ONS Guidelines™ for Opioid-Induced and Non–Opioid-Related Cancer Constipation

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PURPOSE: This evidence-based guideline intends to support clinicians, patients, and others in decisions regarding the treatment of constipation in patients with cancer.

METHODOLOGIC APPROACH: An interprofessional panel of healthcare professionals with patient representation prioritized clinical questions and patient outcomes for the management of cancer-related constipation. Systematic reviews of the literature were conducted. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to assess the evidence and make recommendations.

FINDINGS: The panel agreed on 13 recommendations for the management of opioid-induced and non–opioid-related constipation in patients with cancer.

IMPLICATIONS FOR NURSING: The panel conditionally recommended a bowel regimen in addition to lifestyle education as first-line treatment for constipation. For patients starting opioids, the panel suggests a bowel regimen as prophylaxis. Pharmaceutical interventions are available and recommended if a bowel regimen has failed. Acupuncture and electroacupuncture for non–opioid-related constipation are recommended in the context of a clinical trial.

KEYWORDS opioid-induced constipation; cancer; constipation; acupuncture; guideline; GRADE

***ONF*, *47*(6), 671–691.**

DOI 10.1188/20.ONF.671-691

Constipation is a common condition worldwide, but its actual prevalence is not known because many individuals do not seek medical attention. There is no single accepted definition for constipation, and often patients and clinicians have different perceptions of constipation (Clark et al., 2010). Patients may report feeling constipated if they experience changes in their bowel patterns, but clinicians may view constipation more narrowly as hard or infrequent stools (Izumi, 2014). The estimated incidence of constipation overall is between 2.5% and 79% in adults, and its actual occurrence depends on age, sex, and definition of constipation (Higgens & Johanson, 2004; Peppas et al., 2008). The risk factors for constipation include low-fiber diet, decreased physical activity, irritable bowel syndrome, health conditions (e.g., cancer, Parkinson's disease, endocrine disease), and various medications (e.g., opioids) (Andrews & Storr, 2011; Mugie et al., 2010). Constipation can also lead to increased healthcare use costs. A study by Sommers et al. (2015) found that constipation-related emergency department visits increased by 41.5% between 2006 and 2011, with a mean cost per patient of $2,306. The highest rates of emergency department visits were in very young people (younger than age 1 year) or older adults (aged 85 years or older) (Sommers et al., 2015).

In patients with cancer, constipation is a frequent occurrence, with rates ranging from 43% to 58% (McMillan et al., 2013). Constipation is the third most common symptom in patients with advanced cancer, following pain and anorexia, and the effect of constipation on a patient can vary and range from minor discomfort to a life-threatening impaction (Clemens et al., 2013).

Opioid-induced constipation (OIC) is the most common side effect of opioids and affects 40%–80%

of patients who are taking opioids (Arthur & Hui, 2018; Neefjes et al., 2019; Rhondali et al., 2013). OIC is primarily mediated by the peripheral mu-opioid receptors that line the gastrointestinal tract and cause increased nonpropulsive contractions and the inhibition of water and electrolyte excretion, which leads to delayed gastrointestinal transit and hard, infrequent stools (Arthur & Hui, 2018; Pappagallo, 2001). OIC can be a challenge for clinicians to treat and can result in serious medical complications and negatively affect quality of life and pain management. Despite the prevalence of OIC, how patients and clinicians approach management is not well understood. A qualitative study by Keller et al. (2019) sought to understand the decision-making process for patients and clinicians when managing OIC by assessing treatment preferences, experiences, and communication. Clinicians recognized OIC as a concern but prioritized pain management over constipation. Treatment focused on medications, but clinicians also offered lifestyle education (Keller et al., 2019). From the patient perspective, diet-related management was most common, but patients also reported using over-the-counter medications. Of note, patients reported not receiving adequate education from clinicians about OIC and its treatment, and patients and clinicians noted that cost of treatment was a major concern (Keller et al., 2019).

Constipation is a prevalent, distressing side effect of treatment, as well as a chronic condition among a significant portion of patients with cancer. Evidence-based strategies for the management of constipation will enable clinicians and patients to make treatment decisions to mitigate this symptom and help to improve quality of life for patients.

Aim of the Guideline and Specific Objectives

The aim of this guideline is to provide evidence-based symptom management recommendations for patients with cancer who are experiencing OIC or non–opioid-related constipation. This document incorporates the most recently published research on interventions for the management of constipation. The target audience includes oncology healthcare professionals, patients, and decision makers. Policymakers interested in this guideline include individuals and organizations developing local, national, or international protocols with a goal of improving management of adult patients with cancer who are experiencing constipation. The guideline was based on updates of two systematic reviews of published research evidence on constipation: one in patients with OIC (Hanson et al., 2018) and one in patients with chronic idiopathic constipation (Ford & Suares, 2011).

Guideline Development Methods

The Oncology Nursing Society (ONS) vetted and appointed individuals to the ONS Guidelines™ panel. The membership of the interprofessional panel included oncology nurses at all levels of practice, a gastroenterologist, a registered dietitian, and a patient representative. The panel was coordinated by the senior manager of evidence-based practice and inquiry at ONS (P.G.) with collaboration from a methodologist with expertise in evidence appraisal and guideline development (R.L.M.). The panel completed its work using online and face-to-face meetings and web-based tools (www.gradepro.org), with one two-day in-person meeting to review the evidence and formulate recommendations.

The ONS Guidelines panel developed and graded the recommendations and assessed the certainty in the supporting evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Guyatt, Oxman, Sultan, et al., 2011). The guideline development process was modeled after the Guideline International Network McMaster Guidelines Development Checklist (GIN McMaster Checklist) and included the formation of the panel, guideline review internally and externally, and organizational approval. The GIN McMaster Checklist can be accessed online (https://cebgrade.mcmaster.ca/guidecheck.html). The ONS Guidelines process also adheres to the National Academies of Science, Engineering, and Medicine (NASEM) criteria for trustworthy guidelines (Institute of Medicine, 2011; Schünemann et al., 2014).

Financial and intellectual disclosures of interest of all participants were collected and managed according to ONS policies and the recommendations of NASEM and the GIN McMaster Checklist (Institute of Medicine, 2011; Schünemann et al., 2014). At the time of appointment and again at the recommendations meeting, disclosures were recorded, and the ONS Guidelines panel had no relevant conflicts of interests (no material interest in any commercial entity with a product that could be affected by the guidelines).

Formulation of Specific Clinical Questions and Determining Outcomes of Interest

The ONS Guidelines panel met biweekly to discuss and prioritize clinical questions for this guideline. Panelists were instructed to identify questions that were clinically relevant—questions that patients were asking and

about which clinicians had uncertainty regarding the answer. Questions were formulated according to the PICO (patient, intervention, comparator, and outcome) components. The panel structured the PICO questions according to two patient subgroups: patients at risk of experiencing or with OIC and patients with constipation from other causes. These other causes could be related to treatment (e.g., systemic chemotherapy), medication (e.g., antiemetics), or unknown causes. For the purposes of this guideline, the panel referred to this group as non–opioid-related constipation.

The ONS Guidelines panel selected outcomes of interest for each question a priori. The panel discussed all possible outcomes and prioritized importance for patients and decision making using the GRADE approach (Guyatt, Oxman, Kunz, et al., 2011). The panel rated the following outcomes as critical for clinical decision making across the PICO questions: more than three spontaneous bowel movements (SBMs) per week or more than one SBM per week over baseline, rescue-free bowel movements, quality of life, and adverse events leading to treatment discontinuation.

Literature Search and Quality Assessment

After the PICO questions were developed, a literature search was conducted to identify published systematic reviews that closely addressed the PICO questions. Panel members reviewed the results using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews–2) appraisal tool (Shea et al., 2017). Based on AMSTAR 2, two systematic reviews were identified as high-quality and appropriate for update. One reported on treatment options for chronic idiopathic constipation (Ford & Suares, 2011), and one compared treatment options for OIC (Hanson et al., 2018). A medical librarian recreated the search strategies published in the articles through May 2019. In addition to these updates, de novo reviews were conducted for additional questions addressing the efficacy of acupuncture and electroacupuncture for constipation in patients with cancer. Full search strategies, inclusion and exclusion criteria, review methodology, corresponding PRISMA flow diagrams, and results are reported in the accompanying systematic review (Ginex et al., 2020).

Synthesis of Evidence and Development of Recommendations

The evidence from the updated systematic reviews was summarized and assessed in GRADE evidence profiles. Within the evidence profile, the body of evidence across each outcome is assessed based on factors that either decrease or increase one's certainty: risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude of effect, dose-response gradient, or opposing residual confounding (Balshem et al., 2011; Guyatt, Oxman, Akl, et al., 2011). In addition to the certainty of evidence, the panel formulated recommendations considering the balance of benefits and harms, patients' values and preferences, resource use, equity, acceptability, and feasibility. For each question, the panel entered judgments into the GRADE Evidence-to-Decision framework using the GRADEpro Guideline Development Tool (www.gradepro.org).

During the two-day in-person meeting, the panel developed clinical recommendations based on the evidence summarized in the Evidence-to-Decision framework. For each recommendation, the panel arrived at a consensus on the following: the certainty of the evidence, the balance of benefits and harms of the compared intervention options, and the assumptions about the values and preferences associated with the decision. The panel also discussed the extent of the use of alternative treatment options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus vote based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the ONS Guidelines panel.

Interpretation of Recommendations

The strength of the recommendations in this guideline are labeled as "strong" or "conditional." In some situations, the panel deemed the available evidence insufficient to determine a true effect and identified the area as an evidence gap. Table 1 provides the interpretation of the recommendations for patients, clinicians, healthcare policymakers, and researchers, and the recommendations are summarized in Table 2.

Document Review

Draft recommendations were reviewed and approved by all members of the ONS Guidelines panel and then opened for public comment from December 10 to 24, 2019. In addition to open public comment, a targeted peer comment was conducted with three clinical or research experts on constipation. The goal of public comment and targeted peer comment was to obtain direct feedback on the draft recommendations, as well as feedback to facilitate dissemination of the final guideline to practitioners. Following public comment and targeted peer review, the document was revised to address pertinent comments and clarify text where

needed; however, no changes were made to the recommendations. The ONS Board reviewed and approved the guideline methodology and process. The guidelines were then submitted to the *Oncology Nursing Forum* for peer review.

How to Use These Guidelines

ONS Guidelines are intended to assist clinicians in making decisions about treatment interventions for common symptoms experienced by patients with cancer throughout the treatment trajectory. ONS

TABLE 1. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

Strength of Recommendation	Wording in the Guideline	For the Patient	For the Clinician	For Policymakers	For Researchers
Strong	"The ONS Guidelines™ panel recommends . . ."	Most individuals in this situation would want the intervention and only a small proportion would not.	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	In most cases, the recommendation can be adopted as policy. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	This recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide information that alters the recommendation.
Conditional	"The ONS Guidelines panel suggests . . ."	Most individuals in this situation would want the suggested intervention, but many would not.	Different choices will be appropriate for different individuals. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with individuals when working toward a decision.	Policymaking will require substantial debate and involvement of various stakeholders.	This recommendation is likely to be strengthened by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help identify possible research gaps.
Research and/or knowledge gap	"The ONS Guidelines panel recommends the intervention only in the context of a clinical trial. . . ."	A discussion of benefits/harms and alternatives is warranted.	Clinicians should look for clinical trials testing this intervention, if individuals are interested.	–	Available evidence is insufficient to determine true effect, and this recommendation may be appropriate for research.

GRADE—Grading of Recommendations Assessment, Development and Evaluation; ONS—Oncology Nursing Society
Note. Based on information from Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Sultan, et al., 2011.
Note. From "ONS Guidelines™ for Cancer Treatment–Related Hot Flashes in Women With Breast Cancer and Men With Prostate Cancer," by M. Kaplan, P.K. Ginex, L.B. Michaud, et al., 2020, *Oncology Nursing Forum, 47*(4), p. 376 (https://doi.org/10.1188/20.ONF.374-399). Copyright 2020 by Oncology Nursing Society. Reprinted with permission.

Guidelines are intended to inform education, identify research gaps, and promote policy and advocacy. They may also be used by patients in collaboration with their healthcare team. ONS Guidelines are not medical advice and do not replace care by a cancer care clinician. Using a shared decision-making process, clinicians make decisions with patients, including discussion of patients' values and preferences with respect to their current situations. ONS Guidelines may not include all available treatments for an individual patient. Treatments described in the ONS Guidelines may not be appropriate for all patients or in all scenarios. As scientific advances and new evidence become available, these ONS Guidelines may become outdated. Following the ONS Guidelines does not guarantee improvement or a successful outcome. ONS does not warrant or guarantee any products described.

Implementation of ONS Guidelines will be facilitated by forthcoming interactive dissemination tools and patient education resources. The use of ONS Guidelines will also be facilitated by the tables and figures in the supplementary material.

Recommendations, Key Evidence, and Qualifying Statements

The guideline recommendations are organized in two main sections. Recommendations to prevent constipation in patients receiving opioids are addressed first, followed by recommendations for patients experiencing OIC. The second main section focuses on non–opioid-related constipation in patients with cancer.

Prevention of Opioid-Induced Constipation

Good Practice Statement

The ONS Guidelines panel recommends that, before starting an opioid regimen, patients with cancer have a clear understanding of constipation prophylaxis lifestyle education of increased fiber, water intake, and exercise.

Patients with cancer are at nutritional risk, in part because of the high risk of multiple nutrition impact symptoms, including constipation. These symptoms can be associated with anticancer treatment, supportive medications, or the disease itself. Constipation can lead to decreased food and fluid intake, weight loss, and poor quality of life, among other variables (Huhmann & August, 2008). Because of the high risk for constipation in patients taking opioids, adult patients with cancer on opioids should receive education on diet and lifestyle modification to prevent and manage constipation. Education should include instruction on (a) amount of fiber to consume daily, (b) amount of fluid to consume daily, and (c) physical activity, with further specifications for diet modification as needed. Education must be individualized and based on the patients' diagnosis, diet tolerance, weight trends, past medical history, treatment plan, and other pertinent factors. Education must be provided by a qualified healthcare provider, such as a registered dietitian, nurse, or physician (Academy of Nutrition and Dietetics, 2013; Mueller et al., 2011).

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?

Among adult patients with cancer who are receiving opioids, the ONS Guidelines panel suggests either prophylactic bowel regimen with laxatives and lifestyle education or lifestyle education alone for prevention of constipation (conditional recommendation; low certainty of evidence).

Remarks: Patients who place a higher value on avoidance of constipation may prefer to start on a prophylactic bowel regimen; however, patients who place a higher value on avoiding undue costs, taking pills, or undue harms (diarrhea) may prefer to not start on a bowel regimen prophylactically.

Summary of the Evidence

The evidence for this question is based on a systematic review by Ford and Suares (2011) that addressed this topic and was updated in 2019 (Ginex et al., 2020). Ford and Suares (2011) included seven RCTs that assessed the use of osmotic (n = 5) and stimulant (n = 2) laxatives for the treatment of chronic idiopathic constipation. These seven studies involved 1,411 patients with chronic idiopathic constipation. The ONS Guidelines panel judged this evidence to be indirect but similar enough to patients with cancer who have not yet developed OIC to be used as evidence in this guideline. No additional studies were identified by the updated literature search.

Benefits

Osmotic and stimulant laxatives may increase SBM response when compared with no bowel regimen (risk ratio [RR] = 2.24, 95% confidence interval [CI] [1.93, 2.61]). In addition, osmotic and stimulant laxatives may reduce straining and improve stool consistency (RR = 1.52, 95% CI [1.18, 1.96]; RR = 1.55,

TABLE 2. Summary of Recommendations: ONS Guidelines™ for Opioid-Induced and Non–Opioid-Related Cancer Constipation

Recommendation	Strength of Recommendation	Certainty of Evidence
Opioid-induced constipation		
The ONS Guidelines panel recommends that, before starting an opioid regimen, patients with cancer have a clear understanding of constipation prophylaxis lifestyle education of increased fiber, water intake, and exercise.	Good practice statement	–
Among adult patients with cancer who are receiving opioids, the ONS Guidelines panel suggests either prophylactic bowel regimen with laxatives and lifestyle education or lifestyle education alone for prevention of constipation. **Remarks:** Patients who place a higher value on avoidance of constipation may prefer to start on a prophylactic regimen; however, patients who place a higher value on avoiding undue costs, taking pills, or undue harms (diarrhea) may prefer to not start on a bowel regimen prophylactically.	Conditional	Low
Among adult patients with cancer, the ONS Guidelines panel recommends osmotic or stimulant laxatives and lifestyle education rather than lifestyle education alone for treatment of opioid-induced constipation.	Strong	Moderate
Among adult patients with cancer, the ONS Guidelines panel suggests osmotic PEG and lifestyle education rather than lifestyle education alone for opioid-induced constipation.	Conditional	Low
Opioid-induced constipation; have not responded to a bowel regimen		
Among adult patients with cancer who have opioid-induced constipation and have not responded to a bowel regimen, the ONS Guidelines panel suggests methylnaltrexone and a bowel regimen rather than a bowel regimen alone for treatment. **Remarks:** Subcutaneous methylnaltrexone may present an additional option for patients who are unable to take other forms of PAMORAs.	Conditional	Very low
Among adult patients with cancer who have opioid-induced constipation, the ONS Guidelines panel recommends naldemedine and a bowel regimen rather than a bowel regimen alone for treatment.	Strong	Moderate
Among adult patients with cancer, the ONS Guidelines panel suggests naloxegol and a bowel regimen rather than a bowel regimen alone for opioid-induced constipation.	Conditional	Very low
Among adult patients with cancer, the ONS Guidelines panel recommends prucalopride for treatment of opioid-induced constipation only in the context of a clinical trial.	No recommendation; knowledge gap	–
Among adult patients with cancer, the ONS Guidelines panel recommends lubiprostone for opioid-induced constipation only in the context of a clinical trial.	No recommendation; knowledge gap	–
Among adult patients with cancer, the ONS Guidelines panel recommends linaclotide for opioid-induced constipation only in the context of a clinical trial.	No recommendation; knowledge gap	–
Non–opioid-related constipation in patients with cancer		
Among adult patients with cancer, the ONS Guidelines panel suggests osmotic or stimulant laxatives and lifestyle education over lifestyle education alone for constipation. **Remarks:** Patients with a higher tolerance of constipation symptoms or duration or who place a greater value on avoiding laxatives may not wish to use osmotic or stimulant laxatives.	Conditional	Moderate
Among adult patients with cancer, the ONS Guidelines panel recommends the use of acupuncture for constipation only in the context of a clinical trial.	No recommendation; knowledge gap	–
Among adult patients with cancer, the ONS Guidelines panel recommends the use of electroacupuncture for constipation only in the context of a clinical trial.	No recommendation; knowledge gap	–

ONS—Oncology Nursing Society; PAMORA—peripherally acting mu-opioid receptor antagonist; PEG—polyethylene glycol
Note. PAMORAs should only be considered after a patient has not responded to a bowel regimen.

95% CI [1.33, 1.82], respectively). Osmotic and stimulant laxatives may increase the frequency of bowel movements (mean difference [MD] = 2.55, 95% CI [1.53, 3.57]).

Harms and Burdens

Adverse events leading to treatment discontinuation among people using osmotic and stimulant laxatives may be higher than those not using osmotic and stimulant laxatives (RR = 3.55, 95% CI [1.6, 7.89]) (Kamm et al., 2011; McGraw, 2016; Nakajima et al., 2019). Within the Ford and Suares (2011) systematic review, only one study reported on adverse events, with the RR of experiencing any adverse event being 1.94 (95% CI [1.52, 2.47]). Four trials reported on individual adverse events, including abdominal pain and headache, with no significant differences between groups. Only diarrhea occurred more frequently in the intervention group, with an RR of 13.75 (95% CI [2.82, 67.14]).

Certainty in the Evidence of Effects

The certainty in the estimates for osmotic or stimulant laxatives in addition to lifestyle education was judged as low because of concerns with indirectness of the evidence because the studies were not conducted among people experiencing OIC, and trial participants experienced constipation at the start of the study. The certainty of the evidence was largely driven by the outcomes of adverse events leading to treatment discontinuation and SBM response.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel considered that patients who place a higher value on avoidance of constipation may prefer to start on a prophylactic regimen; however, patients who place a higher value on avoiding undue costs, taking medications, or undue harms (diarrhea) may prefer to not start on a bowel regimen prophylactically. Shared decision making is important for patients and clinicians to discuss options so that patients will have a clear understanding of the risks of constipation and the education and clinical indications for use of a bowel regimen.

Conclusions

Patients who are starting opioids for cancer-related pain are at high risk for developing constipation. The evidence for a prophylactic bowel regimen in addition to lifestyle education was judged to be low certainty; however, the ONS Guidelines panel balanced the desirable and undesirable health effects to make a conditional recommendation for a prophylactic bowel regimen in addition to lifestyle education for patients with cancer who are taking opioids.

Treatment of Opioid-Induced Constipation

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

Among adult patients with cancer, the ONS Guidelines panel recommends osmotic or stimulant laxatives and lifestyle education rather than lifestyle education alone for treatment of OIC (strong recommendation; moderate certainty of evidence).

Summary of the Evidence

The evidence for this question is based on a systematic review by Ford and Suares (2011) that addressed this topic and was updated in 2019 (Ginex et al., 2020). The same systematic review informed the previous question prevention of OIC. Ford and Suares (2011) included seven RCTs that assessed the use of osmotic (n = 5) and stimulant (n = 2) laxatives for the treatment of chronic idiopathic constipation. These seven studies involved 1,411 patients with chronic idiopathic constipation. Although this evidence was indirect to patients with cancer, the ONS Guidelines panel judged that it was informative to the question. No additional studies were identified for the use of osmotic or stimulant laxatives for treatment of OIC.

Benefits

Osmotic and stimulant laxatives may increase SBM response when compared with no bowel regimen (RR = 2.24, 95% CI [1.93, 2.61]). In addition, osmotic and stimulant laxatives may reduce straining and improve stool consistency (RR = 1.52, 95% CI [1.18, 1.96]; RR = 1.55, 95% CI [1.33, 1.82], respectively). Osmotic and stimulant laxatives may increase the frequency of bowel movements (MD = 2.55, 95% CI [1.53, 3.57]).

Harms and Burdens

Adverse events leading to treatment discontinuation among people using osmotic and stimulant laxatives may be higher than those not using osmotic and stimulant laxatives (RR = 3.55, 95% CI [1.6, 7.89]) (Kamm et al., 2011; McGraw, 2016; Nakajima et al., 2019). Within the Ford and Suares (2011) systematic review, only one study reported on adverse events, with the RR of experiencing any adverse event being 1.94 (95% CI [1.52, 2.47]). Four trials reported on individual adverse events, including abdominal pain and headache, with no significant differences between groups. Only

diarrhea occurred more frequently in the intervention group, with an RR of 13.75 (95% CI [2.82, 67.14]).

Certainty in the Evidence of Effects

The ONS Guidelines panel judged the certainty of estimated effects as moderate due to serious indirectness because the studies were not conducted among people experiencing OIC.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel judged the desirable anticipated effects to be moderate and the undesirable anticipated effects to be small. The panel considered the overall certainty of the evidence of effects to be moderate. The balance of effects was judged to favor the intervention based on the large treatment effect. The panel considered the costs and savings to be negligible but did not find any cost-effectiveness studies reported. The panel also considered laxatives to be acceptable to stakeholders and feasible to implement. The panel noted an implementation consideration regarding dosing because the studies were mostly in patients with chronic idiopathic constipation, and dosing for other conditions may be different.

Conclusions

The ONS Guidelines panel determined that there was moderate certainty in the evidence that the desirable effects of osmotic or stimulant laxatives outweigh the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are starting opioids for cancer-related pain and made a strong recommendation for using osmotic or stimulant laxatives in addition to lifestyle education as first-line therapy in patients with cancer who have OIC.

Should osmotic polyethylene glycol and lifestyle education rather than lifestyle education alone be used in adult patients with cancer who have opioid-induced constipation?

Among adult patients with cancer, the ONS Guidelines panel suggests osmotic polyethylene glycol (PEG) and lifestyle education rather than lifestyle education alone for OIC (conditional recommendation; low certainty of evidence).

Summary of the Evidence

A systematic review by Hanson et al. (2018) was identified that included one study (Freedman et al., 1997) that addressed this question. The search strategy for that review was updated prior to the ONS Guidelines panel meeting, and one additional study was identified (Hawley et al., 2020). The studies by Freedman et al. (1997) and Hawley et al. (2020) included patients with OIC. The study by Freedman et al. (1997) included 57 patients with nonmalignant pain and OIC and compared PEG, lactulose, and placebo; the study by Hawley et al. (2020) included 42 patients with cancer and compared PEG and sennosides.

Benefits

PEG may decrease the number of hard stools per week (MD = –0.69, 95% CI [–1.28, –0.1]) and increase the number of soft stools per week (MD = 0.3, 95% CI [–0.95, 1.55]) (Freedman et al., 1997). In the study by Hawley et al. (2020), the authors report that PEG resulted in 1.21 times more expected number of days with a satisfactory bowel movement per days of treatment (95% CI [0.96, 1.55]), with no difference in patient preference between PEG and sennosides.

Harms and Burdens

Patients receiving PEG may experience more frequency of excess gas (MD = 1.1, 95% CI [0.24, 2.44]) or severe cramping (MD = 0.04, 95% CI [–1.15, 1.07]), as measured by episodes per week (Freedman et al., 1997). Hawley et al. (2020) reported similar adverse events among treatment groups receiving PEG and sennosides. Cramps (39%, 36%), nausea (37%, 36%), and vomiting (20%, 23%) were the most common adverse events reported in PEG and sennosides, respectively.

Certainty in the Evidence of Effects

The quality of evidence supporting the use of PEG was low based on very serious concerns of imprecision.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel acknowledged that the desirable anticipated effects were small and that the undesirable anticipated effects were trivial, with the balance of effects probably favoring the intervention. The panel considered that the resources required would result in negligible costs and savings and that PEG is acceptable to stakeholders and feasible to implement. The panel also noted that a thorough discussion of potential side effects is important to guide patient decision making.

Conclusions

The ONS Guidelines panel determined that there was low certainty in the evidence that the desirable effects

of PEG outweigh the undesirable effects in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are starting opioids for cancer-related pain and made a conditional recommendation for using PEG in addition to lifestyle education as first-line therapy in patients with cancer who have OIC.

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?

Among adult patients with cancer who have OIC and have not responded to a bowel regimen, the ONS Guidelines panel suggests methylnaltrexone and a bowel regimen rather than a bowel regimen alone for treatment (conditional recommendation; very low certainty of evidence).

Remarks: Subcutaneous methylnaltrexone may present an additional option for people who are unable to take other forms of peripherally acting mu-opioid receptor antagonists (PAMORAs).

Summary of the Evidence

The identified systematic review (Hanson et al., 2018) included six RCTs that addressed this question (Bull et al., 2015; Michna et al., 2011; Porteney et al., 2008; Rauck et al., 2017; Slatkin et al., 2009; Thomas et al., 2008). An update of this review identified two additional studies (Rauck et al., 2019; Webster & Israel, 2018) that were additional analyses from previous studies. Rauck et al. (2019) published an additional safety analysis, and Webster and Israel (2018) published a post-hoc analysis of patients on concomitant methadone. Varying doses of methylnaltrexone reported were 150 mg, 300 mg, and 450 mg. Outcomes that were reported included rescue-free bowel movement response, laxation response, change in rescue-free bowel movement frequency, reduction in straining, quality of life, and adverse events leading to treatment discontinuation.

Benefits

Methylnaltrexone is a PAMORA approved for the treatment of OIC in adults with chronic noncancer pain or chronic pain who do not require frequent (e.g., weekly) opioid dosage escalation. It is available in oral and subcutaneous formulations. Methylnaltrexone may increase rescue-free bowel movements (defined as more than three rescue-free bowel movements per week) over a standard bowel regimen (RR = 1.33, 95% CI [1.16, 1.52]) and laxation response (RR = 3.5, 95% CI [2.65, 4.62]) (Hanson et al., 2018). Webster and Israel (2018) evaluated the safety and efficacy of oral methylnaltrexone for OIC in patients on concomitant methadone. Patients received differing doses of methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily. Patients treated with oral methylnaltrexone had significant improvement in rescue-free bowel movements during weeks 1–4 with 300 mg (33.6%, $p < 0.01$) and 450 mg (38.2%, $p < 0.001$) dosages versus placebo; improvement with the 150 mg dosage versus placebo was not significant.

Harms and Burdens

Information on adverse events was included in four studies and pooled (Hanson et al., 2018). Adverse events leading to discontinuation of treatment occurred in 4.5% of patients on methylnaltrexone and 3.6% of patients on placebo (RR = 1.51; 95% CI [0.83, 2.71]). PAMORAS should be avoided in patients with conditions that compromise the blood–brain barrier because there is a potential for serious withdrawal or reversal of anesthesia (Seth et al., 2018).

Certainty in the Evidence of Effects

Overall, the certainty in the estimated effects was very low owing to indirectness and imprecision in the evidence. The clinical importance of the MDs was uncertain, which led the panel to rate down for imprecision.

Other Evidence-to-Decision Criteria

The panel considered that the studies compared methylnaltrexone to placebo, which would have a smaller difference in the effect on rescue-free bowel movement and laxation outcomes. Therefore, the panel judged the desirable anticipated effects to be small, with trivial undesirable anticipated effects. The panel had very low certainty in the evidence because of the trial requirements that participants needed to stop their current bowel regimen and were compared to placebo, not standard of care that includes a bowel regimen. The panel considered that the balance of effects probably favors the intervention based on the positive outcomes from the studies. The costs were judged to be large, with the panel recognizing the cost of methylnaltrexone over alternative options, but no cost-effectiveness studies were identified.

Conclusions

The ONS Guidelines panel determined that there was very low certainty in the evidence that the desirable

effects of methylnaltrexone outweighs the undesirable effect in patients with cancer who have OIC. The ONS Guidelines panel issued a conditional recommendation for methylnaltrexone for the management of OIC in patients with cancer.

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?

Among adult patients with cancer who have OIC, the ONS Guidelines panel recommends naldemedine and a bowel regimen rather than a bowel regimen alone for treatment (strong recommendation; moderate certainty of evidence).

Summary of the Evidence

The identified systematic review (Hanson et al., 2018) included four RCTs that addressed this question (Hale et al., 2017 [two RCTs]; Webster et al., 2017; Webster, Nalamachu, et al., 2018) in 2,463 patients comparing naldemedine to placebo in patients with OIC. An update of this review identified two additional studies (Katakami, Harada, et al., 2017; Katakami, Oda, et al., 2017) in 418 patients with cancer and OIC. Outcomes reported in these studies include SBM response, change in SBM frequency, change in frequency of bowel movements without straining, change in bowel movement frequency, quality of life (assessed using PAC-QOL© [Patient Assessment of Constipation–Quality of Life]), adverse events leading to treatment discontinuation, and change in frequency of SBMs.

Benefits

Naldemedine is a PAMORA indicated for the treatment of OIC in adult patients with chronic noncancer pain. Naldemedine, in addition to a bowel regimen, likely increases SBM response (odds ratio = 2.44, 95% CI [1.99, 3.01]) and weekly SBM frequency (MD = 2.02, 95% CI [1.3, 2.74]) as compared to a bowel regimen among patients with OIC. Naldemedine may increase the frequency of bowel movements (MD = 0.95, 95% CI [0.57, 1.33]) and frequency of bowel movements without straining (MD = 1.43, 95% CI [0.75, 2.11]). Quality of life may increase among patients with OIC using naldemedine as compared to bowel regimen alone (MD = 0.3, 95% CI [0.16, 0.44]).

Harms and Burdens

Naldemedine likely increases adverse events leading to treatment discontinuation (RR = 1.41, 95% CI [1.17, 1.7). In a phase 2b study by Katakami, Oda, et al. (2017), treatment-emergent adverse events were more common with naldemedine (0.1 mg: 66.1%; 0.2 mg: 67.2%; 0.4 mg: 78.6%) than with placebo (51.8%). Diarrhea was the most common treatment-emergent adverse event. The phase 3 study plus extension study by Katakami, Harada, et al. (2017) reported that more patients treated with naldemedine as compared to placebo reported treatment-emergent adverse events during the phase 3 portion (44% [43 of 97 patients] with naldemedine as compared to 26% [25 of 96 patients] with placebo; p = 0.01). In the extension phase of the study, 80% (105 of 131 patients) reported adverse events. Diarrhea was the most frequently reported in each component of the phase 3 study (19.6% in phase 3 and 18.3% in the extension phase). The panel recognized the risk of potential for serious withdrawal or reversal of anesthesia from use of PAMORAs in patients with conditions that compromise the blood–brain barrier (Seth et al., 2018).

Certainty in the Evidence of Effects

The ONS Guidelines panel judged the certainty of the evidence of effects to be moderate for naldemedine. The panel rated down for indirectness because some studies were in patients with nonmalignant pain; however, the panel noted that the populations in this body of evidence were less indirect and reflected a more realistic population, similar to patients with cancer who have OIC.

Other Evidence-to-Decision Criteria

The panel judged the desirable effects to be large, with the undesirable anticipated effects small. The panel noted that cost is a concern in that naldemedine is often not covered by insurance and that costs to patients are an important issue and could reduce equity. The panel considered that naldemedine was probably acceptable to stakeholders and feasible to implement.

Conclusions

The ONS Guidelines panel determined that there was moderate certainty in the evidence that the desirable effects of naldemedine outweigh the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are taking opioids for cancer-related pain and made a strong recommendation for using naldemedine in addition to a bowel regimen for treatment of OIC in patients with cancer.

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

Among adult patients with cancer, the ONS Guidelines panel suggests naloxegol and a bowel regimen rather than a bowel regimen alone for OIC (conditional recommendation; very low certainty of evidence).

Summary of the Evidence

The identified systematic review (Hanson et al., 2018) included three RCTs that addressed this question (Chey et al., 2014; Webster et al., 2013, 2014) in 1,559 patients comparing naloxegol to placebo for the treatment of OIC. An update of this review identified one additional study (Webster, Diva, et al., 2018) that was an analysis of pain-related data of a previously reported RCT. The outcomes included were SBM response, change in SBM frequency, change in frequency of bowel movements without straining, stool consistency, adverse events leading to treatment discontinuation, and change in pain score.

Benefits

Naloxegol is a PAMORA indicated for the treatment of OIC in adult patients with chronic noncancer pain. Naloxegol (25 mg) with a bowel regimen may increase SBM response rate (RR = 1.43, 95% CI [1.19, 1.71]) and weekly SBM frequency (MD = 1.02, 95% CI [0.67, 1.37]) over bowel regimen alone, but it is uncertain. Naloxegol with a bowel regimen may reduce the severity of straining as compared to a bowel regimen alone (MD = −0.24, 95% CI [−0.35, −0.14). Overall, these studies showed that 187 of 446 patients (42%) who received naloxegol at this dose had a response to therapy as compared to 131 of 446 patients (29%) who received placebo (Hanson et al., 2018). The additional pain analyses reported by Webster, Diva, et al. (2018) found that opioid analgesia was maintained during treatment with naloxegol in patients with OIC and noncancer pain.

Harms and Burdens

Adverse events leading to treatment discontinuation were pooled. Overall, 141 of 1,500 patients (9%) discontinued therapy because of adverse events as compared to 34 of 809 patients (4%) who received placebo. The pooled relative risk was 2.33 (95% CI [1.62, 3.35]) (Hanson et al., 2018).

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for naloxegol for the treatment of constipation was very low because of the indirectness to patients with cancer and imprecision.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel judged the desirable and undesirable anticipated effects to be small. The panel considered that the balance of effects probably favors naloxegol but was not clear on the magnitude of the balance of effects because of concerns with indirectness of the patient population to patients with OIC and cancer. The panel noted that these studies required patients to stop their bowel regimen to be included in the study, which increases indirectness to the population of patients with cancer who have OIC. The panel acknowledged that costs are large for naloxegol but did not find any studies of cost-effectiveness. The panel judged that naloxegol is probably acceptable to most stakeholders and is feasible to implement.

Conclusions

The ONS Guidelines panel determined that there was very low certainty in the evidence that the desirable effects of naloxegol outweighs the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are taking opioids for cancer-related pain and made a conditional recommendation for the use of naloxegol for treatment of OIC in patients with cancer.

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

Among adult patients with cancer, the ONS Guidelines panel recommends prucalopride for treatment of OIC only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The identified systematic review (Hanson et al., 2018) included one RCT that addressed this question (Sloots et al., 2010) in 196 patients randomized to two different doses of prucalopride or a placebo. An update of this review identified no additional studies. The outcomes that were assessed include SBM response, change in SBM frequency, quality of life (measured with PAC-QOL), adverse events leading to treatment discontinuation, painful defecation, and stool consistency.

Benefits

Prucalopride is a selective 5-HT_4 receptor agonist and enterokinetic that has shown efficacy in

chronic constipation when laxatives are not effective (Camilleri et al., 2008; Quigley et al., 2009; Tack et al., 2009). Prucalopride was approved by the U.S. Food and Drug Administration in 2018 for the treatment of chronic idiopathic constipation in adults. Prucalopride may improve SBM response (RR = 1.36, 95% CI [1.08, 1.7]) and quality of life (RR = 1.57, 95% CI [0.88. 2.8]) when compared to bowel regimen alone, but it is uncertain.

Harms and Burdens

The incidence of treatment-related adverse events was similar across the treatment arms at 49% for placebo, 58% with prucalopride 2 mg, and 50% with prucalopride 4 mg (Sloots et al., 2010). The most frequently reported adverse event was abdominal pain (25%) in the 4 mg group, and abdominal pain was the most common reason for treatment discontinuation in all groups.

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for prucalopride for the treatment of constipation was very low because of the indirectness to patients with cancer and possible publication bias. The panel also noted imprecision because of uncertainty of a clinically meaningful difference in outcomes and the low number of events reported. Publication bias was a concern because an RCT (ClinicalTrials.gov ID: NCT01117051) was terminated by the manufacturer prior to completion, and study results were never published.

Other Evidence-to-Decision Criteria

The panel judged the desirable anticipated effects and the undesirable anticipated effects to be small, with the balance of effects favoring neither the intervention nor the comparison. The panel considered the costs for prucalopride to be large, with no studies on cost-effectiveness, and that cost may reduce equity. The panel acknowledged that prucalopride is probably acceptable to stakeholder but is not widely known or used in clinical practice.

Conclusions

Limited consistent evidence exists to support a recommendation for prucalopride for the treatment of OIC in patients with cancer. Based on the very low quality and limitations of evidence, the ONS Guidelines panel made no recommendation for prucalopride and identified this intervention as an evidence gap that warrants further research.

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

Among adult patients with cancer, the ONS Guidelines panel recommends lubiprostone for OIC only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

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

Benefits

Lubiprostone is a chloride channel activator indicated for the treatment of chronic idiopathic constipation in adults or OIC in adult patients with chronic noncancer pain. Lubiprostone with bowel regimen may increase SBM response over bowel regimen alone, but it is uncertain (RR = 1.15, 95% CI [0.97, 1.37]). Lubiprostone may reduce straining (MD = –0.3, 95% CI [–0.47, –0.13]).

A pooled analysis looked at opioid subgroups. In patients receiving phenanthrene opioids, such as oxycodone, lubiprostone had a positive response, with increased mean changes in SBM frequency from baseline ($p = 0.0001$), increased response rate ($p = 0.0024$), and improved OIC symptoms ($p \leq 0.0229$) when compared to placebo (Webster, Brewer, et al., 2018). For patients receiving phenylpiperidine opioids, such as fentanyl, significant improvement in SBM frequency ($p = 0.0129$) was reported, with positive trends in response rates (21.4% versus 9.8%, $p = 0.0723$) and OIC symptoms when compared to placebo.

Harms and Burdens

Lubiprostone with bowel regimen may lead to more adverse events that cause treatment discontinuation when compared to bowel regimen alone (RR = 2.13, 95% CI [1.25, 3.61]). In the open-label extension study by Spierings et al. (2016), 23 of 439 participants

(5%) discontinued the medication because of adverse events during nine months of follow-up. In the subgroup analysis study, the lubiprostone adverse event profiles were similar, with nausea and diarrhea being the most common treatment-emergent adverse events reported (Webster, Brewer, et al., 2018).

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for lubiprostone for the treatment of OIC was very low because of the indirectness to patients with cancer. In addition, participants in the control arms were unable to receive a bowel regimen. The panel also noted imprecision because of uncertainty of a clinically meaningful difference in outcomes and the low number of events reported.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel judged the desirable anticipated effects to be trivial and the undesirable anticipated effects to be small. The panel judged the balance of effects to probably favor the comparison because of the uncertainty of prior response to laxatives in the patient populations. The panel considered the costs to be large, but it may be covered by insurance, and equity may be reduced related to the costs and out-of-pocket expenses. Lubiprostone is probably acceptable because it is widely available, but it is not commonly used for OIC in patients with cancer.

Conclusions

Limited consistent evidence exists to support a recommendation for lubiprostone for the treatment of OIC in patients with cancer. Based on the low quality and limitations of evidence, the ONS Guidelines panel made no recommendation for lubiprostone and identified this intervention as an evidence gap that warrants further research.

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

Among adult patients with cancer, the ONS Guidelines panel recommends linaclotide for OIC only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The ONS Guidelines panel identified three RCTs that addressed this question (Lacy et al., 2015; Lembo et al., 2010, 2011) in 2,069 patients with chronic constipation. In addition, the panel identified a study of linaclotide for treatment of OIC that has not yet been published (ClinicalTrials.gov ID: NCT02270983). Different doses of linaclotide were used in the studies, and treatment ranged from 4 to 12 weeks.

Benefits

Linaclotide is a 14–amino acid synthetic peptide that stimulates intestinal fluid secretion and transit (Lembo et al., 2011). Linaclotide is approved in the United States at a dose of 145 mcg once daily for the treatment of chronic idiopathic constipation in adults. Linaclotide as compared to placebo may increase SBM frequency (MD = 1.62, 95% CI [0.92, 2.31]) (Ginex et al., 2020).

Harms and Burdens

Adverse events were similar across studies. Lacy et al. (2015) reported that adverse events resulted in premature discontinuation of 5% of patients taking linaclotide 145 mcg, 9% of patients taking linaclotide 290 mcg, and 6% of patients taking placebo. Lembo et al. (2010) reported that the most common and only dose-related adverse event was diarrhea, with six patients discontinuing treatment related to diarrhea. In Lembo et al. (2011), the incidence of adverse events was similar across groups except for diarrhea, which led to discontinuation of treatment in 4% of patients in the linaclotide groups.

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for linaclotide for the treatment of constipation was very low because of the indirectness to patients with cancer. The panel also noted imprecision because of uncertainty of a clinically meaningful difference in outcomes and publication bias because of the lack of published studies in an OIC population.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel judged the desirable anticipated effects to be small and the undesirable anticipated effects to be trivial with linaclotide. The panel considered that the balance of effects probably favors linaclotide. The panel acknowledged the costs to be large, with no evidence of cost-effectiveness and equity reduced because of the costs. The panel judged linaclotide to be acceptable to stakeholders and feasible to implement.

Conclusions

Limited consistent evidence exists to support a recommendation for linaclotide in patients with cancer.

Based on the low quality and limitations of evidence, the ONS Guidelines panel made no recommendation for linaclotide and identified this intervention as an evidence gap that warrants further research.

Prevention and Treatment of 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?

Among adult patients with cancer, the ONS Guidelines panel suggests osmotic or stimulant laxatives in addition to lifestyle education over lifestyle education alone for constipation (conditional recommendation; moderate certainty of evidence).

Remarks: Patients with a higher tolerance of constipation symptoms or duration or who place a greater value on avoiding laxatives may not wish to use osmotic or stimulant laxatives.

Summary of the Evidence

The systematic review by Ford and Suares (2011) was updated, and three additional studies were identified that could be analyzed in a meta-analysis (McGraw et al., 2016; Nakajima et al., 2019; Speed et al., 2010). In addition, the ONS Guidelines panel review identified two RCTs among patients with cancer (Hanai et al., 2015; 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% were patients with cancer), patients with breast cancer, and patients with functional constipation without cancer. Interventions include docusate, self-management, and laxatives. The self-management programs included abdominal massage, abdominal muscle stretching and education (Hanai et al., 2015), dietary management, lifestyle evaluation, defecation and exercise skills training, patient and caregiver support, and a written self-management guide (Shen et al., 2018).

Benefits

In a pooled analysis of seven studies, osmotic or stimulant laxatives increased SBM response as compared to lifestyle factors for patients experiencing functional constipation (RR = 2.24, 95% CI [1.93, 2.61]). In addition, in a pooled analysis of six studies, SBM frequency may increase with osmotic or stimulant laxatives when compared to lifestyle factors alone (MD = 2.55, 95% CI [1.53, 3.57]) (Ginex et al., 2020).

FIGURE 1. Research Priorities Identified by the ONS Guidelines™ Panel Specific to Constipation

Opioid-Induced Constipation

Laxatives
- Head-to-head comparisons of treatment options
- PEG compared to other osmotic laxatives
- Dosing of laxatives for opioid-induced constipation in patients with cancer

PAMORAs
- Trial among patients with cancer who have opioid-induced constipation who are laxative refractory
- Head-to-head trials with other PAMORAs or bowel regimens
- Validated tools to evaluate outcomes
- Quality of life

Prucalopride and lubiprostone
- Trials compared to a bowel regimen
- Safety studies

Non–Opioid-Related Constipation

Acupuncture and electroacupuncture
- Testing of a standard acupuncture protocol
- Head-to-head comparisons with laxatives

ONS—Oncology Nursing Society; PAMORA—peripherally acting mu-opioid receptor antagonist; PEG—polyethylene glycol

Harms and Burdens

For patients with functional constipation, osmotic or stimulant laxatives increase adverse events leading to treatment discontinuation when compared to lifestyle factors (RR = 3.55, 95% CI [1.6, 7.89]) (Ginex et al., 2020).

Certainty in the Evidence of Effects

Overall, the certainty in the estimated effects was moderate because of indirectness. The panel decided that constipation related to treatments received by patients with cancer may differ from the patients included in the trial with functional constipation.

Other Evidence-to-Decision Criteria

The balance of effects was judged by the panel to favor osmotic and stimulant laxatives in addition to lifestyle education over lifestyle education alone with negligible costs and savings. In general, laxatives and lifestyle education are considered acceptable to stakeholders and are feasible to implement.

Conclusions

The ONS Guidelines panel determined that there is moderate certainty in the evidence and made a

conditional recommendation; clinicians and patients should carefully evaluate treatment options and risk factors and develop a personalized treatment plan because of the spectrum of reasons for constipation in this population. Patient preferences and values will inform how they weigh laxatives and other options, as will their individual tolerance and duration of constipation symptoms.

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

Among adult patients with cancer, the ONS Guidelines panel recommends the use of acupuncture for constipation only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The ONS Guidelines panel systematic review identified three RCTs among patients with cancer (Liu et al., 2015; Rithirangsriroj et al., 2015; Shin & Park, 2018) and three RCTs among patients with functional constipation (Lee et al., 2018; Wu et al., 2014; Zheng et al., 2018). The ONS Guidelines panel removed Shin and Park (2018) for evaluation because the intervention was acupressure and not directly related to this question. Sample sizes ranged from 30 to 684, with varying treatment schedules.

Benefits

Acupuncture may increase SBM frequency when compared to lifestyle factors alone, but it is uncertain (MD = 0.85, 95% CI [0.59, 1.1]) (Ginex et al., 2020). Patients may experience a decrease in constipation symptoms (measured using the constipation assessment scale) with acupuncture more than without, but it is uncertain (MD = –0.63, 95% CI [–3.14, 1.88]).

Harms and Burdens

The meta-analysis reported a decreased risk for adverse events among patients receiving acupuncture, but it is very uncertain (RR = 0.53, 95% CI [0.27, 1.02]) (Ginex et al., 2020). Adverse events among the participants in the studies were minimal and not different among treatment groups. Minor events reported included subcutaneous blood stasis (Liu et al., 2015), insomnia, soreness, and minimal pain (Rithirangsriroj et al., 2015).

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for acupuncture for the treatment of constipation was very low because of concerns with study limitations and the indirectness to patients with cancer. The panel also noted imprecision because of uncertainty of a clinically meaningful difference in outcomes and risk of bias in the lack of blinding in some studies.

Other Evidence-to-Decision Criteria

The panel judged the desirable anticipated and unanticipated effects to be trivial with the balance of effects not favoring either acupuncture or the comparison. The panel considered costs to be large because of the multiple sessions required for treatment, and no studies on cost-effectiveness were identified. The panel judged that acceptability would vary among stakeholders and that acupuncture would probably be feasible to implement.

Conclusions

Limited consistent evidence exists to support a recommendation for acupuncture for the treatment of constipation in patients with cancer. Based on the low quality and limitations of evidence, the ONS Guidelines panel made no recommendation for acupuncture and identified this intervention as an evidence gap that warrants further research.

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

Among adult patients with cancer, the ONS Guidelines panel recommends the use of electroacupuncture for constipation only in the context of a clinical trial (no recommendation; knowledge gap).

Summary of the Evidence

The systematic review identified three studies that addressed this question. All were in patients with functional constipation with sample sizes ranging from 67 to 1,075. One compared electroacupuncture to sham acupuncture (Liu et al., 2016), one was a three-arm study that compared low-current acupuncture, high-current acupuncture, and mosapride (Wu et al., 2017), and one compared shallow electroacupuncture to deep electroacupuncture (Da et al., 2015). Time of treatment varied from 4 to 8 weeks, and follow-up ranged from 0 to 12 weeks.

Benefits

Electroacupuncture may increase complete SBM frequency greater than three times per week over

lifestyle factors alone (RR = 3.33; 95% CI [2.42, 4.57]). In addition, patients receiving electroacupuncture rather than lifestyle factors alone may experience increased complete SBM frequency (MD = 0.85, 95% CI [0.64, 1.06]) and greater quality of life (assessed with PAC-QOL) (MD = –0.31, 95% CI [–0.36, –0.25]), but it is uncertain (Ginex et al., 2020).

Harms and Burdens

The meta-analysis reported a decreased risk for adverse events among patients receiving electroacupuncture, but it is very uncertain (RR = 0.45, 95% CI [0.14, 1.44]) (Ginex et al., 2020). Overall adverse events were minimal in the studies. Liu et al. (2016) reported that electroacupuncture-related adverse events during treatment were infrequent in both groups (5.8% of participants in the electroacupuncture group and 4.5% in the sham acupuncture group; p = 0.32), and all were mild or transient with no serious adverse events reported. The most reported electroacupuncture-related adverse events were hematoma, sleeplessness, and sharp pain. Wu et al. (2017) also found minimal adverse events, with the total proportion of adverse events being 2% (4 of 190), and all adverse events occurring in the group receiving mosapride. The difference in adverse events was significant between the electroacupuncture groups and the mosapride group (p = 0.0143 among the three groups). There were no serious adverse events reported in the study by Da et al. (2015). The authors noted that local subcutaneous congestion appeared in two participants and that one participant reported mild abdominal pain.

Certainty in the Evidence of Effects

Overall, the certainty in the evidence of effects for electroacupuncture for the treatment of constipation was very low because of the indirectness to patients with cancer and the variety of methods studied. The panel also noted imprecision because of uncertainty of a clinically meaningful difference in outcomes and the low number of events reported.

Other Evidence-to-Decision Criteria

The ONS Guidelines panel judged this problem to be a priority, with moderate desirable anticipated effects and trivial undesirable anticipated effects. The panel also noted that the balance of effects probably favors electroacupuncture and that the resource requirement and costs of the intervention are large. Although the panel agreed that electroacupuncture is probably feasible, acceptability may vary but is generally acceptable within oncology. The panel noted that research on electroacupuncture in constipation in patients with cancer is needed to inform practice and future guidelines.

SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

All appendices related to this article can be accessed online at https://bit.ly/30y29sl.

Conclusions

Electroacupuncture has shown emerging benefits for the treatment of functional constipation, but there is limited evidence to support a recommendation for electroacupuncture for the treatment of constipation in patients with cancer. Based on the very low quality and limitations of the evidence, the ONS Guidelines panel made no recommendation for electroacupuncture and identified this intervention as an evidence gap that warrants further research.

Discussion

Other Guidelines for Constipation

There are several other national and international guidelines on constipation for patients with cancer and in a general population. Overall, there is a consensus that lifestyle education (e.g., diet, fiber, fluids) and/or laxatives should be considered as first-line therapy for patients with general constipation (Davies et al., 2019; Larkin et al., 2018; National Comprehensive Cancer Network [NCCN], 2019), which is consistent with the ONS Guidelines recommendations. In patients with general constipation and cancer, other pharmaceuticals, such as linaclotide, lubiprostone, or prucalopride, are recommended only in patients who are refractory to laxatives (Davies et al., 2019; Paquette et al., 2016). The American Academy of Pain Management have developed guidelines for the management of OIC that include an algorithm for patients who are starting new opioid therapy and those who are presenting with OIC. They note that first-choice laxatives are biscodyl, sodium picosulfate, senna, and macrogol (Müller-Lissner et al., 2017). For patients with OIC with or without cancer, PAMORAs are recommended when laxatives have not been effective (Crockett et al., 2018; Davies et al., 2019; Larkin et al., 2018; NCCN, 2019), which is consistent with the ONS Guidelines recommendations. In general, a stepwise approach is recommended, starting with a simple approach of lifestyle education, then moving to laxatives and on

to pharmacologic interventions only if lifestyle education and laxatives are not effective.

The ONS Guidelines panel included a question on acupuncture or electroacupuncture for the management of constipation because the panel considered nonpharmacologic interventions important for patient decision making. There are a lack of evidence-based recommendations on nonpharmacologic interventions for constipation. The ONS Guidelines panel reviewed emerging evidence on acupuncture and electroacupuncture and made a recommendation for both in the context of a clinical trial. Additional research on nonpharmacologic interventions for constipation is warranted (see Figure 1).

Clinical Implications and Conclusion

The ONS Guidelines on constipation builds on the existing body of literature that evaluates interventions for treatment. Despite the prevalence of non–opioid-related constipation and OIC and the available clinical practice guidelines, there remains a need for management strategies for patients with constipation. Continuing education and practice improvement focused on management for patients at risk for and experiencing constipation is needed.

There is a growing literature base from well-conducted quality improvement studies that have addressed practice changes to improve care for patients with cancer who have OIC. In one project, a patient education tool for OIC was developed by an interprofessional team after they identified that 47% of their patients had unmanaged constipation (Amankweh et al., 2015). Following the development and implementation of this tool, uncontrolled constipation rates fell to 13%. A fellow-led quality improvement project at a U.S. Department of Veterans Affairs hospital included changes to the electronic health record that led to an increase in assessment of OIC from 52% to 92% and later resulted in 90% of patients reporting adequate management of constipation (Kaur et al., 2016). The success of these local quality improvement projects is an indication of the power that similar projects at the local level can have on patient outcomes. The ONS Guidelines provide evidence-based recommendations to manage constipation in patients with cancer, and now is the time to move this evidence into practice.

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Development of this guideline was wholly funded by the Oncology Nursing Society (ONS), a nonprofit nursing specialty organization that represents oncology nurses. ONS staff supported panel appointment and coordinated meetings but had no role in guideline question identification or voting on recommendations. Members of the ONS Guidelines panel received travel reimbursement to attend one in-person meeting at ONS headquarters in Pittsburgh, PA. No honoraria were provided.

Ginex, Hanson, Thorpe, and Morgan contributed to the conceptualization and design. Ginex, LeFebvre, Thorpe, Moriarty, Maloney, Vrabel, and Morgan completed the data collection. Ginex and Morgan provided statistical support. Rogers, Ginex, Anbari, Hanson, LeFebvre, Lopez, Thorpe, Moriarty, and Morgan provided analysis. Rogers, Ginex, Anbari, Hanson, LeFebvre, Vrabel, and Morgan contributed to the manuscript preparation.

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