ. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. J Pain Symptom Manage 1998;15(1):1–7. https://doi.org/10.1016/S0885-3924(97)00276-5.

[42] Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med 2012;26(1):50–60. https://doi.org/10.1177/0269216311418869.

[43] Bull J, Wellman CV, Israel RJ, Barrett AC, Paterson C, Forbes WP. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. J Palliat Med 2015;18(7):593–600. https://doi.org/10.1089/jpm.2014.0362.

[44] Dupoiron D, Stachowiak A, Loewenstein O, Ellery A, Kremers W, Bosse B, et al. A phase III randomized controlled study on the efficacy and improved bowel function of prolonged-release (PR) oxycodone-naloxone (up to 160/80 mg daily) vs oxycodone PR. Eur J Pain 2017;21(9):1528–37. https://doi.org/10.1002/ejp.1054.

[45] Dzierzanowski T, Kozlowski M. Itopride increases the effectiveness of the management of opioid-induced constipation in palliative care patients: an observational non-interventional study. Arch Med Sci 2022;18(5):1271–8. https://doi.org/10.5114/aoms.2019.85943.

[46] Hawley P, MacKenzie H, Gobbo M. PEG vs. sennosides for opioid-induced constipation in cancer care. Support Care Cancer 2020;28(4):1775–82. https://doi.org/10.1007/s00520-019-04944-5.

[47] Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. J Palliat Med 2008;11(4):575–81. https://doi.org/10.1089/jpm.2007.0178.

[48] Katakami N, Harada T, Murata T, Shinozaki K, Tsutsumi M, Yokota T, et al. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. J Clin Oncol 2017;35(34):3859–66. https://doi.org/10.1200/JCO.2017.73.0853.

[49] Katakami N, Oda K, Tauchi K, Nakata K, Shinozaki K, Yokota T, et al. Phase IIb, randomized, double-blind, placebo-controlled study of naldemedine for the

treatment of opioid-induced constipation in patients with cancer. J Clin Oncol 2017;35(17):1921–8. https://doi.org/10.1200/JCO.2016.70.8453.
[50] Lazzari M, Greco MT, Marcassa C, Finocchi S, Caldarulo C, Corli O. Efficacy and tolerability of oral oxycodone and oxycodone/naloxone combination in opioid-naive cancer patients: a propensity analysis. Drug Des Devel Ther 2015;9:5863–72. https://doi.org/10.2147/DDDT.S92998.
[51] Lee KH, Kim TW, Kang JH, Kim JS, Ahn JS, Kim SY, et al. Efficacy and safety of controlled-release oxycodone/naloxone versus controlled-release oxycodone in Korean patients with cancer-related pain: a randomized controlled trial. Chin J Cancer 2017;36(1):74. https://doi.org/10.1186/s40880-017-0241-4.
[52] Ozaki A, Kessoku T, Tanaka K, Yamamoto A, Takahashi K, Takeda Y, et al. Effectiveness of naldemedine compared with magnesium oxide in preventing opioid-induced constipation: a randomized controlled trial. Cancers (Basel) 2022;14(9). https://doi.org/10.3390/cancers14092112.
[53] Portenoy RK, Thomas J, Moehl Boatwright ML, Tran D, Galasso FL, Stambler N, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage 2008;35(5):458–68. https://doi.org/10.1016/j.jpainsymman.2007.12.005.
[54] Ramesh PR, Kumar KS, Rajagopal MR, Balachandran P, Warrier PK. Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna. J Pain Symptom Manage 1998;16(4):240–4. https://doi.org/10.1016/s0885-3924(98)00080-3.
[55] Roberto A, Greco MT, Legramandi L, Galli F, Galli M, Corli O. A comparison between the administration of oral prolonged-release oxycodone-naloxone and transdermal fentanyl in patients with moderate-to-severe cancer pain: a propensity score analysis. J Pain Res 2017;10:2123–33. https://doi.org/10.2147/JPR.S141928.
[56] Slatkin N, Thomas J, Lipman AG, Wilson G, Boatwright ML, Wellman C, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol 2009;7(1):39–46.
[57] Sykes NP. An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer. Palliat Med 1996;10(2):135–44. https://doi.org/10.1177/026921639601000208.
[58] Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358(22):2332–43. https://doi.org/10.1056/NEJMoa0707377.
[59] Tokoro A, Imai H, Fumita S, Harada T, Noriyuki T, Gamoh M, et al. Incidence of opioid-induced constipation in Japanese patients with cancer pain: a prospective observational cohort study. Cancer Med 2019;8(10):4883–91. https://doi.org/10.1002/cam4.2341.
[60] Wirz S, Nadstawek J, Elsen C, Junker U, Wartenberg HC. Laxative management in ambulatory cancer patients on opioid therapy: a prospective, open-label investigation of polyethylene glycol, sodium picosulphate and lactulose. Eur J Cancer Care (Engl) 2012;21(1):131–40. https://doi.org/10.1111/j.1365-2354.2011.01286.x.
[61] Huang L, Zhou JG, Zhang Y, Wang F, Wang Y, Liu DH, et al. Opioid-induced constipation relief from fixed-ratio combination prolonged-release oxycodone/naloxone compared with oxycodone and morphine for chronic nonmalignant pain: a systematic review and meta-analysis of randomized controlled trials. J Pain Symptom Manage 2017;54(5):737–48 e3. https://doi.org/10.1016/j.jpainsymman.2017.07.025.
[62] Clinicaltrialsregisters.eu. 2006 [Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-001974-28/results. Accessed on 8 June 2023.
[63] Clinicaltrialsregisters.eu. 2011 [Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-012051-20/results. Accessed on 8 June 2023.
[64] Clinicaltrialsregisters.eu. 2012 [Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-005315-18/results. Accessed on 8 June 2023.
[65] Mori H, Tack J, Suzuki H. Magnesium oxide in constipation. Nutrients 2021;13:2. https://doi.org/10.3390/nu13020421.
[66] Hu K, Bridgeman MB. Naldemedine (symproic) for the treatment of opioid-induced constipation. P T 2018;43(10):601–27.
[67] Freedman MD, Schwartz HJ, Roby R, Fleisher S. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. J Clin Pharmacol 1997;37(10):904–7. https://doi.org/10.1002/j.1552-4604.1997.tb04264.x.
[68] EMA. Summary of product characteristics (annex I) 2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/relistor-epar-product-information_en.pdf. Accessed on 19-05-2023.
[69] FDA. RELISTOR (methylnaltrexone bromide) 2017 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021964s018,208271s002lbl.pdf. Accessed 19-05-2023.
[70] Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Database Syst Rev 2022;9(9):CD006332. https://doi.org/10.1002/14651858.CD006332.pub4.
[71] Ginex PK, Hanson BJ, LeFebvre KB, Lin Y, Moriarty KA, Maloney C, et al. Management of opioid-induced and non-opioid-related constipation in patients with cancer: systematic review and meta-analysis. Oncol Nurs Forum 2020;47(6):E211–24. https://doi.org/10.1188/20.ONF.E211-E224.
[72] Gupta A, Nshuti L, Grewal US, Sedhom R, Check DK, Parsons HM, et al. Financial burden of drugs prescribed for cancer-associated symptoms. JCO Oncol Pract 2022;18(2):140–7. https://doi.org/10.1200/OP.21.00466.
[73] Kesselheim AS, Robertson CT, Myers JA, Rose SL, Gillet V, Ross KM, et al. A randomized study of how physicians interpret research funding disclosures. N Engl J Med 2012;367(12):1119–27. https://doi.org/10.1056/NEJMsa1202397.
[74] Finucane TE, Boult CE. Association of funding and findings of pharmaceutical research at a meeting of a medical professional society. Am J Med 2004;117(11):842–5. https://doi.org/10.1016/j.amjmed.2004.05.029.
[75] Villars P, Dodd M, West C, Koetters T, Paul SM, Schumacher K, et al. Differences in the prevalence and severity of side effects based on type of analgesic prescription in patients with chronic cancer pain. J Pain Symptom Manage 2007;33(1):67–77. https://doi.org/10.1016/j.jpainsymman.2006.07.011.
[76] Alvaro D, Caraceni AT, Coluzzi F, Gianni W, Lugoboni F, Marinangeli F, et al. Correction to: what to do and what not to do in the management of opioid-induced constipation: a choosing wisely report. Pain Ther 2020;9(2):669–70. https://doi.org/10.1007/s40122-020-00204-1.