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Traditional laxatives in preventing opioid-induced constipation in adult cancer patients: a systematic review and meta-analysis protocol

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Complete List of Authors:	LONG, Yanfang; Central South University Xiangya School of Nursing; Central South University, Xiangya Research Center of Evidence-based Healthcare Li, Li; Xiangya Hospital Central South University, Teaching and Research Section of Clinical Nursing; Central South University Xiangya School of Nursing Xi, CHEN; The Hong Kong Polytechnic University School of Nursing TIAN, Lingyun; The First Affiliated Hospital of USTC, Department of Nursing He, Haiyan; Central South University Xiangya School of Nursing Li, Ying-lan; Xiangya Hospital Central South University, Nursing Department
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ABSTRACT

Introduction Opioid-induced constipation(OIC) bothers up to 90% cancer patients receiving long-term opioid-related analgesic therapy, resulting in various potential complications, compromised pain management and decreased quality of life. Laxatives are agents that stimulate or facilitate the evacuation of the bowels. Among them, traditional laxatives such as polyethylene glycol and lactose are widely used due to low cost, easy accessibility and tolerability. OIC prophylaxis with laxatives has been recommended for patients initiating opioid therapy. However, systematic reviews to support this practice are lacking. Thus, we aim to conduct a systematic review to evaluate the effects and safety of traditional laxatives in preventing OIC in adult cancer patients.

Methods and analysis The Preferred reporting items for systematic review and meta-analysis protocols 2015 statement will be employed to guide the preparation of this protocol. Database search will be performed in PubMed, Embase, Web of Science, the Cochrane Library, JBI, and EBSCO from inception to 1 December 2023. Reference lists will also be accessed for additional studies, OpenGrey and Google Scholar for the inclusion of gray literature. Combination of Mesh/Emtree and free-text terms will be used when searching core concepts of 'OIC', 'laxative' and 'cancer'. Eligibility criteria will be defined by types of population (cancer patients on opioid therapy), types of intervention (traditional laxatives) and types of studies (RCTs and quasi-experimental trials). Two reviewers will select the eligible studies, extract the data, and assess the methodological risk of bias independently, a third reviewer will be invited to reach an agreement if necessary. Subgroup analysis and sensitivity analysis will be conducted to explore the source of heterogeneity.

Ethics and dissemination Ethical approval is not required for patients won't be included in systematic reviews and meta-analyses. We will publish the study in a peer-review journal and/or communicate with scholars in open conferences.

PROSPERO registration number CRD42024507127.

Strengths and limitations of this study

► The proposed systematic review and meta-analysis is supposed to address the unrecognized and poorly managed opioid-induced constipation from a prophylactic perspective.

► Effects, adverse events and preferences of the traditional laxatives administered in adult cancer patients on an opioid therapy have been fully considered as outcomes.

► A comprehensive search strategy will be developed following Joanna Briggs Institute (JBI) guidance, articles will be widely accessed from databases, reference lists, leaders of OIC management, and laxative manufactures.

► Different types and doses of traditional laxatives might be the main source of clinical heterogeneity. Thus, sensitivity and subgroup analyses will be conducted.

INTRODUCTION

Cancer has become a major threat to public health. In cancer patients, pain is reported to be one of the most annoying and burdensome symptoms. With the implementation of new pain management guidelines, drugs and treatment strategies, a decline has been detected in the prevalence and severity of pain. A latest systematic review and meta-analysis showed that, compared to previous study, the overall prevalence of cancer-related pain was 44.5%, and 30.6% of the cancer patients experienced moderate to severe pain(Snijders et al., 2023).

According to the WHO analgesic ladder and other published guidelines, opioids are the mainstay therapy in treating moderate-to-severe pain. Accompanied with pain relief, patients on chronic opioid use may also suffer from various side effects such as sedation, respiratory depression and opioid-induced bowel dysfunction (OIBD), of which opioid-induced constipation (OIC) are the most common(Ketwaroo et al., 2013), affecting up to 80% of patients receiving opioids(Crockett et al., 2019). By

binding to the μ-opioid receptors in the gastrointestinal tract, opioids increase circular muscle contraction, reduce coordinated peristalsis and secretion of fluids and electrolytes, leading to prolonged transit time and dry, hard stools(Farmer et al., 2019). OIC is defined in Rome IV as new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy, must include two or more of the symptoms, including straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers with the same frequency cutoff (25%), and less than 3 spontaneous bowel movements for each week(Simren et al., 2017).

OIC brings patients receiving opioid therapy a series of negative impacts. Except for serious complications like bowel perforation, anal fissures, and rectal bleeding, OIC also causes impaired quality of life, compromised pain management and increased healthcare and economic burden. The quality of life scores in patients with OIC were reported to be significantly lower(T. Bell et al., 2018). In order to alleviate OIC, a third of patients decreased opioid use, however, almost all of them reported worsening pain as a result(T. J. Bell et al., 2009). In the first year of opioid therapy, OIC patients were more likely to have an all-cause hospitalization (odds ratio=2.47), or pain-related hospitalization (2.15), and the mean unadjusted overall healthcare costs post-index were $21,629 higher than those without constipation(Fine et al., 2019).

Laxatives, in the broadest sense, include all the agents that induce laxation. Among them, traditional laxatives such as osmotic and stimulant ones are most commonly used for constipation management in clinical settings, due to low cost, easy accessibility and tolerability. They act in different ways to counter the bowel responses to μ-opioid receptors activation, either drawing water to intestine and softening stools, or irritating sensory nerve endings to stimulate bowel movements(Crockett et al., 2019). Laxatives has been recommended as first-line OIC treatment by international guidelines(Crockett et al., 2019; Farmer et al., 2019; Okdahl et al., 2023). However, the recommendation was based on limited evidence and systematic reviews (SR) in patients with chronic idiopathic constipation, which is

different from OIC(Crockett et al., 2019). Therefore, the results must be treated with caution when extrapolating them to OIC patients. SR of this population is in urgent need to support this practice.

An updated Cochrane review published in 2015, aiming to determine the effectiveness and differential efficacy of the administration of laxatives among palliative patients with constipation, found no differences in effectiveness between different laxatives(Candy et al., 2015). In such a palliative care setting, constipation would become a more complicated and tough problem as the combined result of the medicines taken for pain control, disease, dietary and mobility factors. Another latest net meta-analysis summarized the effectiveness of the pharmacologic therapies in cancer and advanced Illness patients with OIC, assuring the significant benefit in Methylnatrexone and Naldemedine use(Jesuyajolu et al., 2023). Given the available information, previous SRs mainly focused on the treatment but not the prevention of OIC, they cared more about patients diagnosed with OIC but not those at great risk of developing the symptom. However, a consensus has been reached that once OIC occurs, it is much harder to reverse the process, thus, prevention is the best treatment(Saha et al., 2020). For patients commencing opioid therapy, laxatives are suggested to be co-prescribed for the consideration of OIC prophylaxis(Saha et al., 2020).

To the best of our knowledge, there is a paucity of OIC prophylaxis SR in adult cancer patients using traditional laxatives(Farmer et al., 2018). Since more and more attention has been drawn to evaluate the effects and safety of prophylactic use of traditional laxatives(Ahmad & Alnaeem, 2022; Kistemaker et al., 2023; Ozaki et al., 2022; Tarumi et al., 2013; Wirz et al., 2012), it is now right time to summarize the current evidence on the use of inexpensive, accessible and tolerant traditional laxatives for the prevention of OIC in cancer patients initiating, changing, or increasing opioid therapy.

OBJECTIVES

The systematic review seeks to evaluate the efficacy and safety of traditional laxatives in preventing OIC in adult cancer patients initiating, changing, or increasing opioid therapy, and describe the characteristics of OIC prophylaxis based on traditional laxatives.

METHODS AND ANALYSIS

Study design registration

This systematic review and meta-analysis protocol will be reported in accordance with the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. This protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under the registration ID of CRD42024507127.

Eligibility criteria for study selection

Types of participants

Cancer patients, aged≥18 years old, given traditional laxative(s) for prophylactic purpose when initiating, changing, or increasing opioid therapy will be included, irrespective of the priority of cancer care (curative care, palliative care), and the care setting (outpatient, inpatient, integrated care facilities, home care).

Types of studies

We will include randomized controlled trials (RCT) and quasi-experimental studies without any language restrictions. Data of ongoing studies will be followed up with the authors. Duplicate publications reporting the same parameters will be excluded.

Types of interventions

All traditional laxatives are considered to meet the inclusion criteria, regardless of the type of agents (osmotic, stimulant, lubricant), form of administration (pills, tablets, capsules, patch, suppository) and doses taken.

Types of controls

They could be placebo control, usual care control, controls between laxatives or combinations.

Outcome measure

The eligible studies should report the primary outcomes including defecation frequency, stool consistency assessed with validated instruments such as Bristol Stool Form Scale (BSFS)(Saha et al., 2020), straining and sensation of incomplete evacuation measured with validated tools such as the clinician-administered Bowel Function Index (BFI) questionnaire(Saha et al., 2020), and frequency of rescue therapies like enema and manual maneuvers to facilitate bowel movements. Secondary outcomes are expected to involve laxative-related adverse events (nausea/vomiting, abdominal pain, flatus, diarrhea and fecal incontinence)(Candy et al., 2015), cost and patients' preferences to laxatives.

Search strategy

The literature search process will be guided by the Joanna Briggs Institute (JBI) approach(Aromataris & Riitano, 2014). Minor adjustments might be necessary in finalizing the search strategy.

Electronic data

Starting from the PubMed database, subject terms and synonyms of core concepts "opioid", "constipation", "prevention", "laxatives" and "cancer" will be analyzed during the preliminary search. Followed by Embase, Web of Science, the Cochrane Central Register of Controlled Trials, JBI, and EBSCO, a comprehensive retrieval strategy will be formulated for eligible articles published from database inception to 1 December 2023. Medical subject heading (MeSH) terms and free text terms will be used together. Table 1 shows the detailed search strategy in PubMed.

Search for other resources

There are several other ways to broaden our literature review. Reference lists of included literature will be inspected for additional relevant studies. Open database

such as OpenGrey and Google Scholar will be accessed as well for the inclusion of gray literature. Leaders of the OIC management clinicians and researchers will be contacted to try to identify other studies. Moreover, as funding sponsors of traditional laxatives, the manufacturers of agents can be contacted for potential data when necessary.

Study selection

Two PhD nursing students will conduct the study selection independently. EndNote will be used for deduplication of retrieved studies. In order to reach a high level of consistency within the review team, pilot test will be introduced at the beginning of the selection process. We will refine and clarify the eligibility criteria mentioned above first, then importance order of the criteria will be ranked as “constipation”, “opioid”, “traditional laxatives”, and “age ⩾18 years”. Based on that, we will screen the titles and abstracts to get more focused on the study. Full-texts of included articles will be downloaded for further assessment. Once there is any disagreement between the authors, we will discuss by ourselves first to reach an agreement, if not, a third researcher will be invited to make a decision.

Data extraction

The data will be extracted and recorded independently by the two students as well. An Excel spreadsheet will be created and piloted to collect information on key features and results of included studies. The items will include the first author, the year of publication, region, study design, participants (number, age, sex, drop-outs/withdrawals), laxative(s) (type, dose(s), route of delivery, control used), outcome data (laxation response and assessment method, tolerance and adverse effects, cost and participants’ preferences), significant findings and duration of follow-up.

Dealing with missing data

A variety of potential sources of missing data, such as unpublished studies, unanalyzed or unreported outcomes, might bring bias to a systematic

review(Mavridis & White, 2020). Therefore, data from unpublished articles are supposed to be obtained as much as possible. For full texts or any data of interested studies that are not available, the original investigators will be contacted to add the missing data by email. In addition, we will elucidate the potential impact of missing data on the final findings of the review in the discussion section.

Risk-of-bias appraisal

The Cochrane Handbook for Systematic Reviews of Interventions version 6.4[22] will be used as a guidance to appraise risk-of-bias of included studies methodologically. Six main sources of systematic bias will be assessed in this SR, including random sequence generation, concealment of allocation, blinding of participants, personnel, blinding of outcome assessment, level of completeness of outcome data and selective reporting. Two PhD students will conduct the assessment independently. For each domain, 'low risk' will be assigned for meeting the defined criteria, 'high' for not and 'unclear' for insufficient information. A third review author will be consulted in case of persisting disagreements.

Data synthesis and statistical analysis

Data synthesis

RevMan software will be used for data synthesis. For the primary outcome, frequency of defecation or scale scores, the standardized mean difference (SMD) and corresponding 95% confidence interval (CI) will be calculated for continuous variables. While for the dichotomous variables, the risk ratio (RR) and corresponding 95% CI will be analyzed. P value of <0.05 will be regarded statistically significant. Forest plots will be used for analysis.

Assessment of heterogeneity

Heterogeneity among trials will be examined by visual inspection of forest plots and by the Chi square test calculation for heterogeneity (a P value of 0.10 was considered as statistically significant). I^2 statistic will be used to measure heterogeneity as well. The results will be interpreted in accordance with the ranges given by the Cochrane

Handbook for Systematic Reviews of Interventions version 6.4. When I^2 ranges from 0% to 40%, heterogeneity will not be significant. When it ranges from 30% to 60%, moderate heterogeneity might be possible. If it ranges from 50% to 90%, it may represent substantial heterogeneity and if I^2 equals 75%–100%, it will indicate considerable heterogeneity.

Statistical analysis

When conducting statistical analysis, a meta-analysis will be carried out using a fixed-effect model when parameters that are highly homogenous (I^2<50%). When I^2≥50%, a random effects model (DerSimonian and Laird method) will be appropriate for analysis, and subgroup analyses and sensitivity analyses will be performed to investigate the potential sources of heterogeneity. If the heterogeneity is considerable high (I^2>75%), a narrative description is indicated.

Subgroup analysis

If evident heterogeneity is detected in this meta-analysis (I^2>50%), we would undertake subgroup analyses to investigate the possible sources. Different types, doses, routes of administration of both opioids and traditional laxatives might introduce clinical heterogeneity.

Sensitivity analysis

If there are sufficient studies available, sensitivity analyses will be performed to locate the source of heterogeneity. We will try to exclude the studies appraised at high risk of bias, or unpublished trials, and then compare the new results with those old ones.

Publication bias

In avoiding publication bias, unpublished studies are expected to be involved into the analysis as much as possible during the literature search. Egger's regression test or funnel plots will be employed to identify publication bias. If the distribution of the plots is symmetric, no publication bias is indicated.

Patient and public involvement

This is a secondary analysis of available primary data, no patient will be involved during the process.

Discussion

Nurses have been playing a key role in the prevention and management of symptoms such as constipation and are eager to seek theoretical and clinical data support based on high quality evidences. OIC has bothered a large number of cancer patients on opioid therapy, posing great challenges to clinical nursing staff. Treatment would be much harder to handle than prevention, especially in OIC patients. All patients initiating opioid therapy ought to be assessed carefully and educated about the risk of OIC, lifestyle modifications (hydration, physical activity, and scheduled toileting), and the use of laxatives(Saha et al., 2020). However, previous studies have mainly focused on the treatment than the prevention of OIC. Thus, OIC prophylaxis calls for great attention from both patients' and healthcare providers' perspectives. The systematic review seeks to summarize the current evidence on the use of affordable, easy-to-get and tolerant traditional laxatives for the prevention of OIC in patients on opioid therapy. With the findings from the SR, it might be possible for clinical nurses to implement the evidence into nursing practices, decreasing cancer patients' suffering from side effects of opioids, and further improving the quality of life. Moreover, it might provide references for non-cancer population with the same concerns and worries.

Ethics and dissemination

Ethical approval is not required for patients won't be included in systematic reviews and meta-analyses. We will publish the study in a peer-review journal and/or communicate with scholars in open conferences.

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Competing interests None declared.

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Table 1 Search strategy in PubMed

Code	Search Strategy	Hits
#1	"Constipation"[Mesh] OR "Opioid-Induced Constipation"[Mesh] OR “Constipation, Opioid-Induced” OR “Opioid Induced Constipation” OR “Opioid-Induced Constipation?” OR “Opiate-Induced Constipation?” OR “Constipation, Opiate-Induced” OR “Opiate Induced Constipation” OR “Narcotic Bowel Syndrome” OR “Bowel Syndrome, Narcotic” OR “Narcotic Bowel Syndromes” OR “Opioid-Induced Bowel Dysfunction?” OR “Bowel Dysfunction, Opioid-Induced” OR “Dysfunction, Opioid-Induced Bowel” OR “Opioid Induced Bowel Dysfunction”	16,886
#2	"Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid" [Pharmacological Action] OR “Opioid Analgesic?” OR ”Analgesic, Opioid” OR “Opioid?” OR “Partial Opioid Agonists” OR “Agonists, Partial Opioid” OR “Opioid Agonists, Partial” OR “Opioid Partial Agonists” OR “Agonists, Opioid Partial” OR “Partial Agonists, Opioid” OR “Full Opioid Agonists” OR “Agonists, Full Opioid” OR “Opioid Agonists, Full” OR “Opioid Full Agonists” OR “Agonists, Opioid Full” OR “Full Agonists, Opioid” OR “Opioid Mixed Agonist-Antagonists” OR “Agonist-Antagonists, Opioid Mixed” OR “Mixed Agonist-Antagonists, Opioid” OR “Opioid Mixed Agonist Antagonists”	195,085
#3	"prevention and control" [Subheading] OR "Pre-Exposure Prophylaxis"[Mesh] OR "Post-Exposure Prophylaxis"[Mesh] OR “prevent*” OR “prophyla*”	3,285,398
#4	("Laxatives"[Mesh] OR "Laxatives" [Pharmacological Action]) OR "Lactulose"[Mesh] OR "Polyethylene Glycols"[Mesh] OR "Senna Extract"[Mesh] OR "Sennosides"[Mesh] OR "Bisacodyl"[Mesh] OR "picosulfate sodium" [Supplementary Concept] OR "Magnesium Hydroxide"[Mesh] OR "Magnesium Oxide"[Mesh] OR "Magnesium Sulfate"[Mesh] OR “Laxative?”	99,402
#5	"Neoplasms"[Mesh] OR “Tumor*” OR “Neoplas*” OR “Cancer?” OR “Malignant Neoplasm?” OR “Malignanc*” OR “Neoplasm?, Malignant”	5,598,758
#6	#1 AND #2 AND #3 AND #4 AND #5	42

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Complete List of Authors:	LONG, Yanfang; Central South University Xiangya School of Nursing; Central South University, Xiangya Research Center of Evidence-based Healthcare Li, Li; Xiangya Hospital Central South University, Teaching and Research Section of Clinical Nursing; Central South University Xiangya School of Nursing Xi, CHEN; The Hong Kong Polytechnic University School of Nursing, TIAN, Lingyun; The First Affiliated Hospital of USTC, Department of Nursing He, Haiyan; Central South University Xiangya School of Nursing Li, Ying-lan; Xiangya Hospital Central South University, Nursing Department
Primary Subject Heading:	Nursing
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology
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ABSTRACT

Introduction Opioid-induced constipation (OIC) affects up to 90% of patients with cancer receiving long-term opioid-related analgesic therapy, resulting in various potential complications, compromised pain management, and decreased quality of life. Laxatives stimulate or facilitate bowel evacuation. Traditional laxatives, such as polyethylene glycol and lactulose, are widely used because of their low cost, easy accessibility, and tolerability. OIC prophylaxis with laxatives is recommended for patients receiving opioid therapy. However, systematic reviews that support this practice are lacking. They have primarily focused on patients with existing constipation and the effectiveness of other pharmacological therapies. Thus, we are conducting a systematic review to evaluate the efficacy and safety of traditional laxatives in preventing OIC in adult patients with cancer.

Methods and analysis The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 statement was used to guide the reporting of this protocol. Database searches will be performed in PubMed, Embase, Web of Science, Cochrane Library, and EBSCO from inception to a date within six months of the submission of the full systematic review (estimated December 31, 2024). Reference lists will also be accessed for additional studies, including Google Scholar, for the inclusion of gray literature. A combination of Medical Subject Headings/Emtree and free-text terms will be used when searching the core concepts of 'OIC,' 'laxative,' and 'cancer.' The eligibility criteria will be defined by the type of population (patients with cancer receiving opioid therapy), type of intervention (traditional laxatives), and type of study (randomized controlled trials and quasi-experimental trials). Two reviewers will independently select eligible studies, extract data, and assess the methodological risk of bias. A third reviewer will be invited to reach a consensus if necessary. Subgroup and sensitivity analyses will be conducted to explore sources of heterogeneity.

Ethics and dissemination Ethical approval is not required, as patients will not be

included in systematic reviews and meta-analyses. We will publish this study in a peer-reviewed journal and communicate the results at open conferences.

PROSPERO registration number CRD42024507127.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The literature search process is guided by the Joanna Briggs Institute approach.
- Cochrane tools will be used to assess the quality of the included studies.
- Sensitivity and subgroup analyses will be conducted to investigate potential sources of heterogeneity.
- Only studies published in English databases will be included.

INTRODUCTION

Cancer is a major threat to public health. In patients with cancer, pain is reported to be one of the most distressing and burdensome symptoms. With the implementation of new pain management guidelines, drugs, and treatment strategies, there has been a decline in the prevalence and severity of pain. A recent systematic review (SR) and meta-analysis showed that, compared with observations in previous studies, the overall prevalence of cancer-related pain was 44.5%, and 30.6% of the patients with cancer experienced moderate to severe pain [1].

According to the World Health Organization analgesic ladder and other published guidelines, opioids agonists, such as morphine and oxycodone, are the mainstay therapies for treating moderate-to-severe pain. Along with pain relief, patients on chronic opioid use may also experience various side effects, such as sedation, respiratory depression, and opioid-induced bowel dysfunction, with opioid-induced constipation (OIC) being the most common [2], affecting up to 90% of patients receiving opioid therapy for cancer-related pain [3]. By binding to μ-opioid receptors in the gastrointestinal tract, opioids increase circular muscle contraction, reduce coordinated peristalsis, and decrease fluid and electrolytes secretion, leading to prolonged transit time and dry, hard stools [4]. OIC is defined by the Rome IV criteria as new or worsening

symptoms of constipation when initiating, changing, or increasing opioid therapy, and it must include two or more of the following symptoms: straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, manual maneuvers with the same frequency cutoff (25%), and fewer than three spontaneous bowel movements per week [5].

OIC has a series of negative effects on patients receiving opioid therapy. In addition to serious complications, such as fecal impaction, bowel perforation, anal fissures, and rectal bleeding, OIC also causes impaired quality of life, compromised pain management, and increased healthcare and economic burdens. The quality-of-life scores of patients with OIC have been reported to be significantly lower [6]. To alleviate OIC, one-third of patients reduce opioid use; however, almost all of them report worsening pain [7]. In the first year of opioid therapy, patients with OIC are more likely to experience all-cause hospitalization (odds ratio = 2.47), or pain-related hospitalization (odds ratio = 2.15), and the mean unadjusted overall healthcare costs post-index were $21,629 higher than for those without constipation [8].

In the broadest sense, laxatives include all agents that induce defecation. Among them, traditional laxatives, distinct from recently developed agents [9], such as osmotic and stimulant agents, are most commonly used for constipation management in clinical settings because of their low cost, easy accessibility, and tolerability. They act in different ways to counter the bowel responses to μ-opioid receptor activation, either by drawing water into the intestine and softening stools or by irritating sensory nerve endings to stimulate bowel movements [9]. Laxatives have been recommended as first-line OIC treatment according to international guidelines [10,11]. However, this recommendation is based on limited evidence and SRs involving patients with chronic idiopathic constipation, which differs from OIC in terms of pathophysiological mechanisms [5,9,12-14]. Therefore, these results must be interpreted with caution when extrapolating to patients with OIC. A SR of this population is urgently needed to support this practice.

An updated Cochrane review, published in 2015, aimed to determine the effectiveness and differential efficacy of laxative administration among palliative care patients with

constipation and found no differences in effectiveness between different laxatives [15]. In such a palliative care setting, constipation becomes a more complex and challenging problem, occurring as a combined result of the medications used for pain control, disease, diet, and mobility factors. Another recent network meta-analysis summarized the effectiveness of the pharmacological therapies in patients with cancer and advanced illness, confirming the significant benefits of methylnatrexone and naldemedine use [16]. Given the available information, previous SRs mainly focused on the treatment, not the prevention, of OIC; they addressed patients diagnosed with OIC but not those at great risk of developing symptoms. However, a consensus has been reached that once OIC occurs, it is much harder to reverse the process; thus, prevention is the best approach [16]. In patients receiving opioid therapy, laxatives are recommended to be co-prescribed as OIC prophylaxis [17].

To the best of our knowledge, there is a paucity of SRs on OIC prophylaxis in adult patients with cancer using traditional laxatives [18]. Since more attention has been drawn to evaluating the efficacy and safety of traditional laxatives for prophylactic use [19-23], it is now the right time to summarize the current evidence on the use of inexpensive, accessible, and well-tolerated traditional laxatives to address the often unrecognized and poorly managed OIC from a preventive perspective. Therefore, this SR aims to evaluate the efficacy and safety of traditional laxatives in preventing OIC in adult patients with cancer initiating, changing, or increasing opioid therapy and to describe the characteristics of OIC prophylaxis based on traditional laxatives.

METHODS AND ANALYSIS

Study design and registration

This SR and meta-analysis protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement [24]. This protocol has been registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under registration ID CRD42024507127.

Eligibility criteria for study selection

Types of participants

Patients with cancer, aged ≥18 years, given traditional laxative(s) for prophylactic purposes when initiating, changing, or increasing opioid therapy will be included, irrespective of the stage and type of cancer, the priority of cancer care (curative or palliative care), and the care setting (outpatient, inpatient, integrated care facilities, or home care).

Types of studies

Randomized controlled trials and quasi-experimental studies written in English will be included. Data from ongoing studies will be followed by the authors. Duplicate publications reporting the same parameters will be excluded.

Types of interventions

All traditional laxatives will be considered, regardless of the type of agent (osmotic, stimulant, bulk-forming, or lubricant), form of administration (pills, tablets, capsules, patches, or suppositories), and doses administered.

Types of controls

These may include placebo controls, usual care controls, or controls comparing different laxatives or their combinations.

Outcome measures

Eligible studies should report the primary outcomes, including defecation frequency and stool consistency, assessed with validated instruments, such as the Bristol Stool Form Scale [17], straining, and the sensation of incomplete evacuation, measured with validated tools, such as the clinician-administered Bowel Function Index questionnaire [17], and the frequency of rescue therapies, including enemas and manual maneuvers to facilitate bowel movements. Secondary outcomes are expected to include laxative-related adverse events (nausea/vomiting, abdominal pain, flatulence, diarrhea, and fecal incontinence) [15], costs, and patient preference for laxatives.

Search strategy

The literature search will be guided by the Joanna Briggs Institute approach [25]. Minor adjustments may be necessary to finalize the search strategy.

Electronic data

Starting with the PubMed database, subject terms and synonyms of the core concepts "opioid," "constipation," "prevention," "laxatives," and "cancer" will be analyzed during the preliminary search. Following this, searches will be conducted in Embase, Web of Science, Cochrane Library, and EBSCO. A comprehensive retrieval strategy will be formulated for eligible articles published from database inception to a date within six months of the submission of the full SR (estimated December 31, 2024). Medical Subject Headings and free-text terms will be used together. Supplementary Material S1 shows the detailed search strategy for the databases.

Search for other resources

There are several other methods to broaden the literature search. The reference lists of included studies will be inspected for additional relevant studies. Google Scholar will also be accessed to include gray literature in the first ten pages. Leaders in OIC management, clinicians, and researchers will be contacted to identify other studies. Moreover, as sponsors of traditional laxatives, the manufacturers of the agents can be contacted for potential data when necessary.

Study selection

Two PhD nursing students will independently select the studies. EndNote will be used to deduplicate the retrieved studies. A pilot test will be conducted at the beginning of the selection process to ensure a high level of consistency within the review team . We will refine and clarify the eligibility criteria mentioned previously and then rank the importance of the criteria as "constipation," "opioid," "traditional laxatives," and "age ≥18 years." Based on this, we will screen titles and abstracts to focus more closely on this study. Full texts of the included articles will be downloaded for further assessment. If there is any disagreement between the authors, we will first discuss it ourselves to reach an agreement; if not, a third researcher will be invited to make a decision.

Data extraction

The data will be extracted and recorded independently by two students. An Excel spreadsheet will be created and piloted to collect information on the key features and results of the included studies. The items will include the first author, year of publication, region, study design, participants (number, age, sex, and dropouts/withdrawals), laxative(s) (type, dose(s), route of delivery, and control used), outcome data (laxation response and assessment method, tolerance and adverse effects, cost, and participants' preferences), findings, and duration of follow-up.

Dealing with missing data

Various potential sources of missing data, such as unpublished studies and unanalyzed or unreported outcomes, may introduce bias into an SR [26]. Therefore, as much data as possible will be obtained from unpublished articles. For full texts or any data from relevant studies that are not available, the original investigators will be contacted at least once via email to request missing data, in order to minimize potential bias. Sensitivity analyses will be performed to assess how sensitive the results are to reasonable changes in the assumptions made. In addition, we will elucidate the potential impact of missing data on the final findings of the review in the Discussion section.

Risk-of-bias appraisal

The Cochrane Collaboration Tools [27], ROB-2.0 (The Cochrane Risk of Bias Tool, version 2 for randomized trials, updated in 2011) and ROBSIN-I (Risk Of Bias in Non-randomized Studies - of Interventions, 2017 version) for randomized controlled trials and non-randomized studies, respectively, will be used to methodologically appraise the risk of bias in the included studies. The main sources of systematic bias will be assessed in this SR, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, and selective reporting. Two PhD students will independently conduct the assessments. For each domain, 'low risk' will be assigned if the defined criteria are met, 'high risk' if they are not, and 'unclear' for insufficient information. A third review

author will be consulted in cases of persistent disagreement.

Data synthesis and statistical analysis

Data synthesis

RevMan software will be used for data synthesis. For the primary outcome, the frequency of defecation or scale scores, standardized mean difference (SMD), and corresponding 95% confidence interval will be calculated for continuous variables. An SMD of zero means that there is no difference between the groups, and a negative SMD means that the experimental group had a lower mean score than that of the control group, and vice versa. SMD values of 0.2 to 0.5 are considered a small effect, values of 0.5 to 0.8 a moderate effect, and values > 0.8 a large effect. Because SMD is not intuitive to interpret, the findings may be translated into units of one or more specific measurement instruments [27]. For dichotomous variables, the risk ratio and corresponding 95% confidence interval will be analyzed. Statistical significance will be set at $P < 0.05$. Forest plots will be used for the analysis.

Assessment of heterogeneity

Heterogeneity among trials will be examined by visual inspection of forest plots and by the Chi-square test for heterogeneity (a P-value of 0.10 will be considered statistically significant). The I^2 statistic will be used to measure heterogeneity. The results will be interpreted in accordance with the ranges provided in the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4. When I^2 ranges from 0% to 40%, heterogeneity is not considered significant. Moderate heterogeneity may be possible when the I^2 ranges from 30% to 60%. If it ranges from 50% to 90%, it may represent substantial heterogeneity, and if I^2 is 75%–100%, considerable heterogeneity will be indicated.

Statistical analysis

For the statistical analysis, a meta-analysis will be performed using a fixed-effect model when the parameters are highly homogeneous ($I^2<50\%$). When $I^2\geq50\%$, a random-effects model (DerSimonian and Laird method) will be appropriate for analysis, and

subgroup and sensitivity analyses will be conducted to investigate potential sources of heterogeneity. If the heterogeneity is considerably high (I^2>75%), a narrative description will be provided.

Subgroup analysis

If heterogeneity is detected in this meta-analysis (I^2>50%), subgroup analyses will be performed to investigate possible sources. The different types, doses, and routes of administration of opioids and traditional laxatives may introduce clinical heterogeneity.

Sensitivity analysis

If a sufficient number of studies is available, sensitivity analyses will be performed to locate the source of heterogeneity. We will try to exclude studies assessed as having a high risk of bias or unpublished trials and then compare the new results with the original ones.

Publication bias

To avoid publication bias, unpublished studies will be included in the analysis as much as possible during the literature search. Egger's regression test or funnel plots will be used to identify publication bias. Publication bias will not be indicated if the distribution of the plots is symmetrical.

Grading the quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation working group methodology will be used to assess the strength of evidence for the outcomes, based on aspects, such as risk of bias, indirectness, inconsistency, imprecision, and publication bias [28]. The quality of the evidence will be judged as high, moderate, low, or very low, according to the confidence in the estimate of the effect.

Patient and public involvement

This is a secondary analysis of the available primary data, and no patients were involved in the process.

DISCUSSION

Nurses play a key role in the prevention and management of symptoms, such as constipation, and are eager to seek theoretical and clinical data based on high-quality evidence. OIC has affected a large number of patients with cancer on opioid therapy, posing great challenges to clinical nursing staff. Treatment is much harder than prevention, especially for patients with OIC. All patients initiating opioid therapy should be carefully assessed and educated about the risk of OIC, lifestyle modifications (hydration, physical activity, and scheduled toileting), and laxative use [17]. However, studies have mainly focused on the treatment rather than the prevention of OIC. Thus, OIC prophylaxis requires great attention from both patients and healthcare providers. This SR aims to summarize the current evidence on the use of affordable, easy-to-obtain, and well-tolerated traditional laxatives for the prevention of OIC in patients receiving opioid therapy. With the findings from this SR, it might be possible for clinical nurses to implement evidence-based practices, decrease patients' suffering from the side effects of opioids, and further improve their quality of life. Moreover, it may provide a reference for non-cancer populations with similar concerns.

Ethics and dissemination

Ethical approval is not required for patients who are not included in systematic reviews and meta-analyses. We will publish this study in a peer-reviewed journal and communicate with scholars at open conferences.

Contributors L-YF is the first author and registered the protocol in the PROSPERO database. L-YF obtained funding, critically revised the protocol and contributed to the drafting of the final manuscript. L-YF and H-HY have been collecting and analyzing the data. CX, T-LY and L-YL revised and reviewed this article. All authors have read and approved the final manuscript. LL is the guarantor of the study.

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Competing interests None declared.

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Appendix 1 Search strategies for databases

Pubmed

#1 "Opioid-Induced Constipation"[Mesh] OR "narcotic bowel syndrome*"[Title/Abstract] OR "opiate induced constipation*"[Title/Abstract] OR "opioid induced bowel dysfunction*"[Title/Abstract] OR "opioid induced constipation*"[Title/Abstract]

#2 (("Laxatives"[Mesh] OR "Cathartics"[Mesh]) OR "bowel evacuant*"[Title/Abstract] OR "bowel preparation solution*"[Title/Abstract] OR "bulk forming laxative*"[Title/Abstract] OR "bulk laxative*"[Title/Abstract] OR "cathartic agent"[Title/Abstract] OR "cathartic*"[Title/Abstract] OR "laxantia"[Title/Abstract] OR "laxati*"[Title/Abstract] OR "laxative agent"[Title/Abstract] OR "purgative*"[Title/Abstract] OR "stimulant laxative"[Title/Abstract])) OR "Lactulose"[Mesh] OR "Polyethylene Glycols"[Mesh] OR "Senna Extract"[Mesh] OR "Sennosides"[Mesh] OR "Bisacodyl"[Mesh] OR "Magnesium Hydroxide"[Mesh] OR "Magnesium Oxide"[Mesh] OR "Magnesium Sulfate"[Mesh] OR "Mineral oil"[Mesh] OR "Glycerol"[Mesh] OR "Dioctyl Sulfosuccinic Acid"[Mesh] OR "Phenolphthalein"[Mesh] OR "Rheum"[Mesh] OR "Sorbitol"[Mesh] OR "Aloe"[Mesh] OR "Psyllium"[Mesh] OR "Castor Oil"[Mesh] OR "picosulfate sodium"[Supplementary Concept] OR "magnesium citrate"[Supplementary Concept]

#3 "prevention and control"[Subheading] OR "Pre-Exposure Prophylaxis"[Mesh] OR "Post-Exposure Prophylaxis"[Mesh] OR "control"[Title/Abstract] OR "disease prevention"[Title/Abstract] OR "disease prophylaxis"[Title/Abstract] OR "health protection"[Title/Abstract] OR "Post Exposure Prevention"[Title/Abstract] OR "Post Exposure Prophylaxis"[Title/Abstract] OR "Pre Exposure Prophylaxi*"[Title/Abstract] OR "precautionary action"[Title/Abstract] OR "prevention"[Title/Abstract] OR "preventive action"[Title/Abstract] OR "preventive measure*"[Title/Abstract] OR "preventive medication"[Title/Abstract] OR "preventive therapy"[Title/Abstract] OR "preventive treatment"[Title/Abstract] OR "prophylactic institution"[Title/Abstract] OR "prophylactic management"[Title/Abstract] OR "prophylactic medication"[Title/Abstract] OR "prophylactic therapy"[Title/Abstract] OR "prophylactic treatment"[Title/Abstract] OR "prophylaxis"[Title/Abstract]

#4 "Neoplasms"[Mesh] OR "Benign Neoplasm*"[Title/Abstract] OR "cancer*"[Title/Abstract] OR "Malignanc*"[Title/Abstract] OR "malignant neoplas*"[Title/Abstract] OR "malignant tumo?r"[Title/Abstract] OR "neoplas* malignancy"[Title/Abstract] OR "Neoplasia*"[Title/Abstract] OR "Neoplasm*"[Title/Abstract] OR "oncologi* malignancy"[Title/Abstract] OR "Tumor*"[Title/Abstract] OR "tumor* malignancy"[Title/Abstract]

#5 #1 AND #2 AND #3 AND #4

Web of Science

#1 TS=("Opioid-Induced Constipation" OR "narcotic bowel syndrome*" OR "opiate induced constipation*" OR "opioid induced bowel dysfunction*" OR "opioid induced constipation*")

#2 TS=((Laxatives OR Cathartics OR "bowel evacuant*" OR "bowel preparation solution*" OR "bulk forming laxative*" OR "bulk laxative*" OR "cathartic agent" OR cathartic* OR laxantia OR laxati* OR "laxative agent" OR purgative* OR "stimulant laxative") OR (Lactulose OR "Polyethylene Glycols" OR "Senna Extract" OR Sennosides OR Bisacodyl OR "Magnesium Hydroxide" OR "Magnesium Oxide" OR "Magnesium Sulfate" OR "Mineral oil" OR Glycerol OR "Dioctyl Sulfosuccinic Acid" OR Phenolphthalein OR Rheum OR Sorbitol OR Aloe OR Psyllium OR "Castor Oil" OR "picosulfate sodium" OR "magnesium citrate"))

#3 TS=("prevention and control" OR "Pre-Exposure Prophylaxis" OR "Post-Exposure Prophylaxis" OR control OR "disease prevention" OR "disease prophylaxis" OR "health protection" OR "Post Exposure Prevention" OR "Post Exposure Prophylaxis" OR "Pre Exposure Prophylaxi*" OR "precautionary action" OR prevention OR "preventive action" OR "preventive measure*" OR "preventive medication" OR "preventive therapy" OR "preventive treatment" OR "prophylactic institution" OR "prophylactic management" OR "prophylactic medication" OR "prophylactic therapy" OR "prophylactic treatment" OR prophylaxis)

#4 TS=(Neoplasms OR "Benign Neoplasm*" OR cancer* OR Malignanc* OR "malignant neoplas*" OR "malignant tumo?r" OR "neoplas* malignancy" OR Neoplasia* OR Neoplasm* OR "oncologi* malignancy" OR Tumor* OR "tumoral malignancy" OR "tumorous malignancy")

#5 #1 AND #2 AND #3 AND #4

Embase

#32. #28 AND #29 AND #30 AND #31

#31. #26 OR #27

#30. #23 OR #24 OR #25

#29. #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#28. #1 OR #2

#27. 'benign neoplasm*':ti,ab,kw OR 'cancer*':ti,ab,kw OR 'malignanc*':ti,ab,kw OR 'malignant neoplas*':ti,ab,kw OR 'malignant tumo?r':ti,ab,kw OR 'neoplas* malignancy':ti,ab,kw OR 'neoplasia*':ti,ab,kw OR 'neoplasm*':ti,ab,kw OR 'oncologi* malignancy':ti,ab,kw OR 'tumor*':ti,ab,kw OR 'tumoral malignancy':ti,ab,kw OR 'tumorous malignancy':ti,ab,kw

#26. 'malignant neoplasm'/exp

#25. 'control':ti,ab,kw OR 'disease prevention':ti,ab,kw OR 'disease prophylaxis':ti,ab,kw OR 'health protection':ti,ab,kw OR 'post exposure prevention':ti,ab,kw OR 'post exposure prophylaxis':ti,ab,kw OR 'pre exposure prophylaxi*':ti,ab,kw OR 'precautionary action':ti,ab,kw OR prevention:ti,ab,kw OR 'preventive action':ti,ab,kw OR 'preventive measure*':ti,ab,kw OR 'preventive medication':ti,ab,kw OR 'preventive therapy':ti,ab,kw OR 'preventive treatment':ti,ab,kw OR 'prophylactic institution':ti,ab,kw OR 'prophylactic management':ti,ab,kw OR 'prophylactic medication':ti,ab,kw OR 'prophylactic therapy':ti,ab,kw OR 'prophylactic treatment':ti,ab,kw OR 'prophylaxis':ti,ab,kw

#24. 'prevention'/exp

#23. 'prophylaxis'/exp

#22. 'bowel evacuant*':ti,ab,kw OR 'bowel preparation solution*':ti,ab,kw OR 'bulk forming laxative*':ti,ab,kw OR 'bulk laxative*':ti,ab,kw OR 'cathartic agent':ti,ab,kw OR 'cathartic*':ti,ab,kw OR 'laxantia':ti,ab,kw OR 'laxati*':ti,ab,kw OR 'laxative agent':ti,ab,kw OR 'purgative*':ti,ab,kw OR 'stimulant laxative':ti,ab,kw

#21. 'ispagula'/exp

#20. 'castor oil'/exp

#19. 'picosulfate sodium'/exp

#18. 'magnesium citrate'/exp

#17. 'aloe'/exp

#16. 'sorbitol'/exp

#15. 'rheum'/exp

#14. 'phenolphthalein'/exp

#13. 'docusate sodium'/exp

#12. 'glycerol'/exp

#11. 'magnesium sulfate'/exp

#10. 'magnesium oxide'/exp

#9. 'magnesium hydroxide'/exp

#8. 'mineral oil'/exp

#7. 'sennoside'/exp

#6. 'bisacodyl'/exp

#5. 'lactulose'/exp

#4. 'macrogol derivative'/exp

#3. 'laxative'/exp

#2. 'narcotic bowel syndrome*':ti,ab,kw OR 'opiate induced constipation*':ti,ab,kw OR 'opioid induced bowel dysfunction*':ti,ab,kw OR 'opioid induced constipation*':ti,ab,kw

#1. 'opioid induced constipation'/exp

Cochrane Library

#1 MeSH descriptor: [Opioid-Induced Constipation] explode all trees

#2 ('narcotic bowel syndrome*' OR 'opiate induced constipation*' OR 'opioid induced bowel dysfunction*' OR 'opioid induced constipation*'):ti,ab,kw

#3 MeSH descriptor: [Laxatives] explode all trees

#4 MeSH descriptor: [Cathartics] explode all trees

#5 ('bowel evacuant*' OR 'bowel preparation solution*' OR 'bulk forming laxative*' OR 'bulk laxative*' OR 'cathartic agent' OR 'cathartic*' OR 'laxantia' OR 'laxati*' OR 'laxative agent' OR 'purgative*' OR 'stimulant laxative'):ti,ab,kw

#6 MeSH descriptor: [Polyethylene Glycols] explode all trees

#7 MeSH descriptor: [Lactulose] explode all trees

#8 MeSH descriptor: [Bisacodyl] explode all trees

#9 MeSH descriptor: [Sennosides] explode all trees

#10 MeSH descriptor: [Senna Extract] explode all trees

#11 MeSH descriptor: [Mineral Oil] explode all trees

#12 MeSH descriptor: [Magnesium Hydroxide] explode all trees

#13 MeSH descriptor: [Magnesium Oxide] explode all trees

#14 MeSH descriptor: [Magnesium Sulfate] explode all trees

#15 MeSH descriptor: [Glycerol] explode all trees

#16 MeSH descriptor: [Dioctyl Sulfosuccinic Acid] explode all trees

#17 MeSH descriptor: [Phenolphthaleins] explode all trees

#18 MeSH descriptor: [Rheum] explode all trees

#19 MeSH descriptor: [Sorbitol] explode all trees

#20 MeSH descriptor: [Aloe] explode all trees

#21 MeSH descriptor: [Psyllium] explode all trees

#22 MeSH descriptor: [Castor Oil] explode all trees

#23 ('picosulfate sodium' OR 'magnesium citrate'):ti,ab,kw

#24 MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees

#25 MeSH descriptor: [Post-Exposure Prophylaxis] explode all trees

#26 ('control' OR 'disease prevention' OR 'disease prophylaxis' OR 'health protection' OR 'Post Exposure Prevention' OR 'Post Exposure Prophylaxis' OR 'Pre Exposure Prophylaxi*' OR

'precautionary action' OR 'prevention' OR 'preventive action' OR 'preventive measure*' OR 'preventive medication' OR 'preventive therapy' OR 'preventive treatment' OR 'prophylactic institution' OR 'prophylactic management' OR 'prophylactic medication' OR 'prophylactic therapy' OR 'prophylactic treatment' OR 'prophylaxis'):ti,ab,kw

#27 MeSH descriptor: [Neoplasms] explode all trees

#28 ('Benign Neoplasm*' OR 'cancer*' OR 'Malignanc*' OR 'malignant neoplas*' OR 'malignant tumo?r' OR 'neoplas* malignancy' OR 'Neoplasia*' OR 'Neoplasm*' OR 'oncologi* malignancy' OR 'Tumor*' OR 'tumoral malignancy' OR 'tumorous malignancy'):ti,ab,kw

#29 #1 OR #2

#30 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#31 #24 OR #25 OR #26

#32 #27 OR #28

#33 #29 AND #30 AND #31 AND #32

EBSCO

S13 S9 AND S10 AND S11 AND S12

S12 S7 OR S8

S11 S5 OR S6

S10 S3 OR S4

S9 S1 OR S2

S8 "Benign Neoplasm*" OR "cancer*" OR "Malignanc*" OR "malignant neoplas*" OR "malignant tumo?r" OR "neoplas* malignancy" OR "Neoplasia*" OR "Neoplasm*" OR "oncologi* malignancy" OR "Tumor*" OR "tumoral malignancy" OR "tumorous malignancy"

S7 (MH "Neoplasms+")

S6 "control" OR "disease prevention" OR "disease prophylaxis" OR "health protection" OR "Post Exposure Prevention" OR "Post Exposure Prophylaxis" OR "Pre Exposure Prophylaxi*" OR "precautionary action" OR prevention OR "preventive action" OR "preventive measure*" OR "preventive medication" OR "preventive therapy" OR "preventive treatment" OR "prophylactic institution" OR "prophylactic management" OR "prophylactic medication" OR "prophylactic therapy" OR "prophylactic treatment" OR "prophylaxis"

S5 (MH "Pre-Exposure Prophylaxis") OR (MH "Postexposure Follow-Up")

S4 "bowel evacuant*" OR "bowel preparation solution*" OR "bulk forming laxative*" OR "bulk laxative*" OR "cathartic agent" OR "cathartic*" OR "laxantia" OR "laxati*" OR "laxative agent" OR "purgative*" OR "stimulant laxative") OR ("Lactulose" OR "Senna Extract" OR "Sennosides" OR "Bisacodyl" OR "Magnesium Hydroxide" OR "Magnesium Oxide" OR "Glycerol" OR "Dioctyl Sulfosuccinic Acid" OR "Phenolphthalein" OR "Rheum" OR "Sorbitol" OR "Aloe" OR "picosulfate sodium" OR "magnesium citrate"

S3 (MH "Cathartics") OR (MH "Castor Oil") OR (MH "Magnesium Sulfate") OR (MH "Mineral Oil") OR (MH "Polyethylene Glycols") OR (MH "Psyllium")

S2 "narcotic bowel syndrome*" OR "opiate induced constipation*" OR "opioid induced bowel dysfunction*" OR "opioid induced constipation*"

S1 (MH "Opioid-Induced Constipation")