ONLINE EXCLUSIVE

Management of Opioid-Induced and Non–Opioid-Related Constipation in Patients With Cancer: Systematic Review and Meta-Analysis

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PROBLEM IDENTIFICATION: A systematic review and meta-analysis was conducted to inform the development of national clinical practice guidelines on the management of cancer constipation.

LITERATURE SEARCH: PubMed®, Wiley Cochrane Library, and CINAHL® were searched for studies published from May 2009 to May 2019.

DATA EVALUATION: Two investigators independently reviewed and extracted data from eligible studies. The Cochrane Collaboration risk-of-bias tool was used, and the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the certainty of the evidence.

SYNTHESIS: For patients with cancer and opioid-induced constipation, moderate benefit was found for osmotic or stimulant laxatives; small benefit was found for methylnaltrexone, naldemedine, and electroacupuncture. For patients with cancer and non–opioid-related constipation, moderate benefit was found for naloxegol, prucalopride, lubiprostone, and linaclotide; trivial benefit was found for acupuncture.

IMPLICATIONS FOR PRACTICE: Effective strategies for managing opioid-induced and non–opioid-related constipation in patients with cancer include lifestyle, pharmacologic, and complementary approaches.

KEYWORDS constipation; symptom management; opioid-induced constipation; cancer; opioids
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Constipation occurs in about 60% of patients with cancer and can be distressing to patients during treatment, survivorship, and palliative care (McMillan et al., 2013). Constipation is the third most common side effect reported by patients with advanced cancer, following pain and anorexia (Clemens et al., 2013). For terminally ill patients with cancer, constipation and bowel dysfunction occurs in as many as 80% of patients and in as many as 90% of patients who are prescribed opioids (Downing et al., 2007; Rhondali et al., 2013). Constipation is often multicausal—a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014)—and it often goes unrecognized and undertreated (McMillan et al., 2013).

Opioids have undesirable side effects, including sedation, respiratory depression, and gastrointestinal symptoms such as opioid-induced constipation (OIC) (Benyamin et al., 2008). OIC is defined as an abnormal change in typical bowel habits or patterns of defecation following opioid therapy and is characterized by a decrease in the frequency of spontaneous bowel movements (SBMs) (less than three per week), the development or worsening of straining to pass a bowel movement, a feeling of incomplete evacuation, stool with a harder consistency, or a patient's perception of distress associated with bowel habits (Gaertner et al., 2015; McMillan, 2004; Reville et al., 2009). OIC is caused when opioids bind to enteric nervous system receptors in the gastrointestinal track and induce delayed gastric emptying, decreased intestinal secretion, slow contractions, decreased motility, increased fluid absorption from stool, and increased

sphincter tone, all of which combined can result in the retention of hard, dry stools (McMillan et al., 2013; Mori et al., 2013). OIC is the most frequent side effect for patients with advanced cancer who are receiving opioids, and it is important to consider OIC in patients starting or taking opioids for cancer-related pain. Side effects of OIC may lead patients to skip or decrease opioid doses or stop taking opioid medications altogether to relieve unmanaged constipation, which can result in increased pain and reduced functional capacity and have a detrimental impact on quality of life (QOL) (Camilleri et al., 2014). OIC can be challenging to treat, result in serious medical complications, and negatively affect QOL and symptom management for patients with cancer. Therefore, effective management of OIC deserves dedicated attention.

Patients with cancer are also at risk for constipation from other causes. Risk factors for constipation can include a positive family history, low levels of dietary fiber, a lack of physical activity, weakness in the abdominal and pelvic floor muscles, and chronic medical conditions (Mari et al., 2020; Mearin et al., 2016). Treatment for constipation is often long-term or involves recurring courses of short-term treatment (Forootan et al., 2018), which can lead to major impairments in patients' QOL and become an economic burden to patients and national healthcare resources (Mari et al., 2020). The annual direct medical costs for managing constipation are estimated to exceed $230 million, and hospital costs linked to constipation are estimated to be $4.25 billion in the United States (Martin et al., 2006; McCormick, 2019).

For this systematic review, two general categories of constipation in patients with cancer were considered: (a) constipation caused by treatment with opioids and (b) constipation from other causes. Constipation from other causes is referred to as non–opioid-related constipation, which includes constipation caused by specific medications or from side effects of decreased oral intake, decreased activity levels, or other causes resulting from the cancer treatment. This review was also not limited to one specific cancer site or stage, which helps to broaden the scope of the review and evaluate the available literature that is applicable to all patients with cancer.

It is critical to prevent and manage constipation for patients with cancer, as well as preemptively implement interventions to improve QOL and decrease economic and symptom burdens. The physical, psychological, and socioeconomic distress caused by constipation is substantial. Despite the prevalence and severity of constipation in patients with cancer, there is a paucity of research on management strategies. Education and practice improvements are needed that focus on evidence-based symptom management for patients with cancer who are at risk for or who are experiencing constipation.

A systematic review and meta-analysis was conducted to inform the development of the Oncology Nursing Society (ONS) Guidelines™ on the management of constipation in patients with cancer. This systematic review presents the comparative efficacy of lifestyle, pharmacologic, and complementary therapy interventions for the prevention and treatment of opioid-induced and non–opioid-related constipation in a general population of patients with cancer.

Methods

This systematic review was conducted in three stages: (a) published systematic reviews matching the PICO (population, intervention, comparator, outcomes) questions were reviewed and appraised to determine if any met sufficient quality to inform the guidelines, (b) an updated literature search was performed for published systematic reviews meeting these criteria, and (c) a de novo systematic review was conducted for questions for which no published systematic review of sufficient quality or no relevant published systematic review was identified. The current systematic review was guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009), and the review protocol was registered in PROSPERO (CRD42019135774).

PICO Questions

Each review question was guided by the PICO format, which frames clinical questions with the following components: defining a specific patient population, intervention, comparator, and outcomes. The questions were identified by a group of clinical experts including nurses, a gastroenterologist, a dietitian, and a patient representative. This group was tasked with identifying timely, relevant questions that patients with cancer have regarding constipation or questions about which clinicians have uncertainty. For each question, the clinical experts selected patient-important outcomes a priori. The questions focused on patients with any stage or diagnosis of cancer and interventions aimed at preventing or treating opioid-induced or non–opioid-related constipation. A full list of the PICO questions is provided in the Appendix.

Search Strategy and Inclusion Criteria

At the outset, several published systematic reviews that closely addressed the PICO questions were reviewed by the clinical experts using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews–2) approach (Shea et al., 2017). Two reviews were determined to be of sufficient quality to inform the PICO questions (Ford & Suares, 2011; Hanson et al., 2019). Although neither review was specific to the population of patients with cancer, the clinical experts determined that the inclusion of idiopathic constipation was informative to the PICO questions. A librarian replicated the MEDLINE® and Wiley Cochrane Library search strategies from the review by Hanson et al. (2019) to update the literature search through February 26, 2019. For the second review by Ford and Suares (2011), a librarian modified the searches in PubMed®, CINAHL®, and Wiley Cochrane Library to search for studies published through April 30, 2019. For the remaining PICO questions that were not addressed in these two systematic reviews, a librarian conducted a search from May 1, 2009, through May 1, 2019, in PubMed, CINAHL, and Wiley Cochrane Library for studies evaluating acupuncture or electroacupuncture as an intervention for cancer-related constipation. Limited citations were identified from these separate searchers; therefore, on May 30, 2019, a librarian searched the past 10 years of evidence in PubMed, CINAHL, and Wiley Cochrane Library for treatment of constipation not limited to cancer to identify additional sources of indirect evidence relevant to the PICO questions. Full search strategies are presented in the supplementary materials.

Grey literature, such as conference abstracts, were excluded unless the study results or data were subsequently published in a peer-reviewed journal. All citation results from the searches were imported into Covidence® software. Two reviewers independently and in duplicate screened all titles and abstracts based on the inclusion and exclusion criteria. Randomized controlled trials (RCTs) or nonrandomized studies with a comparison group that focused on the management or treatment of constipation in the adult population were included. Studies were excluded if they were not published in English, were focused on postoperative constipation, did not have a control group, involved pediatrics, were systematic reviews, or were focused on motility, or if the outcomes did not measure relief of constipation, surgical interventions, and treatment of irritable bowel syndrome. Citations that were approved by the two reviewers proceeded to full-text screening, with any conflicts resolved by the team leader.

Data Extraction

Two reviewers independently and in duplicate extracted all data into a pilot-tested Microsoft Excel® spreadsheet. Any discrepancies or errors were resolved after consulting with the original source and with the consensus of the two reviewers. If consensus could not be reached, a decision was made with consultation from the team leader or methodologist. Outcome data were entered into Review Manager® (RevMan) software, version 5.4.

Data Synthesis and Analysis

When possible, outcome data for each comparison were analyzed quantitatively by calculating a pooled effect in RevMan. The pooled analysis was presented as a risk ratio (RR) for dichotomous variables and either a mean difference (MD) or standard MD for continuous variables. The DerSimonian and Laird (1986) random- and fixed-effects models were used to determine the overall effect size and 95% confidence intervals (CIs). In situations for which quantitative data could not be pooled, outcomes were expressed narratively.

Risk-of-Bias and Certainty of the Evidence Assessment

The Cochrane Collaboration risk-of-bias tool was used to assess individual study bias for RCTs (Higgins et al., 2011). Domains reported in this tool include sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Each domain was rated to be at low bias, high bias, or unclear risk of bias. The two reviewers independently assessed risk of bias for included studies, with disagreements resolved by discussion and consensus with another investigator (see Appendix).

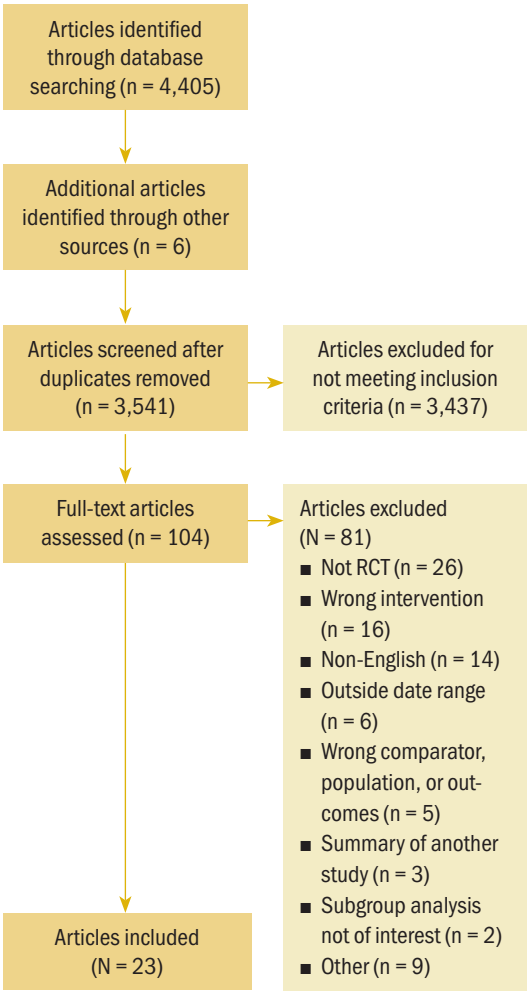
The overall certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Guyatt et al., 2011). The certainty in the estimate of effects across the body of evidence for each outcome was rated according to the following domains: study limitations (risk of bias), inconsistency (heterogeneity), indirectness, imprecision, and publication bias. The overall certainty of evidence across all study outcomes was classified as high, moderate, low, or very low. The graded

evidence across outcomes for each comparison was presented in a summary of findings table generated from GRADEpro GDT.

Results

The results of the literature search are illustrated in a PRISMA diagram (see Figure 1). In total, 4,405 citations were identified from the electronic databases. Six additional articles were identified in reviewing other sources. After removing duplicates and screening titles and abstracts, 104 full-text articles were reviewed. Of these, 24 articles (23 studies) consisting of 8,724 participants were identified that met the inclusion criteria.

FIGURE 1. PRISMA Flow Diagram



PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT—randomized controlled trial

The PICO questions related to OIC were addressed by an update to an existing systematic review (Hanson et al., 2019). Hanson et al. (2019) synthesized and graded the evidence for the following interventions relevant to the current review: osmotic or stimulant laxatives; osmotic laxatives, particularly polyethylene glycol (PEG); peripherally acting mu-opioid receptor antagonist (PAMORAs), including naloxegol, naldemedine, and methylnaltrexone; lubiprostone; and prucalopride. This review summarized the evidence of effectiveness of these interventions predominantly among people without cancer; however, some of the studies reviewed also included patients with cancer (Hanson et al., 2019).

Bowel Regimen and Osmotic Polyethylene Glycol for Opioid-Induced Constipation

Should a prophylactic bowel regimen and lifestyle education rather than lifestyle education alone be used in adult patients with cancer receiving opioids who are not yet constipated or who have opioid-induced constipation?

The evidence on prophylactic bowel regimens for patients with cancer receiving opioids is limited (Hanson et al., 2019). The systematic review by Ford and Suares (2011) on the use of osmotic or stimulant laxatives in patients with idiopathic constipation was considered the best available evidence to inform this question (Hanson et al., 2019). Ford and Suares (2011) included seven studies that examined the efficacy of laxatives in the treatment of chronic idiopathic constipation (N = 1,411 patients; 876 patients received laxatives, and 535 patients received placebo). The updated literature search identified three additional studies that assessed the use of laxatives in patients with functional constipation (McGraw, 2016; Nakajima et al., 2019; Speed et al., 2010).

Laxatives were more effective than placebos for SBM response (pooled RR = 2.24, 95% CI [1.93, 2.61]; absolute risk reduction [ARR] from 25 more to 43 more per 100; moderate certainty of evidence). For the outcome of bowel movement frequency, the MD between the two groups was 2.55 (1.53 more to 3.57 more, low certainty of evidence). Adverse events leading to treatment discontinuation were more prevalent in patients receiving laxatives compared to those receiving placebo (RR = 3.55, 95% CI [1.6, 7.89]; ARR from 16 more to 179 more per 1,000; moderate certainty of evidence).

Should osmotic polyethylene glycol and lifestyle education rather than lifestyle education alone be used

in adult patients with cancer who have opioid-induced constipation?

The evidence on osmotic PEG for patients with cancer experiencing OIC is limited. The summary of evidence from Hanson et al. (2019) was informed by an RCT conducted by Freedman et al. (1997) that compared osmotic PEG or lactulose to a placebo for 57 patients in a methadone outpatient program. This study did not include a specific definition of OIC or a specific definition of constipation, and the primary endpoint was self-reported stool consistency (Freedman et al., 1997). The authors reported that PEG and lactulose were more effective than placebo for improving bowel consistency. No adverse events resulted in withdrawal from the study; however, PEG was found to lead to more adverse events, particularly diarrhea (Freedman et al., 1997).

Peripherally Acting mu-Opioid Receptor Antagonists for Opioid-Induced Constipation

In addition to the studies identified in the Hanson et al. (2019) review, five studies were identified in this updated review that reported on the use of PAMORAs for OIC in patients who are refractory to laxatives. All were extension studies or secondary analyses of studies included in Hanson et al. (2019), and these studies were synthesized and analyzed with data from the Hanson et al. (2019) review. Findings are presented for the individual PAMORAs of methylnaltrexone, naldemedine, and naloxegol.

Should methylnaltrexone (subcutaneous or oral) and a bowel regimen rather than a bowel regimen alone be used for adult patients with cancer who have opioid-induced constipation?

Six RCTs were included in the review by Hanson et al. (2019) that addressed this question (Bull et al., 2015; Michna et al., 2011; Portenoy et al., 2008; Rauck et al., 2017; Slatkin et al., 2009; Thomas et al., 2008). The updated review identified two additional studies (Rauck et al., 2019; Webster & Israel, 2018), which are additional analyses from previous studies. Rauck et al. (2019) is an additional safety analysis, and Webster and Israel (2018) is a post-hoc analysis of patients on concomitant methadone.

Methylnaltrexone may increase rescue-free bowel movements (RFBMs) (defined as more than three RFBMs per week) when compared to standard bowel regimens (RR = 1.33, 95% CI [1.16, 1.52]; ARR = 13 more per 100, from 6 more to 20 more; very low certainty of evidence) and laxation response (RR = 3.5, 95% CI [2.65, 4.62]; ARR = 30 more per 100, from 20 more to 44 more; low certainty of evidence). Adverse events leading to treatment discontinuation were increased in patients receiving methylnaltrexone (RR = 1.51, 95% CI [0.83, 2.71]; ARR = 2 more per 100, from 1 fewer to 6 more; very low certainty of evidence).

Webster and Israel (2018) evaluated the safety and efficacy of oral methylnaltrexone in patients with OIC on concomitant methadone. In this study, patients received differing doses of methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily. Patients who received oral methylnaltrexone had a significantly increased mean percentage of dosing days with RFBMs within four hours of dosing during weeks 1–4 with 300 mg (34%, $p < 0.01$) and 450 mg (38%, $p < 0.001$) as compared to placebo. Improvement with the 150 mg dose of oral methylnaltrexone compared to placebo was not significant. Rauck et al. (2019) was a safety analysis of a phase 3 RCT that consisted of 803 patients with chronic noncancer pain and confirmed OIC. Adverse events were similar between patients who received methylnaltrexone (59%) and placebo (63%), with the most common adverse events being abdominal pain, nausea, and diarrhea (Rauck et al., 2019).

Should naldemedine (0.2 mg) in addition to a bowel regimen rather than a bowel regimen alone be used for adult patients with cancer who have opioid-induced constipation?

Hanson et al. (2019) identified four RCTs that compared naldemedine to placebo (Hale et al., 2017; Webster et al., 2017; Webster, Nalamachu, et al., 2018). These studies consisted of 2,463 patients with OIC and noncancer pain. Two additional studies (Katakami et al., 2018; Katakami, Harada, et al., 2017; Katakami, Oda, et al., 2017) assessed the use of naldemedine in 418 patients with cancer and OIC. Outcomes reported included SBM response, changes in the frequency of SBMs, changes in the frequency of bowel movements without straining, changes in bowel movement frequency, constipation QOL, and adverse events leading to treatment discontinuation or changes in the frequency of SBMs.

Naldemedine (0.2 mg) increased SBM response (odds ratio = 2.44, 95% CI [1.99, 3.01]; ARR = 501 more per 1,000, from 344 more to 699 more; moderate certainty of evidence) and changes in SBM frequency (MD = 2.02 more SBMs per week, from 1.3 more to 2.74 more; moderate certainty of evidence) compared to placebo. QOL, as measured by the Patient Assessment of Constipation–QOL (PAC-QOL©), was unchanged between treatment groups (MD = 0.3 higher, from 0.16 higher to 0.44 higher; moderate

certainty of evidence). Adverse events leading to treatment discontinuation were increased in patients receiving naldemedine (RR = 1.41, 95% CI [1.17, 1.7]; ARR = 4 more per 100, from 2 more to 8 more; moderate certainty of evidence).

Should naloxegol and a bowel regimen rather than a bowel regimen alone be used for adult patients with cancer who have opioid-induced constipation?

Hanson et al. (2019) identified three studies that compared naloxegol to a bowel regimen for 1,559 patients with OIC and reported on the outcome of an increase in SBMs (three or more) per week (Chey et al., 2014; Webster et al., 2013, 2014). The updated literature search identified a subsequent analysis of the results from Webster et al. (2013) for the outcome of pain (Webster, Diva, et al., 2018), which reported on the results from two trials consisting of 1,352 participants.

Naloxegol may increase the frequency of SBM response as compared to a bowel regimen (RR = 1.43, 95% CI [1.19, 1.71], very low certainty of evidence). Adverse events leading to treatment discontinuation were increased in patients receiving naloxegol (RR = 2.33, 95% CI [1.62, 3.35]; ARR = 6 more per 100, from 3 more to 10 more; very low certainty of evidence). Naloxegol did not appear to reduce severity of straining (MD = 0.24 lower, from 0.35 lower to 0.14 lower; low certainty of evidence) or improve stool consistency (MD = 0.33 higher, from 0.2 higher to 0.46 higher; very low certainty of evidence).

Other Medications for Opioid-Induced Constipation

Should lubiprostone and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced constipation?

Hanson et al. (2019) included three RCTs that addressed this question (Cryer et al., 2014; Jamal et al., 2015; Spierings et al., 2016). The studies consisted of 1,284 patients and compared the use of lubiprostone to placebo for the treatment of OIC and noncancer pain. The updated review identified one additional study that was a pooled analysis of the opioid subgroups in those three previous studies (Webster, Brewer, et al., 2018). Outcomes reported included SBM response, changes in SBM frequency, changes in the frequency of bowel movements without straining, stool consistency, and adverse events leading to treatment discontinuation.

Lubiprostone had minimal effect on SBM response (RR = 1.15, 95% CI [0.97, 1.37]; ARR = 5 more per 100, from 1 fewer to 12 more; very low certainty of evidence), reduction in straining (MD = 0.3 lower, from 0.47 lower to 0.13 lower; low certainty of evidence), and stool consistency (MD = 0.2 lower, from 0.37 lower to 0.03 lower; low certainty of evidence). Adverse events leading to treatment discontinuation were increased in the lubiprostone group (RR = 2.13, 95% CI [1.25, 3.61]; ARR = 3 more per 100, from 1 more to 8 more; low certainty of evidence).

Should linaclotide and a bowel regimen rather than a bowel regimen alone only be used in adult patients with cancer who have opioid-induced constipation?

Three RCTs consisting of 2,069 patients with chronic constipation were identified in the updated review that addressed this question (Lacy et al., 2015; Lembo et al., 2010, 2011). In addition, a clinical trial on linaclotide for the treatment of OIC was identified (NCT02270983). Different doses of linaclotide were used in each of the studies, and treatment periods ranged from 4 to 12 weeks.

The study by Lacy et al. (2015) included the primary endpoint of three or more SBMs per week, with an increase of one or more from baseline for 9–12 weeks, and compared 145 mg linaclotide to placebo. The primary endpoint was met by 16% of patients (n = 24) receiving linaclotide compared to 8% of patients (n = 13) receiving a placebo. Lembo et al. (2010) also reported that all doses of linaclotide improved the primary endpoint of weekly SBMs compared to placebo. The overall number of weekly SBMs increased from baseline by 2.6 with 75 mg linaclotide, by 3.3 with 150 mg linaclotide, by 3.6 with 300 mg linaclotide, and by 4.3 with 600 mg linaclotide as compared to by 1.5 with placebo ($p < 0.05$ for each pair-wise comparison of linaclotide to placebo) (Lembo et al., 2011). Lembo et al. (2011) reported on two RCTs, with the primary efficacy endpoint of three or more complete SBMs per week and an increase of one or more complete SBMs from baseline during at least 9 of the 12 weeks of the study. This endpoint was reached by 21% and 16% of patients who received 145 mg of linaclotide in each study and by 19% of patients who received 290 mg of linaclotide as compared to patients who were given a placebo ($p < 0.01$) (Lembo et al., 2011).

At the 12-week follow-up, the use of linaclotide in addition to a bowel regimen increased complete SBMs (MD = 1.96 higher, from 1.12 higher to 3.44 higher; low certainty of evidence), changes in complete SBMs from baseline (MD = 1.57 higher, from 1.11 higher to 2.04 higher; low certainty of evidence), and changes in SBMs from baseline (MD = 2.11 higher, from 1.68 higher to 2.54 higher; low certainty of evidence) (Lembo et al., 2011).

Should prucalopride and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced constipation?

Hanson et al. (2019) identified one RCT that addressed this question (Sloots et al., 2010), which consisted of 196 patients randomized to two different doses of prucalopride or a placebo. In addition, the results of an RCT that was stopped early were pooled in the analysis reported by Hanson et al. (2019). The updated literature search identified no additional studies. Outcomes that were assessed by Sloots et al. (2010) included SBM response, changes in SBM frequency, constipation QOL, adverse events leading to treatment discontinuation, painful defecation, and stool consistency.

Prucalopride moderately increased SBM response (RR = 1.36, 95% CI [1.08, 1.7]; ARR = 15 more per 100, from 3 more to 29 more; very low certainty of evidence). The incidence of non–opioid-related adverse events was similar across the treatment arms at 49% for placebo, 58% with 2 mg prucalopride, and 50% with 4 mg prucalopride (Sloots et al., 2010). The most frequently reported adverse event was abdominal pain in the 4 mg group (25%), with abdominal pain also being the most common reason for treatment discontinuation in all groups.

Laxatives for Non–Opioid-Related Constipation

Should osmotic or stimulant laxatives and lifestyle education rather than lifestyle education alone be used in adult patients with cancer who have non–opioid-related constipation?

The literature search by Ford and Suares (2011) was updated, and three additional studies were identified that could be analyzed in a meta-analysis (McGraw, 2016; Nakajima et al., 2019; Speed et al., 2010). In addition, the current review identified two RCTs among patients with cancer (Hanai et al., 2016; Tarumi et al., 2013) and one RCT among patients with functional constipation (Shen et al., 2018) that could not be pooled in the meta-analysis. Sample sizes ranged from 30 to 203, with a variety of patient populations, including hospice (about 94% patients with cancer), patients with breast cancer, and patients with functional constipation without cancer. Interventions included docusate, self-management, and laxatives. Self-management programs included abdominal massage, abdominal muscle stretching and education (Hanai et al., 2016), dietary management, lifestyle evaluation, defecation and exercise skills training, patient and caregiver support, and a written self-management guide (Shen et al., 2018).

Three studies could not be pooled in the current review's meta-analysis and are described narratively instead. Tarumi et al. (2013) investigated the addition of docusate to sennosides as compared to sennosides alone for 10 days in a group of patients in hospice. No significant differences were found between the groups in stool frequency, volume, or consistency, or in difficulty or completeness of evacuation. In a study of constipation caused by antiemetics in a group of women receiving systemic chemotherapy for breast cancer, Hanai et al. (2016) found that a self-management program produced statistically and clinically significant improvement in constipation severity by approximately 40% ($p = 0.019$, 95% CI [−5.46, −0.51]), a decrease in the likelihood of a small volume of stool ($p = 0.03$), and a decrease in depression ($p = 0.02$). The severity of constipation was about 40% lower in the self-management group compared to the control group, with a mean Constipation Assessment Scale score of 5 or fewer in the intervention group, indicating mild constipation not requiring medical intervention. The self-management program was also acceptable to patients, with 44% and 26% of patients rating the program as excellent and good, respectively.

In a study of self-management of functional constipation, the constipation scores on all clinical symptoms (Bristol stool scale, defecation interval, incomplete evacuation, evacuation difficulty) at one month postdischarge were each significantly lower in the intervention group than in the control group ($p < 0.05$ for all outcomes). At one month postdischarge, the proportion of patients with good health hygiene (e.g., diet, physical activity, defecation patterns, use of laxatives) was significantly higher in the intervention group as compared to the control group ($p < 0.05$ for all outcomes) (Shen et al., 2018).

Osmotic or stimulant laxatives in addition to lifestyle education increased SBM response (RR = 2.24, 95% CI [1.93, 2.61]; ARR = 33 more per 100, from 25 more to 43 more; moderate certainty of evidence), improved changes in bowel movement frequency (MD = 2.55 higher, from 1.53 higher to 3.57 higher; low certainty of evidence), reduced straining (RR = 1.52, 95% CI [1.18, 1.96]; ARR = 29 more per 100, from 10 more to 53 more; moderate certainty of evidence), and improved stool consistency (RR = 1.55, 95% CI [1.33, 1.82]; ARR = 32 more per 100, from 19 more to 48 more; moderate certainty of evidence). However, adverse events leading to treatment discontinuation

were also increased in patients receiving osmotic or stimulant laxatives (RR = 3.55, 95% CI [1.6, 7.89]; ARR = 66 more per 1,000, from 16 more to 179 more; moderate certainty of evidence).

Acupuncture for Non–Opioid-Related Constipation

Should acupuncture and lifestyle education rather than lifestyle education alone be used in adult patients with cancer who have non–opioid-related constipation?

The current systematic review identified three RCTs among patients with cancer (Liu et al., 2015; Rithirangsriroj et al., 2015; Shin & Park, 2018) and four RCTs among patients with functional constipation (Lee et al., 2018; Wu et al., 2014, 2017; Zheng et al., 2018). The study by Shin and Park (2018) was excluded from evaluation because the intervention used acupressure and did not directly relate to this question. Sample sizes ranged from 30 to 684 patients, with varying treatment schedules.

Constipation was an outcome measure in a study of wrist/ankle acupuncture with ginger moxibustion as compared to antiemetics for preventing gastrointestinal reactions in women with gynecologic cancer receiving chemotherapy (Liu et al., 2015). The authors reported that the treatment group had a significantly lower incidence rate of constipation than the control group (1 of 30 patients compared to 12 of 30 patients) (Liu et al., 2015). A study by Rithirangsriroj et al. (2015) compared acupuncture to antiemetics for the prevention of delayed chemotherapy-induced nausea and vomiting in patients with gynecologic cancer and reported constipation as an outcome measure. Although not a primary outcome of the study, the authors reported that the acupuncture group had less frequent constipation ($p = 0.02$) than the antiemetic group. In addition, scores on the Functional Assessment of Cancer Therapy–General questionnaire were significantly higher in the acupuncture group overall as compared to the antiemetic group ($p = 0.03$). No variations in treatment preferences were reported in about 40%–45% of patients. Forty patients provided a treatment preference; an analysis of these patients found that the number of patients who preferred acupuncture over antiemetics was significant ($p = 0.004$) (Rithirangsriroj et al., 2015).

The results of the three studies that evaluated the effects of acupuncture on functional constipation were mixed. Wu et al. (2014) compared deep and shallow acupuncture to lactulose and found that constipation-related symptoms were improved in the three groups as compared with baseline at each time point ($p < 0.01$) and that acupuncture was not superior to lactulose. Zheng et al. (2018) assessed three types of acupuncture compared to mosapride for relieving functional constipation, and all treatments comparatively improved stool outcomes. Lee et al. (2018) compared acupuncture to sham acupuncture for the treatment of functional constipation and reported clinically meaningful improvements in complete SBMs.

Acupuncture did not have a beneficial effect on SBM response (MD = 0.85 higher, from 0.59 higher to 1.1 higher), responses on the Constipation Assessment Scale (MD = 0.63 lower, 3.14 lower to 1.88 higher; very low certainty of evidence), or responses on the Bristol stool scale (MD = 0.41 higher, 0.26 higher to 0.55 higher; low certainty of evidence). Patients who received acupuncture reported fewer adverse events (RR = 0.53, 95% CI [0.27, 1.02]; ARR = 51 fewer per 1,000, from 79 fewer to 2 more; very low certainty of evidence), less use of rescue medication (RR = 0.2, 95% CI [0.03, 1.51]; ARR = 267 fewer per 1,000, from 323 fewer to 170 more; very low certainty of evidence), and a decrease in the development of constipation (RR = 0.47, 95% CI [0.3, 0.73]; ARR = 228 fewer per 1,000, from 301 fewer to 116 fewer; very low certainty of evidence).

Electroacupuncture for Non–Opioid-Related Constipation

Should electroacupuncture and lifestyle education rather than lifestyle education alone be used in adult patients with cancer who have non–opioid-related constipation?

The current review identified three studies that addressed this question. All studies included patients with functional constipation, with sample sizes ranging from 67 to 1,075. One study compared electroacupuncture to sham acupuncture (Liu et al., 2016), one study compared high- to low-current acupuncture with a control arm that received mosapride (Wu et al., 2017), and one study compared shallow electroacupuncture to deep electroacupuncture (Da et al., 2015). Treatment times varied from 4 to 8 weeks, with follow-up that ranged from none to 12 weeks.

In the study comparing electroacupuncture to sham acupuncture, Liu et al. (2016) found an increase of 1.76 (95% CI [1.61, 1.89]) from baseline in mean weekly completed SBMs during weeks 1–8 in the electroacupuncture group and 0.87 (95% CI [0.73, 0.97]) in the sham acupuncture group. The between-group difference was 0.9 (95% CI [0.74, 1.1], $p < 0.001$). The proportion of patients having three or more complete

SBMs per week on average in the intervention group was 31% and 38% during the 8-week treatment and 12-week follow-up period, respectively, as compared to 12% and 14% in the control group ($p < 0.001$).

A three-arm study comparing low-current electroacupuncture, high-current electroacupuncture, and mosapride included the primary outcome of three or more SBMs per week and an increase of one or more SBMs from baseline during at least three of four weeks (Wu et al., 2017). This outcome was reached by 53%, 66%, and 52% of patients who received low-current electroacupuncture, high-current electroacupuncture, and mosapride, respectively. High-current electroacupuncture improved QOL more than mosapride ($p < 0.05$) and reduced the proportion of severe constipation more than low-current electroacupuncture and mosapride ($p < 0.05$). The authors concluded that, although electroacupuncture is effective and safe at both high and low currents, the therapeutic effects are not superior to mosapride (Wu et al., 2017).

A study by Da et al. (2015) compared shallow to deep electroacupuncture and found that both significantly increased complete SBMs as compared to baseline (from 0.5 [SD = 0.59] per week to 2 [SD = 1.67] per week with deep electroacupuncture and from 0.48 [SD = 0.59] per week to 1.33 [SD = 1.09] per week with shallow electroacupuncture), with $p < 0.05$ for both groups. No difference was found in patient-reported outcomes on the Bristol stool scale and PAC-QOL questionnaire between the two groups (Da et al., 2015).

Electroacupuncture increased complete SBM response (three or more per week) at follow-up at eight weeks (RR = 3.33, 95% CI [2.42, 4.57]; ARR = 281 more per 1,000, from 171 more to 431 more; low certainty of evidence). Adverse events leading to treatment discontinuation were decreased in the electroacupuncture group (RR = 0.45, 95% CI [0.14, 1.44]; ARR = 9 fewer per 1,000, from 14 fewer to 7 more; very low certainty of evidence).

Discussion

Statement of the Principle Findings

Constipation is prevalent in patients with cancer and can be a side effect from medications, such as opioids or antiemetics, or caused by a change in diet or usual routine. It could also be a long-term issue that patients had prior to their cancer diagnosis. The findings from this updated systematic review are consistent with previous studies that have found laxatives to be beneficial in the prevention and treatment of OIC and non–opioid-related constipation. PAMORAs (e.g., methylnaltrexone, naldemedine, naloxegol) are options for patients with OIC who are refractory to laxatives. Other medications, such as lubiprostone, prucalopride, and linaclotide, may also be effective in relieving OIC. For patients with cancer who have non–opioid-related constipation, the effects of acupuncture are uncertain; however, electroacupuncture may be beneficial.

SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

All appendices mentioned within this article can be accessed online at https://bit.ly/3c4yewT.

Strengths and Limitations

Although the body of evidence comparing interventions for the management of OIC and non–opioid-related constipation was limited, a rigorous and transparent methodology was used for the identification of eligible studies, meta-analysis, and grading of the evidence. Both randomized and nonrandomized comparison studies were eligible for inclusion in the analysis.

Grey literature was identified in the initial search, but only published, peer-reviewed studies were included in the analysis. In addition, this systematic review only included studies published in the English language. Because of the wide practice of acupuncture and other complementary treatments in China, it is possible that some relevant non-English studies were excluded.

Relation to Other Studies and Guidelines

Two systematic reviews were identified that provided insights into the management of constipation (Nelson et al., 2017; Paré & Fedorak, 2014) and were consistent with the findings of the current review. Paré and Fedorak (2014) reported that stimulant and osmotic (nonstimulant) laxatives provided better relief of functional constipation than placebo. Nelson et al. (2017) compared the efficacy of pharmacologic approaches for chronic idiopathic constipation and concluded that current pharmaceutical interventions had similar efficacy. Although these reviews provide an overview of symptom management for constipation, they were not specific to patients with cancer and did not identify nonpharmacologic approaches, such as acupuncture, which have shown efficacy in previous studies. The limited evidence on nonpharmacologic interventions for constipation is a knowledge gap that warrants further research.

Several guidelines have been published on constipation in advanced cancer and offer guidance on the management of constipation in patients with advanced cancer. Palliative care guidelines from the National Comprehensive Cancer Network (2020) recommend laxatives in addition to lifestyle factors for prevention and treatment, with the addition of PAMORAs or a prokinetic agent if constipation persists. The European Society of Medical Oncology also recommends laxatives and lifestyle factors for prevention and treatment, with the addition of methylnaltrexone or a naloxone/opioid combination for OIC that is refractory to laxatives (Larkin et al., 2018). Lastly, the Multinational Association of Supportive Care in Cancer recommendations for constipation management in advanced cancer include lifestyle factors and laxatives as first-line treatment, with PAMORAs for OIC refractory to laxatives (Davies et al., 2020).

Implications for Nursing

Constipation is a common and distressing condition in patients with cancer that is often unrecognized and poorly treated despite its clinical importance (Larkin et al., 2018). Guidance for practice is limited and not routinely incorporated into patient care. Evidence-based practice and quality improvement projects can provide opportunities to address these limitations by testing practice changes that incorporate assessments and interventions for patients with constipation. Examples of these types of interventions using technology (Kaur et al., 2016; Tomich & Sipe, 2019) and education (Amankwah et al., 2015) are available. Learning how to incorporate best practices into patient care workflows will enable clinical staff to promptly intervene and manage constipation, which can lead to improved patient outcomes.

Conclusion

This systematic review provides low to moderate evidence on lifestyle, pharmacologic, and complementary medicine approaches for the prevention and management of opioid-induced and non–opioid-related constipation in patients with cancer. In addition, this review was used to inform the accompanying ONS Guidelines on the management of constipation for these patients. It is critical for healthcare providers to implement evidence-based practice for the management of constipation in patients with cancer in clinical settings. Given a paucity of studies with a high level of evidence for constipation, current care includes an overreliance on expert recommendations, consensus, and practice. Future research is warranted to improve the quality of evidence for interventions, such as PAMORAs and acupuncture, for managing constipation in patients with cancer.

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