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Efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid-induced constipation: a systematic review

by

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Dedication

Mom, thank you for being my personal editor on this and many other projects throughout my many years of education. The family rate was well within my budget!

Arthur, you are my rock and my strength. Without your undying love and support I would have starved, lived in a hurricane, and likely lost my mind. Thank you for everything, I love you.

Abstract

Opioid-induced constipation (OIC) is an unpleasant and ubiquitous side effect of opioid treatment. Ineffective treatment of OIC can result in decreased adherence to opioid therapy, decreased quality of life, and increased morbidity and mortality. The constipating effects of opioids result from their inhibitory effects on μ, κ, and δ receptors in the gastrointestinal tract causing hard and dry stools, prolonged transit time, decreased gastric secretions, and ineffective colonic emptying. Current treatment of OIC occurs by trial and error; little evidence exists to guide practice. Docusate sodium, sennosides, and lactulose are common drugs used in constipation prevention and management in OIC. This systematic review investigates whether PEG is superior to doscusate sodium, sennosides, and/or lactulose in the treatment of OIC. Despite extensive search strategies, no studies met our inclusion criteria. Consequently, insufficient evidence exists to address this clinical question. Further research is required and high-powered, well-designed clinical trials are economically feasible.

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Table of contents

List of tables

List of figures

List of abbreviations

OIC	=Opioid-induced constipation
μ	=Mu
CNS	=Central nervous system
δ	=Delta
κ	=Kappa
GI	=Gastrointestinal
PNS	=Peripheral nervous system
OBD	=Opioid bowel dysfunction
QOL	=Quality of life
PEG	=Polyethylene glycol
NP	=Nurse Practitioner
RCT	=Randomized controlled trial
CENTRAL	=Cochrane registry of controlled trials
CANO	=Canadian association of nurses in oncology
ONS	=Oncology Nursing Society
ASCO	=American society of clinical oncology
PRISMA	=Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STARD	=Standards for the Reporting of Diagnostic Accuracy

List of appendices

Chapter 1- Introduction

Opioids are the mainstay of treatment for patients suffering from acute or chronic, moderate to severe pain, because of their proven analgesic efficacy.[1,2] However, therapy is frequently complicated by side effects that can affect adherence to treatment,[3] quality of life,[4] and morbidity and mortality.[3,5,6] The most common and often debilitating of these side effects is constipation,[7] which is often intractable.[8]

In this section I discuss the pathophysiology of opioid induced constipation (OIC) as well as its definition, clinical significance, and treatment. In conclusion, this project's contribution to nursing knowledge will be outlined.

Pathophysiology

Opioid receptors are located throughout the body in the central and peripheral nervous systems. Endogenous and exogenous opioid receptor stimulation[7] results in positive and negative systemic effects.[1,7] Positive effects, such as analgesia, are effectively achieved with the binding of opioids to mu (μ) receptors, the primary receptors for pain management in the central nervous system (CNS).[2,7] Delta (δ), and kappa (κ) receptors also play a role in decreasing pain signals in the CNS, but to a lesser degree.[2] Negative effects, such as alterations in gastrointestinal (GI) function occur as a result of non-selective binding of opioids to μ, δ, κ receptors, especially in the peripheral nervous system (PNS).[7]

The μ, δ, and κ receptors belong to the family of G-protein-coupled receptors, known for their inhibitory effects on adenylate cyclase. These

inhibitory effects signal transmission at the membrane level, where they decrease neuronal excitability and acetylcholine release.[1,2] Overall, they have an inhibitory effect on the neuron potentials.[1]

These three receptors affect GI function through different mechanisms. Similar to its central role in analgesia in the CNS, the μ receptor is also the main receptor responsible for side effects associated with opioids in the PNS. Mu receptors regulate ion transport[1] responsible for motility, secretion,[2,7] absorption, and blood flow.[7] When opioid agonists bind to μ receptors, excitatory neurotransmissions are inhibited.[8,9] As a result, the mucosal secretion and rhythmic contractions necessary for digestion are affected.[3] Delays in gastric emptying, oral-cecal transit, and colonic transit time occur. An increase in transit time allows for greater reabsorption of fecal fluid.[7] In addition, the CNS suppresses signals in the secretomotor neuronal population that reduce secretions into the lumen and luminal contents in the small intestine, decreasing liquidity of stools.[8] Ultimately, hard stools form and are difficult to pass, resulting in constipation.[2,3,8] Finally, suppression of the excitability of motor neurons caused by opioid agonists decreases muscle tone and interrupts the coordination required for effective gastric emptying,[8] aggravating constipation further.

Delta and κ receptors also mediate GI function, but again they play a less important role. Delta receptors are more abundant in the CNS, but their GI effects are related to their activity in the PNS. The blockade of δ receptors in the myenteric and submucosal neurons of the GI tract results in inhibition of motility

and secretion. Unlike δ receptors, κ receptors are more numerous in the PNS. When opioids bind to κ receptors, signal inhibition results in bowel dysfunction.[2]

Unfortunately, many patients cannot tolerate the gastrointestinal side effects of opioids, and there is no decline in this intolerance with long-term use.[7,10] Opioid medications will accumulate in GI tissue[9] and GI side effects persist for as long as opioid therapy is administered.[3] Moreover, when titrating medication escalation to achieve pain control, constipation can worsen.[3] Whether the opioid action occurs in the CNS or PNS, exogenous opioids affect signals at the μ, δ, and κ receptors and contribute to the resulting therapeutic actions and side effects.[2]

Definition

A standardized definition of OIC is needed in clinical practice; yet to date, no widely accepted definition of OIC exists.[3] This has resulted in a lack of research into appropriate first-line treatment for this clinical condition.[11] Since constipation is an ever-increasing clinical issue,[3] a definition of OIC is important for further clinical investigation.

There are reasons why no widely accepted definition of OIC exists. First of all, in many patients it can be difficult to ascertain whether opioid therapy is the primary or secondary cause of constipation. For example, other underlying physiologic conditions such as dehydration, metabolic disturbances, or mechanical causes can also result in constipation.[3] However, in many patients receiving opioid treatment, constipation begins with initiation of therapy[10] and opioid treatment often remains the primary cause of constipation for the duration

of therapy.[3] Appreciably, when underlying physiologic conditions do exist, opioid administration can exacerbate the constipation and make it even more difficult to manage.[3,7] Second, research studies examining OIC often use the same clinical criteria outlined for functional or chronic constipation. Although this may seem reasonable, there are fundamental differences in the pathophysiology of OIC, as outlined above. Use of these same criteria fails to recognize that OIC may require different therapy because of the pathophysiology associated with opioid use. Furthermore, systematic reviews and clinical guidelines enable evidence-based practice for treatment of *well-defined* functional[12] and chronic constipation,[13] whereas there is minimal evidence to guide practice when treating OIC.

A distinctive and comprehensive definition of OIC is required to enable clinicians to appropriately diagnose, research, and treat this condition. In the literature, a cluster of signs and symptoms associated with the effects of opioid use on gastrointestinal motility has led to the recognition of opioid bowel dysfunction (OBD).[3,7,14] Since constipation is the primary symptom of OBD,[3] the associated signs and symptoms provide clinicians with the necessary diagnostic indications that OIC is present and requires treatment.

OBD occurs with short- or long-term opioid use, and is characterized by:

- Hard, dry stools
- Straining
- Feeling of incomplete evacuation
- Bloating
- Abdominal distention

- Increased gastroesophageal reflux[7]

Although OBD describes some of the signs and symptoms of OIC, it is not an all-encompassing condition. Other symptoms of OIC in addition to those described above include abdominal pain, nausea, vomiting, loss of appetite, and headache.[6]

The definitions of chronic and functional constipation[12] have been more widely investigated and described in the literature. Although OBD shares many of the signs and symptoms associated with these other types of constipation; examination of these other definitions indicates that OBD lacks comprehensiveness. Important descriptors for constipation, such as frequency of stool passage and other signs and symptoms in the above paragraph, are missing.

OIC requires an all-encompassing definition in order to capture the discomfort and associated symptoms that occur with constipation. For the purposes of this paper, we will define OIC as active opioid therapy in addition to at least one of the following:

- Stools that are hard and difficult to pass
- Straining with bowel movement
- Fewer than three stools per week

With this definition, we recognize that the other signs and symptoms such as hard and dry stools, feeling of incomplete evacuation, bloating, abdominal distention, increased gastroesophageal reflux, abdominal pain, nausea, vomiting, loss of appetite, and headache may or may not occur.

Clinical significance

OIC is an unpleasant and ubiquitous side effect of opioid therapy. Whereas 2-10% of the general population suffers from constipation;[10] constipation associated with opioid use has been reported to be as high as 90% in patients with non-cancer pain,[3] and as high as 95% in patients with cancer pain.[6] Since opioids are prescribed for a number of pain conditions, including cancer and non-cancer pain, and drug management (e.g. methadone) programs, OIC is a prevalent clinical issue that can affect patients regardless of age, gender, and socioeconomic status. In addition, since opioids are the standard of care for moderate and severe pain management according to the World Health Organization's analgesic ladder,[15] OIC is also a global clinical issue. The distress associated with OIC can affect adherence to therapy, quality of life, morbidity and possibly mortality.

Adherence to therapy

Adherence with opioid therapy often decreases when OIC occurs. Decreased adherence is frequently related to the side effects that occur with constipation including symptoms of OBD,[3] described above. Moreover, constipation itself has been described as more concerning than the pain that the patient is suffering.[3] As such, some patients would rather endure pain than continue opioid treatment if it causes constipation.[16] This qualitative data demonstrates that a timely constipation diagnosis and effective management are imperative in order to achieve a successful pain management regimen.

Quality of life

In contrast to evidence that supports that long-term use of opioids for pain management can improve QOL in patients, constipation can decrease QOL thus limiting the benefits associated with opioid use.[3] Quality of life is often decreased by the presence of signs and symptoms of OIC,[6] and, as OIC and its associated symptoms worsen, so do measured QOL scores.[4] Understandably, the early symptoms of constipation (e.g. anorexia, nausea) and progressive symptoms (e.g. bowel impaction), all have a negative social, psychological, and physical impact, thus affecting quality of life.[6]

Morbidity and mortality

OIC is associated with increased morbidity and mortality, and as OIC worsens, a distressing cycle of worsening symptoms occurs. If prevention of constipation with non-pharmacologic or pharmacologic therapy is ineffective, anorexia, nausea, or bowel impaction can occur.[6] In hospice cancer patients, worsening constipation not only increased nausea and anorexia, it also increased the risk of delirium and urinary retention.[17] Furthermore, compared with non-constipated patients, constipated patients receiving opioid therapy for more than 6 months were more likely to visit their physicians, miss work, feel that their performance at work was impaired, and have symptoms that impaired their ability to undertake activities of daily living.[18] When worsening OIC results in hard stools, trauma to the rectal tissue can occur with stool passage or the possible need for suppositories or enemas. Finally, there has been a suggestion that interventions

for obstructive constipation can cause morbidity and mortality by creating a portal of entry for bacteria, especially if the host is also immunocompromised.[5]

Untreated constipation can also affect survival and increase health care costs. Obstructive constipation causing life threatening bowel obstruction may require inpatient treatment or invasive surgery, resulting in lengthy hospital stays.[7,11] Moreover, a recent study by Hjalte, Berggren, Bergendahl, and Hjortsberg[4] examined the costs associated with OIC. Not surprisingly, those with the most severe constipation had the highest healthcare costs, including indirect (e.g. sick leave) and outpatient costs totaling on average 1,525 EUR (2,180 CAD) per month. Again, early identification and treatment OIC of could prevent many of these negative sequalae.

Treatment

Treatment guidelines for OIC are lacking; consequently, choice of intervention and prescribing practices are based on trial and error. Treatment goals should be the prevention of constipation with non-pharmacologic and/or pharmacologic means, including normalizing a bowel routine prior to initiating therapy and establishing goals for frequency of bowel movements.[6,19] If prevention fails, more aggressive treatment will be required to prevent the negative sequalae previously described.

Non-pharmacologic treatment

Current non-pharmacologic recommendations include increasing dietary fiber and fluid intake, increasing exercise and activity, and encouraging a scheduled time for a bowel movement.[7,20] However, these recommendations are

often insufficient to manage constipation necessitating the need for pharmacologic intervention.[3]

Pharmacologic treatment

A wide range of pharmacological agents have been used in the attempt to prevent and manage OIC. Saline, osmotic, stimulant and detergent laxatives are recommended for OIC, whereas bulk and lubricant laxatives are not. Bulk laxatives should be avoided especially when physical activity or fluid intake are limited, or severe constipation is suspected.[6,13] Lubricant laxatives are avoided because they cause decreased absorption of fat vitamins, they increase the risk of fecal incontinence, and long-term use can cause perianal inflammation.[10]

The principal drugs used in the management of OIC are lactulose, docusate sodium, sennosides, and polyethylene glycol (PEG). The mechanisms of action for lactulose (an osmotic laxative), docusate sodium (a detergent laxative), and sennosides (a stimulant laxative), and PEG (an iso-osmotic laxative) are different. They are described in Table 1-1.

Research continues to investigate new agents for OIC, but more research is needed in order to determine their safety and efficacy. Opioid antagonists are relatively new drugs that have shown promise in the treatment of OIC. However, their use is limited because they are expensive, and they are only indicated for OIC after treatment with the above drugs has failed.[21] Furthermore, the opioid antagonist agents alvimopan, methylnaltrexone, naloxone, and nalbuphine were recently discussed in a systematic review by McNicol, Boyce, Schumann, and Carr (2008).[11] The authors concluded that insufficient data exists to recommend

any of the four drugs in OIC. In addition, long-term safety, and the incidence of rare, severe events are unknown. Until further evidence demonstrates their safety and efficacy in OIC, patients will require treatment[6] and clinicians currently require evidence to institute appropriate management of OIC.

Contribution to nursing knowledge

As mentioned in the previous paragraphs, increasing use of opioids for non-cancer and cancer pain management, and for substance withdrawal (e.g. methadone maintenance) has resulted in a growing clinical issue – OIC. The ineffective management of constipation is largely related to lack of evidence for assessment, diagnosis, and treatment of the condition. This lack of evidence complicates appropriate management of OIC for all members of the health care team from prescribing clinicians to front-line nursing staff. Ultimately, this can negatively impact the patient.[6]

Registered nurses manage large populations of patients who require pharmacologic management of their OIC. In our local institutions, nurses are frequently responsible for the management of constipation in both inpatient and outpatients settings across a variety of patient groups. In the hospital, registered nurses are the primary providers for constipation management. Often, attending physicians prescribe as-needed medications that require a thorough assessment by the nurse in order to monitor and treat their patients' constipation. In outpatient settings nurses often counsel patients on the most appropriate medications to assist in the management of constipation. Notably, docusate sodium, sennosides,

lactulose, and PEG are all available without a prescription. Therefore, it is within a nursing's scope of practice to provide this information.

Nurse Practitioners (NPs) have an increased scope of practice compared to registered nurses; they are responsible for the diagnosis and prescription of medications to treat OIC. In hospital, they assess patients upon admission and identify clinical issues, including constipation. Appropriate diagnosis of OIC is complicated since, as described in the above paragraphs, a comprehensive definition and description of the condition is lacking. Inappropriate identification of the cause of constipation could impact efficacy of the treatment. Additionally, even when a proper diagnosis is made, constant reassessment is required to ensure that the treatment plan is effective. For example, the NP must assess whether the constipation persists and whether a re-evaluation of the treatment plan is required. In outpatient clinics, initial assessment and further reassessment occurs in a similar fashion. Appropriate management of constipation, especially OIC, is complicated when NPs have minimal evidence on which to base their treatment decisions. This has led to trial and error prescribing among NPs and other prescribing clinicians. Furthermore, it has led to ineffective clinical management of this widespread problem, resulting in negative effects for the patient.[6]

A study comparing the efficacy of commonly used medications in the management of OIC is required. A recent systematic review demonstrated PEG's superiority to lactulose in children and adults with chronic constipation.[13] This high-quality evidence has facilitated practice changes for chronic constipation. A systematic review that compares the efficacy and side-effect profiles of docusate

sodium, sennosides, and lactulose to PEG would assist clinicians in treatment decisions for OIC. The systematic review would also outline a definition of OIC to assist with inclusion and exclusion criteria for the study. Furthermore, this definition would assist interdisciplinary team members in the future, as it would standardize diagnostic criteria. Finally, use of this definition in future research regarding OIC would assist with comparison and meta-analyses among studies.

In conclusion, opioids affect GI motility through a variety of mechanisms, ultimately resulting in dry, hard stools that are difficult to pass. A standard definition of OIC is required for the assessment, research, and treatment of OIC in the future. Current evidence for both non-pharmacologic and pharmacologic treatment of OIC is lacking. Since non-pharmacologic means of treatment are often ineffective, pharmacologic intervention is required. The trial and error prescribing that currently exists for the treatment of OIC is unacceptable. A systematic review would help to address and/or further identify some of the current gaps in knowledge.

Table 1-1

Laxatives

Category	Example	Action	Benefit	Side Effects	Contraindications
Detergent	Docusate sodium (Colace ®) and docusate calcium (Surfak ®)	Facilitate the mixing of acqueous and fatty substances[6] by reducing surface tension[22]	Soften stool[6]		May increase systemic absorption of mineral oil when administered together[22]
Osmotic/ Saline	Lactulose and sorbitol	Poorly absorbed ions or molecules create a local osmotic gradient within the intestinal lumen[6] Peristalsis is stimulated by increase in pressure from reabsorption of fluid and electrolytes, and decreased gut pH in the colon[13]	Stimulates peristalsis via increase in pressure[6]	Electrolyte abnormalities[6] Altered bowel flora can cause bloating, flatulence, colic, and excessive diarrhea[13]	Galactosemia, intestinal obstruction[13]
Iso-osmotic laxative	Polyethylene Glycol (PEG) Standard dose with electrolytes (Golytely® and Colytely®); low dose without electrolytes (PEG 3350, Miralax®)	Iso-osmotic laxative are physiologically inert- they are not absorbed or metabolized in the gut. Opposes water absorption from stool in the large bowel, increasing water content and volume of the stools[6]	Makes stools softer and easier to pass[6]	Abdominal distention. Pain, nausea, excessive diarrhea[13]	Intestinal perforation or obstruction, paralytic ileus, severe inflammatory conditions of the GI tract (e.g. Crohn's, ulcerative colitis, megacolon)[13]

Stimulant	Senna (Senokot® and ExLax®) and Bisacody (Dulcolax® and Corretol®)	Irritate the nerve endings in the colonic mucosa, stimulating peristalsis. May also limit water absorption by altering fluid and electrolyte transportation within the intestinal mucosa[6]	Stimulate peristalsis[6] Suitable for patients unresponsive or intolerant to fibre[13]	Abdominal discomfort (cramping), electrolyte imbalances (hypokalemia),[13] allergic reactions, and hepatotoxicity. Melanosis coli (a pigmentation disorder of the bowel) has also been reported with senna containing compounds[6]	Intestinal Osbtruction[6] Prolonged use can possible cause laxative dependency and loss of normal bowel function[22]

References

[1] Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol* 2011 quiz 843; May;106(5):835-842.

[2] De Schepper HU, Cremonini F, Park MI *et al.* Opioids and the gut: pharmacology and current clinical experience. *Neurogastroenterol Motil* 2004 Aug;16(4):383-394.

[3] Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 2007 Jul;61(7):1181-1187.

[4] Hjalte F, Berggren AC, Bergendahl H *et al*. The direct and indirect costs of opioid-induced constipation. *J Pain Symptom Manage* 2010 Nov;40(5):696-703.

[5] Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med* 2008 May;11(4):575-581.

[6] Woolery M, Bisanz A, Lyons HF *et al*. Putting evidence into practice: evidence-based interventions for the prevention and management of constipation in patients with cancer. *Clin J Oncol Nurs* 2008 Apr;12(2):317-337.

[7] Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg* 2001 Nov;182(5A Suppl):11S-18S.

[8] Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil* 2004 Oct;16(Suppl 2):17-28.

[9] De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. *Pharmacol Ther* 1996;69(2):103-115.

[10] Caraccia-Economou D. Bowel management: constipation, diarrhea, obstruction, and ascites. In: Ferrell B, Coyle N, editors. Textbook of Palliative Nursing. 2nd ed. New York, NY: Oxford University Press, Inc.; 2006. p. 219-238.

[11] McNicol E, Boyce DB, Schumann R *et al*. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med* 2008 Sep;9(6):634-659.

[12] Rome Foundation. Appendix A: Rome III diagnostic criteria for functional gastrointestinal disorders. 2006; Available at: http://www.romecriteria.org/criteria/. Accessed Nov 17, 2011.

[13] Lee-Robichaud H, Thomas K, Morgan J *et al*. Lactulose versus Polyethylene Glycol for Chronic Constipation. *Cochrane Database Syst Rev* 2010(7):007570.

[14] Holzer P. Treatment of opioid-induced gut dysfunction. *Expert Opin Investig Drugs* 2007 Feb;16(2):181-194.

[15] World Health Organization. WHO's pain ladder. 2011; Available at: http://www.who.int/cancer/palliative/painladder/en/index.html. Accessed Nov 17, 2011.

[16] Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage* 2002 Jul;24(1):71-90.
[17] McMillan SC. Presence and severity of constipation in hospice patients with advanced cancer. *Am J Hosp Palliat Care* 2002 Nov-Dec;19(6):426-430.
[18] Annunziata K, Bell T. Impact of opioid-induced constipation on healthcare resource utilisation and patient functioning. *Eur J Pain* 2006;10(suppl S1):S172.
[19] Clemens KE, Klaschik E. Management of constipation in palliative care patients. *Curr opin support palliat care* 2008 Mar;2(1):22-27.
[20] Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician* 2006 Oct 15;74(8):1347-1354.
[21] Garnock-Jones KP, McKeage K. Methylnaltrexone. *Drugs* 2010 May 7;70(7):919-928.
[22] Cahill B. Management of cancer pain. In: Henke-Yarbro C, Hansen-Frogge M, Goodman M, editors. Cancer nursing: principles and practice. 6th ed. Burlington, MA: Jones & Barlett Learning; 2005. p. 662-697.

Chapter 2- The protocol

Introduction

Currently, little evidence exists to guide the treatment of opioid-induced constipation (OIC).[1,2] As a result, pharmacologic intervention is frequently done on a trial and error basis. Commonly used pharmaceutical strategies for OIC include sennosides and docusate sodium two to three times per day. If these medications are ineffective, lactulose, polyethylene glycol (PEG) granules, oral fleets, enemas, and suppositories are used.[2]

Recently, PEG demonstrated superior efficacy compared to lactulose in a systematic review in *chronic* constipation.[3] As the pathophysiology between chronic constipation and OIC differs, we wanted to undertake a systematic review to determine if PEG was superior to current pharmaceutical strategies in OIC. We opted to do a systematic review because of its sound methodology that would allow for an objective appraisal of the literature. Additionally, we hope to conduct a meta-analysis. This would enhance precision estimates of current treatment approaches[4] for OIC and enable evidence-based treatment of this condition. This unpublished protocol was created to outline our research plan to conduct a systematic review to address our clinical question.

Objective

The primary objective is to determine the safety and efficacy of lactulose, docusate sodium, and sennosides compared to polyethylene glycol (PEG) granules in the treatment of OIC.

Methods

Criteria for selecting studies for this review

Types of studies. Randomized controlled trials (RCTs) which compare lactulose, docusate sodium, or sennosides to PEG, in adults with OIC. In accordance with Cochrane methodology, we will exclude studies if they are any design other than RCT.

Type of participants. Participants 18 years of age or older with OIC. Adults may be inpatients, outpatients, or palliative care patients with planned long-term treatment with opioids for the management of cancer pain, chronic non-cancer pain, or substance withdrawal (e.g. methadone maintenance). We will exclude studies if they focus *exclusively* on children, pregnant women, spinal cord injury patients, intensive-care unit patients, Parkinson's disease patients, or patients with other neurological diseases as the pathophysiology of constipation in these diseases is different than in OIC. Studies that focus exclusively on post-operative patients will also be excluded since pain management is intended to be short-term, thus laxative use should be short-term.

Types of interventions. RCTs must compare at least one of lactulose, docusate sodium, or sennosides; but PEG must be present in all studies. Also, the doses of the opioid, and all laxatives must be reported in the study to allow for comparison among studies.

Types of outcome measures. All outcomes will be analyzed in an outcome data table in order to help determine trends and to assist with the narrative

analysis and synthesis of included studies (see Table 2-1). In order to answer the study objectives, the following outcomes will be examined.

Primary outcomes.

1. Efficacy- frequency of bowel movements
2. Quality of stools (hard, soft, loose)

Secondary outcomes

1. Side effects
2. Drug interactions
3. Use of additional laxatives e.g. enemas, other laxative agents
4. Relief of constipation associated symptoms- e.g. bloating, abdominal pain, straining

Studies must report on frequency of stools in order to be eligible for inclusion, although they may, or may not report on quality of stools, or secondary outcomes. Studies that only report on quality of stools or secondary outcomes will be considered in the discussion section.

Search methods for identification of studies

Electronic searches. We will search the following databases with the assistance of a research librarian: Cochrane Central Registry of Controlled Trials (CENTRAL), MEDLINE, CINAHL, EMBASE, International Pharmaceutical Abstracts, Scopus, DARE, Web of Science, Proquest, Grey Matters and Grey Source.

We will use the following search strategy for MEDLINE (see Table 2-2), and will adapt the search strategy for other databases.

The search strategy will not limit the year since low-dose PEG is a relatively new medication and we want to capture all of the relevant literature. Language will also not be limited since little research was discovered while scoping the literature and we will attempt to translate all articles where feasible. Support from Cochrane, colleagues, or Google translate will be explored to assist with this process. Search terms will not delineate age; it should be easy to identify and exclude RCTs that focus solely on children. Finally, search strategies will use the term constipation instead of opioid-induced constipation in order to maintain an inclusive search. Again, identifying and excluding articles with title and abstract or full article review should be straightforward.

Screening other resources. In an attempt to avoid publication bias, a thorough search of the grey literature will be done (as outlined above) in addition to hand searching and reference browsing. The primary review author (TK) will hand search reference lists and drug monographs to identify any further studies, and will reference browse conference proceedings for oncology (Canadian Association of Nurses in Oncology [CANO], Oncology Nursing Society [ONS], American Society of Clinical Oncology [ASCO]), palliative care (International Congress on Palliative Care), and gastroenterology (American Gastroenterological Association, Canadian Association of Gastroenterology, Canadian Society of Gastroenterological Nurses and Associates, and the Society of Gastroenterological Nurses and Associates GI nurses association). Since the publication studies using PEG for chronic constipation began in 1990, screening

will be limited to that year. Finally, we will attempt to contact pharmaceutical manufacturers for the details of unpublished and ongoing trials.

Data collection and analysis

Selection of studies. Two review authors (TK, KH) will independently scan the title, abstract, and keywords of every record retrieved against inclusion and exclusion criteria to determine if studies require further assessment. The two authors will pilot the selection process and meet after screening 100 articles to discuss and document discrepancies and any oversight. Any disagreements will be resolved by consensus; where consensus cannot be reached, a third reviewer (GC) will be contacted. All data will be managed in RefWorks after study selection is complete and all disagreements have been resolved.

Data extraction and management. Two review authors (TK, KH) will independently extract data regarding details of study population, intervention, and outcomes using a standard data extraction form specifically adapted for this review. A Kappa statistic will be used to assess interrater reliability. Any disagreements will be resolved by consensus; where consensus cannot be reached, a third reviewer (GC) will be contacted. When papers arising from the same study are found, they will be analyzed as a single study. In addition, both published and unpublished data will be handled the same way. Electronic records will be kept for reference of internal consistency.

The data extraction form will include the following items (see Tables 2-3, 2-4, and 2-5):

1. General Information-Study identification; Author information: Title; Objective of Study: Funding organization; Sample Setting
2. Participants: Inclusion/Exclusion Criteria, Recruitment Procedures Used; Characteristics of Participants; Opioid Medication; Unit of Allocation/Number of Participants; Participants Included in Analysis, Withdrawals/Losses; Type of Analysis Used
3. Intervention: Definition of Constipation; Description of Interventions and Controls; Descriptions of Co-Intervention(s); Fidelity (same dose, time, instruction, etc.)
4. Outcomes: Outcome and Follow-Up; Instruments and Reliability/Validity of Instruments; Subgroup Analysis/Additional Outcomes; Outcomes; Statistical Techniques; Results of Study; Adverse Events

For an explanation of the elements in the data form see *Appendix A*.

Assessment of risk of bias in included studies. Two review authors (TK, KH) will independently assess each included study using the Cochrane Collaboration's tool for assessing Risk of Bias[5] (see Table 2-6). Any disagreements will be resolved by consensus; where consensus cannot be reached, a third reviewer (GC) will be contacted. Study appraisal and data extraction will be done simultaneously on each article. However, data extraction will be done first to minimize the impact of known article quality on data extraction. To ensure accuracy and comprehensiveness among the two authors; we (TK, KH) will meet after extraction and appraisal of five articles to discuss and document discrepancies and oversight.

Measures of treatment effect. We will present the frequency of bowel movements in two ways: as a weighted mean difference with 95% confidence intervals which is appropriate for continuous data measured on the same scale (in this case number of days to bowel movement); data will also be translated to a dichotomous outcome based on our definition of constipation, which will be reported as a relative risk. The quality of stools and associated symptoms (e.g. hard, soft, loose, sense of complete evacuation, straining) will be presented as a relative risk. Where studies report the quality of stools on a continuum, continuous data will be translated into dichotomous data to allow for relative risk calculations. Binary outcomes (e.g. side effects) will be presented as relative risk with corresponding 95% confidence intervals. Continuous data (e.g. scales used to rate constipation associated symptoms) will be presented as mean differences with a corresponding 95% confidence interval. When included studies use different scales to grade subjective symptoms, standardized mean difference calculations will be done to combine continuous data.[6] Relative risk will be used for its ease of interpretation, its ability to compare to other treatments via absolute risk reduction, and its use in calculation for number needed to treat.

Unit of analysis issues. All included studies will be RCTs. The unit of analysis will be the individual participant. The primary outcome, frequency of bowel movements, is expected to be a continuous variable (either number of days or number of times per week). Depending on the number of studies, side effects may be stratified in narrative format by side effects experienced, or analyzed as a dichotomous outcome (e.g. Side effect A- present, absent). Use of additional

laxatives and drug interactions will be analyzed in the same way as side effects. Where studies investigate different types of opioids, the opioid dose will be standardized using an opioid equivalency table (see Table 2-7 and 2-8) for both cancer and non-cancer pain. This will account for the various doses of opioid, since higher doses are known to be associated with increased severity of constipation.[7] If subjects included in the studies are cancer patients, the equivalency table for cancer pain will be used. If the included subjects are non-cancer patients, the equivalency table for non-cancer pain will be used. If the subjects in the studies have both cancer and non-cancer pain, and are not stratified by group, we will use the non-cancer equivalency table, as this will give higher morphine-equivalent values, and constipation should be more difficult to treat in these patients (which will under-estimate, rather than over-estimate treatment effect). We will remain conscientious of this decision throughout our data analysis and subsequent discussion.

Dealing with missing data. Authors of included studies will be contacted twice to supply missing data. When missing data is unavailable for retrieval, causing significant gaps in data, studies will undergo further screening. Inclusion and exclusion criteria will be re-examined to determine if studies will be included as potentially relevant, or if studies will be excluded on the basis of insufficient data. This decision will be made by consensus between two reviewers (TK, KH) and a third reviewer (GC) will be contacted if consensus cannot be reached. Missing data for drop out and attrition will be assessed for each study, and if data

are available, using intention to treat principle.[6] Extent to which the results and conclusions of the study could have been altered will be assessed and discussed.

Assessment of heterogeneity. If the number and characteristics of studies suggests that meta-analysis may be feasible, we will measure heterogeneity across studies using the Chi^2 test. We will also use the I^2 statistic to quantify inconsistencies throughout the trials; where 0%= no heterogeneity, and larger values indicate increasing heterogeneity. If I^2 is <25%, a fixed-effect model for meta-analysis will be used. A random effects model will be used for moderate levels of heterogeneity determined by an I^2 value of 25-50% .[8] If a high-level of heterogeneity is determined by statistical tests, meta-analysis will not be done; instead, meta-regression will be done to determine possible factors influencing the estimated treatment effect.[6]

Assessment of reporting biases. We will perform a funnel plot analysis to check for any publication bias to examine potential bias in our calculated overall effect size.

Data synthesis. Two review authors (TK, KH) will independently enter data into Review Manager.[9] If studies are homogeneous, we will pool results as outlined above. Narrative synthesis of studies will be done to examine if observed effects are consistent across studies and to determine possible reasons for inconsistencies. The narrative synthesis will also provide an analysis of the relationships within and between studies for an overall assessment of the strength of the evidence.[10]

Subgroup analysis and investigation of heterogeneity. Forrest plots will be done separately for lactulose, docusate sodium, sennosides and PEG to determine heterogeneity (other statistical tests for heterogeneity are described above). When homogeneity is present in a drug group, meta-analysis will be done to determine the effect size for that drug. If heterogeneity exists, meta-regression will be done in an attempt to examine whether a particular characteristic within the studies is related to the extent of the treatment benefit.[11] If sufficient studies exist, subgroup analysis will also be considered for age, baseline constipation severity, opioid dose, gender, co-interventions (e.g. other laxatives, fiber or fluid intake, and activity level), co-morbidities (e.g. cancer), and reason for opioid use (e.g. acute pain, chronic pain, treatment of drug dependence) in order to help clinicians determine if the overall treatment effect would benefit other patient groups.[12]

Sensitivity analysis. If a sufficient number of studies are found, we will carry out sensitivity analysis to determine the overall robustness of the results, and to help interpret and explain differences across studies.[12] Sensitivity analysis will be done according to study quality as assessed by the risk of bias tool.

Dissemination strategies

Since OIC is a condition that affects patients from many patient groups, we know that various clinicians will consider the outcomes of this study. Accordingly, we hope to publish our results in *Family Practice*, an internationally read journal for general practitioners in developed and developing countries.[13] Additionally, the publication of this study will automatically index our title in several databases, including Medline, where it will be accessible to other

clinicians and researchers interested in this topic area. Finally, we will look for opportunities to present our findings at medical rounds in our local hospitals and at conferences locally, nationally, and internationally.

Table 2-1

Outcome data table

*e.g. Lactulose

Study	Number of Stools per Week	Frequency of Hard Stools per Week	Frequency of Soft Stools per Week	Frequency of Loose Stools per Week	Side Effects	Drug Interactions	How many times were additional laxatives used per week?	Relief of constipation associated symptoms

* Note an outcome data table will be done for each laxative

Table 2-2

MEDLINE search terms

Searches	Results	Search Type
1	Constipation/	8859
2	(constipat* or dyschezia or colonic inertia or f?eces or f?ecal or retention or delayed bowel movement or obstipation or costiveness or irregular* or egest).tw.	213319
3	1 or 2	216243
4	laxatives/	252
5	3 and 4	160
6	Polyethylene Glycols/	29093
7	(peg or peg granules or laxaday or polyethylene glycol or ethylene glycol or ethylene oxide or PEO or polyethers or movicol or polyethylene glycol 3350 or miralax or glycoLax or GoLYTELY or glycolax or fortrans or trilyte or colyte).tw.	39368
8	6 or 7	54902
9	Dioctyl Sulfosuccinic Acid/	432
10	(colace or docusate sodium or docusate salt* or docusate calcium or sulfosucc* or dioctyl calcium sulfosuccinate or correctol or diocto or docusoft or dok or dos or ex-lax or sof-lax or gentlax or peri-colace or correctol).tw.	3107
11	9 or 10	3363
12	Lactulose/	1533
13	Senna Extract/	329
14	(senokot or sennosides or lactulose or disaccharide or generlac or cephulac or cholac or constilac or enulose or cilac or heptalac or actilax or duphalac or kristalose or apo-lactulose).tw.	8040
15	12 or 13 or 14	8584
16	11 or 15	11938

17	8 and 16	212
18	3 and 17	65
19	18 or 5	215

Table 2-3

General information- identification/interventions

Identification	Author Information	Title	Objective of Study	Funding Organization	Sample Setting	Fidelity	Definition of Constipation	Description of Interventions and Controls	Descriptions of Co-Intervention(s)
RefWorks ID: Year: Country: Language:	Authors: ☐ Published ☐ Unpublished Contact Information:			☐ Pharmaceutical Company ☐ Other (describe):				<u>Non-PEG</u> Dose: Route: Timing: <u>PEG</u> Dose: Route: Timing:	Co-Intervention: Dose: Route: Timing:

Table 2-4

Participant characteristics

Inclusion/Exclusion Criteria	Recruitment Procedures Used	Characteristics of Participants	Opioid Medication	Unit of Allocation/ Number of Participants	Participants Included in Analysis /Withdrawals	Type of Analysis Used
Inclusion: Exclusion:	☐ Randomized ☐ Single Blind ☐ Double Blind Describe:	Mean age: Gender: %M; %F Ethnicity: SES: Baseline characteristics: Co-morbidities:	Opioid Medication: Dose: Route: Timing: Morphine equivalency table conversion:	Unit of Allocation: Number of Participants: N=	Included in Analysis: N= ; % Withdrawals/Lost to Follow-up: N= ; % Reasons:	☐ Intention-to-treat ☐ Other (describe):

Table 2-5

Outcomes

Outcome and Follow Up	Instruments	Subgroup Analysis or Additional Outcomes	Outcomes	Statistical Techniques	Results of Study	Adverse Events	Comments
Outcome Unit of Analysis: Length of Follow-Up:	Instrument Used: Reliability/ Validity:	☐ Sub-group analysis If yes, describe: Drug interactions: Relief of Associated Symptoms:	☐ Yes- outcomes were pre-specified Outcomes: Measurement Tool:			Side Effects for Non-PEG: Side Effects for PEG: Other:	

Table 2-6

Risk of Bias Tool

The Cochrane Collaboration's tool for assessing risk of bias[5]

Reviewer's Initials: ___ Study ID: _____ Date (dd/mm/yy): _____

Time to complete: _____ Time for consensus: _____

Domain	Description	Review authors' judgment	Consensus (circle)
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR	YES NO UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR	YES NO UNCLEAR
Blinding of participants, personnel and outcome assessors, *Outcome:*		Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR	YES NO UNCLEAR
Incomplete outcome data, *Outcome:*		Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR	YES NO UNCLEAR
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome	YES NO

		reporting? YES / NO / UNCLEAR	UNCLEAR
Other sources of bias		Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR	YES NO UNCLEAR
Overall risk of bias		HIGH / LOW / UNCLEAR	HIGH LOW UNCLEAR

Table 2-7

Equianalgesic dose table for cancer pain

Drug	PO Dose	PO: SC/IV Ratio	SC/IV Dose
Morphine	10 mg	2:1	5 mg
Codeine	100 mg	2:1	50 mg
Oxycodone*	5 mg	--	--
Hydromorphone	2 mg	2:1	1 mg
Methadone**	1 mg	--	Too irritating
Fentanyl- Infusion***	--	--	0.05 mg
Fentanyl Patch	Use chart supplied by manufacturer		
Morphine 10 mg PO=	Codeine 100mg PO Oxycodone 5-7.5mg PO Hydromorphone 2 mg PO Methadone 1 mg PO		

* The equianalgesic dose ratio of morphine to oxycodone is controversial. It appears to be between 1.5:1 and 2:1

** Many tables quote the equianalgesic dose ratio of morphine to methadone as being 1:1, i.e. morphine 1 mg PO= methadone 1 mg PO. This ratio was determined by using single dose studies. In cancer pain, when multiple doses are required the ratio of morphine to methadone becomes approximately 10:1, i.e. morphine 10 mg PO= methadone 1 mg PO

*** The equianalgesic dose ratio of morphine to fentanyl has not been accurately determined. It appears to be 100:1, i.e. morphine 1 mg SC= fentanyl 10 micrograms SC. The equianalgesic ratio between parenteral fentanyl and transdermal fentanyl patch is not well described, but appears to be approximately 1:1

Reference

Taken directly from
Pereira, J., & Bruera, E. (2001). *Alberta Hospice Palliative Care Resource Manual* (2nd ed.). Calgary, AB: Alberta Cancer Board.

Table 2-8

Equianalgesic dose table for non-cancer pain

	Equivalence to oral morphine 30 mg	To convert to oral morphine equivalent, multiply by:	To convert from oral morphine, multiply by:
Morphine	30 mg	1	1
Codeine	200 mg	0.15	6.67
Oxycodone	20 mg	1.5	0.667
Hydromorphone	6 mg	5	0.2
Meperidine	300 mg	0.1	10
Methadone and Tramadol	Morphine equivalence dose not reliably established		
Transdermal Fentanyl	60-134 mg morphine= 25 mcg/h 135-179 mg= 37 mcg/h 180-224 mg= 50 mcg/h 225-269 mg= 62 mcg/h 270-314 mg= 75 mcg/h 315-359 mg= 87 mcg/h 360-404 mg= 100 mcg/h		

Reference

Taken directly from:
DeGroote, M. (2010). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Retrieved from http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_appb08.html.

References

[1] McNicol E, Boyce DB, Schumann R *et al*. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med* 2008 Sep;9(6):634-659.

[2] Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician* 2006 Oct 15;74(8):1347-1354.

[3] Lee-Robichaud H, Thomas K, Morgan J *et al*. Lactulose versus Polyethylene Glycol for Chronic Constipation. *Cochrane Database Syst Rev* 2010(7):007570.

[4] Egger M, Davey-Smith G, O'Rourke K. Rationale, potentials, and promise of systematic reviews. In: Egger M, Davey-Smith G, Altman D, editors. Systematic reviews in healthcare: meta-analysis in context London, UK: BMJ Books; 2001. p. 3-19.

[5] Higgins J, Altman D. Chapter 8: assessing risk of bias in included studies. In: Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.0) Chichester, UK: John Wiley & Sons, Ltd.; 2008.

[6] Deeks J, Altman D, Bradburn M. Statistical methods for examining heterogeneity and combing results from several studies in meta-analysis. In: Egger M, Davey-Smith G, Altman D, editors. Systematic reviews in health care: meta-analysis in context London, UK: BMJ Books; 2001. p. 285-312.

[7] Caraccia-Economou D. Bowel management: constipation, diarrhea, obstruction, and ascites. In: Ferrell B, Coyle N, editors. Textbook of Palliative Nursing. 2nd ed. New York, NY: Oxford University Press, Inc.; 2006. p. 219-238.

[8] Higgins JP, Thompson SG, Deeks JJ *et al*. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-560.

[9] Cochrane IMS. RevMan. 2011; Available at: http://ims.cochrane.org/revman. Accessed Nov 17, 2011.

[10] Center for Reviews and Dissemination. Systematic reviews: CRD's guide for undertaking reviews in health care. University of York, UK: Center for Reviews and Dissemination; 2009.

[11] Thompson S. Why and how sources of heterogeneity should be investigated. In: Egger M, Davey-Smith G, Altman D, editors. Systematic reviews in health care: meta-analysis in context London, UK: BMJ Books; 2001. p. 157-175.

[12] Davey-Smith G, Egger M. Going beyond the grand mean: subgroup analysis in meta-analysis of randomized trials. In: Egger M, Davey-Smith G, Altman D, editors. Systematic reviews in health care: meta-analysis in context London, UK: BMJ Books; 2001. p. 143-156.

[13] Oxford Journals. Family practice. 2011; Available at: http://www.oxfordjournals.org/our_journals/famprj/about.html.

Chapter 3- The Systematic Review

Introduction

Opioid-induced constipation (OIC) is an unpleasant and ubiquitous side effect of opioid therapy. Whereas 2-10% of the general population suffers from constipation;[1] constipation associated with opioid use has been reported to be as high as 90% in patients with non-cancer pain,[2] and as high as 95% in patients with cancer pain.[3] Since opioids are prescribed for a number of pain conditions, including cancer pain, non-cancer pain, and drug management (e.g. methadone) programs, OIC is a prevalent clinical issue that can affect patients regardless of age, gender, and socioeconomic status. In addition, since opioids are the standard of care for moderate and severe pain management according to the World Health Organization's analgesic ladder,[4] OIC is a global clinical issue. Finally, the distress associated with OIC in affected patients can affect adherence,[2] quality of life,[5] morbidity[2,3,6], and possibly mortality.[6]

Definition

No widely accepted definition of OIC exists. As such, treatment of this clinical condition lacks robust research and little clinical evidence exists to guide treatment. In contrast, researchers in functional and chronic constipation, and even irritable bowel syndrome have thoroughly defined their clinical conditions including both frequency of bowel movements and associated signs and symptoms.[7,8] These definitions assist with early recognition, diagnosis, and ultimately, appropriate treatment. In fact, based on a MEDLINE search done by one of our authors, existing research for these clinical conditions is more

extensive and includes systematic reviews and clinical guidelines for treatment. Conversely, the only existing systematic reviews for OIC focus on treatment with opioid-antagonists.

Recognition of the signs and symptoms of OIC have led to a well described, but not all-encompassing condition called opioid bowel dysfunction (OBD). OBD is characterized by hard and dry stools, straining, feeling of incomplete evacuation, bloating, abdominal distention, and increased gastroesophageal reflux.[9] However, other signs and symptoms frequently associated with constipation include abdominal pain, nausea, vomiting, loss of appetite and headache.[3] In addition, OBD does not describe frequency of stool passage. Therefore, for the purposes of this paper, we define OIC as active opioid therapy in addition to at least one of the following: stools that are hard and difficult to pass, straining with bowel movement, and fewer than three stools per week. Furthermore, associated symptoms such as those described above, may or may not be present.

Pathophysiology

There are several mechanisms that lead to the constipating effects of opioids. The cumulative effect is constipation related to hard and dry stools, prolonged transit time, and ineffective gastric emptying. The binding of opioids with gut and central nervous system receptors inhibits the release of acetylcholine from the myenteric plexus, which has an inhibitory effect on neuron potential.[10] A decrease in peristalsis occurs shortly after opioid administration, and the subsequent constipating effects are dose-related.[3] This increases transit time of

intestinal contents, resulting in increased reabsorption of water and fecal impaction.[9] OIC is further complicated by a decrease in intestinal, gastric, biliary, and pancreatic secretions, which compounds this problem. Finally, an increase in anal sphincter tone, and a decrease in defecatory reflex interrupts the coordination required for effective colonic emptying.[11]

Treatment

Since little evidence exists to guide practice, pharmacologic intervention is frequently done on a trial and error basis, potentially resulting in negative outcomes. If the patient does not receive prompt relief, this results in reduced adherence to opioid treatment, decreased quality of life, and increased morbidity and mortality. Patients have reported they would rather suffer pain than constipation.[2] Accordingly, some would even rather endure pain than continue with opioid treatment.[12] Predictably, patients also report worsening quality of life scores as constipation and its associated symptoms worsen.[5] In addition, compared to non-constipated patients, constipated patients receiving opioid therapy for more than six months were more likely to visit their physicians, miss work, feel that their performance at work was impaired, and have symptoms that impaired their ability to undertake activities of daily living.[13] Finally, obstructive constipation causing life threatening bowel obstruction may require inpatient treatment or invasive surgery, resulting in lengthy hospital stays.[9,14]

Current strategies for the management of OIC include non-pharmacologic and pharmacologic means. Non-pharmacologic strategies include exercise, increased intake of fiber and fluids, and a regular toilet routine.[9] In our and other

institutions, typical trial and error regimens include use of sennosides and docusate sodium two to three times per day. If these medications are ineffective, lactulose, polyethylene glycol (PEG) granules, oral fleets, enemas, and suppositories are used.[15]

Objective

A recent systematic review by Lee-Robichaud, Thomas, Morgan, and Nelson[8] demonstrated superior clinically efficacy of PEG to lactulose in children and adults with *chronic* constipation. Therefore, we wanted to investigate whether or not PEG was superior to docusate sodium, sennosides, and lactulose in OIC in order to make evidenced-based treatment recommendations. The question that guided this review was: Do docusate sodium, sennosides, and lactulose used in constipation prevention and management of OIC have equal efficacy and adverse effect profiles compared to PEG granules in adults receiving opioid treatment for a variety of conditions?

Methods

An unpublished protocol was created and reviewed by the authors prior to beginning the systematic review. In anticipation of the study, we also completed an unpublished scoping review that determined that little evidence existed. Therefore, we expected that completed research articles comparing various treatment regimens for OIC would be minimal. To ensure that our search was as extensive as possible, we sought the support of two research librarians, one of whom had a special interest in pharmacy science. With their assistance we kept the search terms broad, in order to maintain an inclusive search strategy.

Search strategy

In December, 2010, we conducted a search of the databases Cochrane Central Registry of Controlled Trials (CENTRAL), MEDLINE, CINAHL, EMBASE, International Pharmaceutical Abstracts, Scopus, DARE, Web of Science, Proquest, Grey Matters and Grey Source. We did not restrict the year of publication, as the inclusion of PEG in the search terms would limit studies to when PEG was introduced in the early 1990s. Language was also not restricted in an attempt to discover all articles related to the topic, with the goal of translating relevant articles with support from colleagues or Google Translate™ where feasible. Moreover, we did not include any restrictions on age. Again, we wanted to have an inclusive search and felt that it would be easy to identify and exclude randomized controlled trials (RCTs) that focused solely on children. The keywords and MeSH terms used for MEDLINE can be seen in Table 3-1. Our research librarians adapted these keywords, so that appropriate search terms could be used in the other databases.

Screening other resources

In order to avoid publication bias, a thorough search of the grey literature was done via search engines outlined above. In addition, hand searching of reference lists, drug monographs, and conference proceedings was done to identify any further studies. The available conference proceedings that we reviewed were: Canadian Association of Nurses in Oncology, Oncology Nursing Society, American Society of Clinical Oncology (only relevant sections, i.e. we did not review breast cancer, prostate cancer, etc.), International Congress on

Palliative Care, American Gastroenterological Association, and Canadian Association of Gastroenterology. We also attempted to review the Canadian Society of Gastroenterological Nurses and Associates, and the Society of Gastroenterological Nurses and Associates; however, these associations did not keep previous conference proceedings. Since the publication studies using PEG for chronic constipation began in 1990, screening was limited to the start date of that that year through to 2011.

Study selection and data extraction

Studies were included if they met the following inclusion criteria: (i) Study design: RCT. (ii) Patient population: patients 18 years or older with constipation associated with chronic opioid use – e.g. chronic cancer or non-cancer pain, or substance withdrawal (i.e. methadone program); opioid dose must be reported for comparative purposes. (iii) Intervention: must compare at least one of – lactulose, docusate sodium, or sennosides – to PEG (PEG must be included in all studies); dosing for laxatives must be reported for comparative purposes. (iv) Setting of care: patients may be inpatients, outpatients, or palliative care patients. (v) Outcome measures: primary outcomes measures- efficacy (measures by frequency of bowel movements), quality of stool (hard, soft, or loose), secondary outcome measures – side effects, drug interactions, use of additional laxatives, relief of constipation associated symptoms.

Two of the reviewers (TK, KH) independently scanned the title, abstract, and keywords of every record retrieved against inclusion and exclusion criteria to determine which studies require further assessment. The same two authors

independently assessed those full articles for suitable inclusion in the study. Disagreements were managed by consensus, and a third author was consulted when necessary. Also, the same reviewers independently extracted data regarding details of study population, intervention, and outcomes using a standard data extraction form specifically adapted for this review. Interrater reliability was not assessed, as no articles fit the inclusion criteria, and only one article is included for discussion purposes. If necessary, two attempts were made to contact trial authors to provide missing data of the article included for discussion. Response was received for the article that will be discussed, but the necessary information required to meet full inclusion criteria was not available.

Validity assessment

Two researchers (TK, KH) independently performed quality assessment using the Cochrane Collaboration's tool for assessing risk of bias.[16] This tool was created to examine risk of bias in RCTs. It allows the assessor to search for potential sources of bias, including whether or not the trial performed sequence generation, allocation concealment, blinding, completed data, and selective outcome reporting, before giving an overall risk score to the article. Again, any disagreements were resolved by consensus.

Statistical methods

Although our protocol had planned rigorous statistical analysis, these were not required as no articles met the inclusion criteria.

Results

Study identification

Figure 3-1 (PRISMA diagram)[17] outlines our electronic searches. We retrieved 1572 references, 13 of which were selected for full article review. Regrettably, hand searching did not identify any further studies, but, reference list browsing did identify three articles. Unfortunately, none of the articles found in any of the searches met the full inclusion criteria. We have, nevertheless, included one article for discussion purposes – a study by Freedman, Schwartz, Roby, and Fleisher[18]. Table 3-2 describes the details of the included article (full data tables are available in supplementary data online). Had the authors reported the doses of methadone and PEG, the article would have met full inclusion criteria. We were able to contact one of the original authors who replied that these data were no longer available. As a research team, we felt that the study was a good example of what type of research is required in the future to address this topic.

Study quality

Risk of bias in the Freedman et al. study[18] (see Table 3-3) was scored as high for a few reasons. First, it was unclear whether or not allocation concealment actually occurred. Also, the way the study reported outcomes made it unclear whether or not only selective outcomes were reported. Finally, because doses of opioid and PEG were not reported it was difficult to assess whether or not the dosing of either drug affected frequency of bowel movements. For example, it was unclear if patients taking methadone were allowed to take higher doses of PEG, thus making it difficult to assess efficacy of the laxative. Although the

internal validity may have scored high for risk of bias, the study did have some strengths. The participants of the study were suffering from primary OIC (as patients with previous constipation or other causes of constipation were excluded), and the study design was similar to patient conditions in the real world, making the study's external validity sound.

Discussion

Statement of principal findings

At this time, there are insufficient studies to determine if PEG is superior to lactulose, docusate sodium, and sennosides for OIC. There were also insufficient studies to undertake statistical analyses of the available literature.

The Freedman et al. article[18] found no significant differences between PEG and lactulose. However, the generalizability of these results is questionable. First of all, the population was small (n=57) and no power calculation was reported, making it difficult to observe statistically significant differences between groups. Second, patients received each medication (lactulose and PEG) and the placebo for only two weeks. As such, they may have not received the drug long enough to detect any differences between groups.

Current context and future research directions

More randomized controlled trials are required related to patients with OIC. Although PEG's superiority has been determined in *chronic* constipation,[8] further research into laxative therapy is required for OIC. The pathophysiology that occurs with opioid administration differs from the pathophysiology of other

causes of constipation, including chronic constipation. Consequently, clinical evidence cannot be directly transferred between patient groups.

Trial design is important when considering limited resources to perform studies and the study quality required to change practice. Ideally, studies should report certain characteristics to allow for comparison among studies including, but not limited to dose of opioid, dose of laxative, and characteristics of constipation. Constipation should be reported according to an all encompassing standard definition that records at minimum: stools that are hard and difficult to pass, straining with bowel movement, fewer than three stools per week, and any other associated symptoms. This is especially important because the number of bowel movements per week does not always indicate whether or not constipation is present.[14] In addition, the adoption of a standard definition across studies is in accordance with the *Standards for the Reporting of Diagnostic Accuracy (STARD)*. Through research, these standards improve the precision and completeness of diagnostic accuracy; thus improving internal and external validity.[19]

Study design should also allow patients to be on laxative therapy for a period of time that would allow analysis of efficacy of treatment and the appearance of potential side effects. To observe short-term side effects, a minimum of 3-4 weeks of laxative therapy would be ideal. However, assessment of long-term efficacy would likely require several months of treatment. Other important study characteristics are the reporting of both laxative and opioid doses. This would allow for comparison among studies, statistical comparison (such as

meta-analysis), and calculation of confounding variables. Ultimately, since opioid medications are widely used throughout the world, with constipation being one of the most common side effects,[2,9] well-powered studies are achievable, and the time frame required for recruitment and data analysis is feasible. These trials would be relatively inexpensive, compared to protocols where costly opioid-antagonists require supplies and, in some cases, a health care professional to give the injection.

In the last decade, funded research for OIC has a strong focus on opioid antagonists such as naloxone, alvimopan, and methylnaltrexone. Although this research is important, we call for research on lactulose, docusate sodium, sennosides and PEG to gain a better understanding of the efficacy and side effect profiles of these laxatives, for several reasons. First, lactulose, docusate sodium, sennosides, and PEG are relatively inexpensive and easy for patients to use and adhere to. Clinicians can successfully teach patients how to self-titrate these medications based on the consistency of their stool.[18] Furthermore, these medications have relatively safe side effect profiles and are often available without a prescription. However, patients may still require evidence-based clinician guidance from registered nurses, nurse practitioners, or physicians. Second, opioid antagonists are indicated for use only when response to laxative therapy has not been sufficient. Arguably, if clinicians had high quality evidence to guide laxative decision-making in OIC, we may be able to increase laxative response and avoid the need for opioid antagonists. Third, laxative therapy is much more affordable than opioid antagonists. Whereas *each injection* of

methylnaltrexone bromide costs patients $35CAD (and they may require 2-3 injections per week); patients can use once daily dosing of generic brand PEG for $26CAD per *month*.[20]

Lack of research on constipation treatment has been an issue even prior to the introduction of the newer agents, such as the opioid antagonists. The widespread use of docusate sodium, sennosides, and lactulose for constipation prevention and management has been in our local hospitals for several years, without a solid research base. Currently, there is general lack of knowledge among prescribing clinicians that these treatment practices are not based on evidence. These prescribing practices occur because this has been the standard of practice for decades. Clinicians must recognize the lack evidence and the importance of supporting future research. An additional barrier to research, not only in constipation, is funding for drug trials. Models for funding are often based on breakthrough research to prove that a new medication is safe for use. Trials are often driven by economics, or potential for profit. Rarely do trials compare their drugs to current treatment. The goal is to demonstrate that a new medication is safe so that it can be brought to market, not to compare the efficacy of a new and more costly medication to the often cheaper existing treatment.

In the future, randomized controlled trials that investigate treatment for OIC should focus on a comparison of one of – lactulose, docusate sodium, or sennosides – to PEG. These comparisons are important since these are currently the most frequently used medications in the management of OIC. Furthermore, PEG's superiority and safety has already been proven in chronic constipation,[8]

making it a promising treatment for OIC. If similar results are found in OIC, it would eliminate the trial and error prescribing that currently exists. Prompt and effective treatment of OIC would also help decrease the negative effects associated with constipation.

Conclusions

OIC is a common side effect of opioid therapy. Insufficient evidence exists to determine the efficacy and side effect profiles of lactulose, docusate sodium, sennosides, and PEG in the treatment of OIC. A standard, and all-encompassing definition of OIC that reports stools that are hard and difficult to pass, straining with bowel movement, and fewer than 2-3 stools per week, and any other associated symptoms is essential. Such a definition would assist with standardization across studies and improve internal and external validity. More research is required to assist with evidenced based treatment of OIC. Studies that examine the efficacy of laxatives in OIC are feasible because these medications are inexpensive, and there are large patient populations in which to examine this research question. Large, international, well-designed studies to investigate this issue are encouraged.

Table 3-1

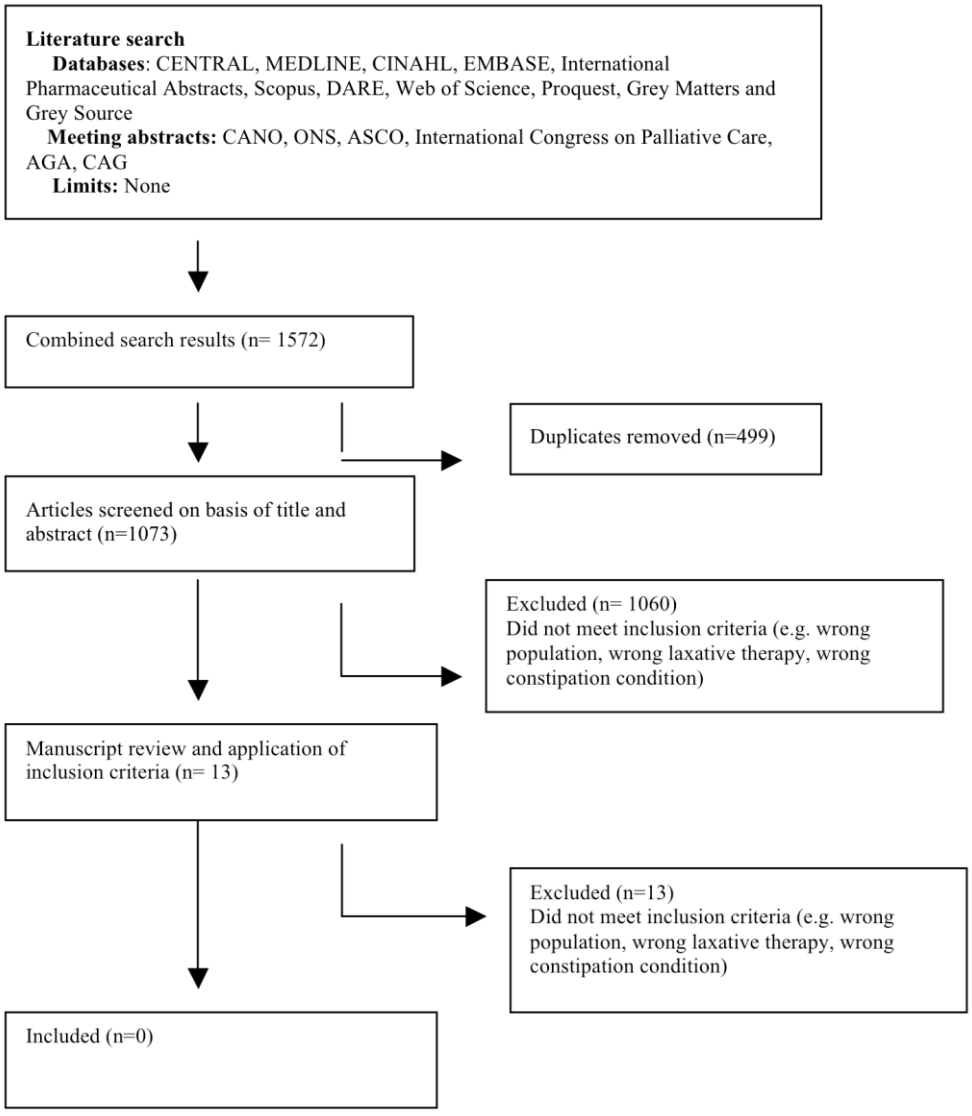
MEDLINE search terms

Searches	Results	Search Type
1	Constipation/	8859
2	(constipat* or dyschezia or colonic inertia or f?eces or f?ecal or retention or delayed bowel movement or obstipation or costiveness or irregular* or egest).tw.	213319
3	1 or 2	216243
4	laxatives/	252
5	3 and 4	160
6	Polyethylene Glycols/	29093
7	(peg or peg granules or laxaday or polyethylene glycol or ethylene glycol or ethylene oxide or PEO or polyethers or movicol or polyethylene glycol 3350 or miralax or glycoLax or GoLYTELY or glycolax or fortrans or trilyte or colyte).tw.	39368
8	6 or 7	54902
9	Dioctyl Sulfosuccinic Acid/	432
10	(colace or docusate sodium or docusate salt* or docusate calcium or sulfosucc* or dioctyl calcium sulfosuccinate or correctol or diocto or docusoft or dok or dos or ex-lax or sof-lax or gentlax or peri-colace or correctol).tw.	3107
11	9 or 10	3363
12	Lactulose/	1533
13	Senna Extract/	329
14	(senokot or sennosides or lactulose or disaccharide or generlac or cephulac or cholac or constilac or enulose or cilac or heptalac or actilax or duphalac or kristalose or apo-lactulose).tw.	8040
15	12 or 13 or 14	8584

16	11 or 15	11938
17	8 and 16	212
18	3 and 17	65
19	18 or 5	215

Figure 3-1

PRISMA flow diagram



CANO = Canadian Association of Nurses in Oncology; ONS= Oncology Nursing Society; ASCO= American Society of Clinical Oncology; AGA= American Gastroenterological Association; and CAG= Canadian Association of Gastroenterology

Table 3-2
Details of discussed article *Note: full data extraction can be seen on the online supplementary data (or Appendices B, C, and D)

Article	Setting/ Recruitment	Objective/ Definition of Constipation	Description of Interventions and Controls	Descriptions of Co-Intervention(s)	Inclusion/ Exclusion Criteria	Outcome/ Follow-Up	Results	Adverse Events
Freedman, M., Schwartz, J., Roby, R. & Fleisher, S. (1997) Tolerance and efficacy of polyethylene glycol 3350/ electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial	*Setting:* Outpatients on a methadone drug maintenance program *Recruitment:* Randomized to all three treatment regimens; used Latin square assignment Study described as double blind	*Objective:* To study PEG with electrolytes in treating non-organic constipation in methadone maintenance patients with constipation despite the use of lactulose *Definition:* not reported	1st week=control period; no interventions **Non PEG: *#1-*** Placebo; **Dose:** 240mL; **Route:** PO; **Timing**: Every night **#2-** Lactulose **Dose:** 30 mL; **Route:** PO; **Timing:** Every night **PEG 3350 WITH ELECTROLYTES** **Dose:** Not reported; **Route:** PO; **Timing:** Every night	**Co-Intervention:** Milk of magnesia **Dose:** Not reported **Route:** Not reported- but PO is most common **Timing:** as needed **Co-Intervention:** Dulcolax **Dose:** Not reported **Route:** Not reported **Timing:** as needed	**Inclusion:** *Methadone maintenance for remainder of study *Constipation *Previous use of laxatives *≥18 years of age **Exclusion:** *Women if pregnant or lactating *Patients with elevated TSH, history of colonic surgery, childhood constipation with ≥ 1 purgative procedure/ month, adult onset constipation , heme positive stool of unknown etiology, unreliable follow up examination, history of rectal bleeding	**Outcome Unit of Analysis:** Weekly stools (hard, soft, or loose) reported in patient self-reported diary **Length of Follow Up:** 7 weeks; 1 week control period follow by 2 weeks on either placebo, lactulose, or PEG.	*Lactulose and PEG resulted in fewer hard stools than placebo and control period *No significant differences between lactulose or PEG *Increased frequency of loose (diarrheal stools) with PEG compared to control; no change in electrolytes between groups *Increased requirements for co-interventions only in control period	**Side Effects for Non-PEG:** Reported adverse effects not significant compared to control **Side Effects for PEG:** *Increased frequency of loose stools compared with control; but no change in electrolytes **Other:** *No drug-related adverse reactions that resulted in withdrawal from study

Table 3-3
Risk of bias tool

The Cochrane Collaboration's tool for assessing risk of bias[16]

Study ID: Freedman, Schwartz, Roby, and Fleisher (1997). *Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate-induced constipation: A double-blinded placebo-controlled trial*.

Domain	Description	Review authors' judgment	Consensus (circle)
Sequence generation	"… cross over design utilizing a latin square assignment to evaluate 3 regimens in random order, was performed" (p. 905)	Was the allocation sequence adequately generated? YES / NO / UNCLEAR	YES NO UNCLEAR
Allocation concealment	Not reported	Was allocation adequately concealed? YES / NO / UNCLEAR	YES NO UNCLEAR
Blinding of participants, personnel and outcome assessors, *Outcome:*	Study is described as a "prospective, randomized, double-blinded cross over design" "…treatments included 240mL of identically flavored (1) placebo (water), (2) lactulose (30mL diluted with water to 240 mL), or (3) Go-lytely Lax." (p.905) Who prepared the medications and whether their packaging was similar was not described.	Was knowledge of the allocated intervention adequately prevented during the study? YES / NO / UNCLEAR	YES NO UNCLEAR
Incomplete outcome data, *Outcome:*	"57 drug dependent men and women who were enrolled in a methadone maintenance program" (p.905) were included. "57 patients completed the protocol" (p.905). There was no incomplete data.	Were incomplete outcome data adequately addressed? YES / NO / UNCLEAR	YES NO UNCLEAR

Selective outcome reporting	Patient diaries reported 1) number and consistency of stools, 2) completeness of evacuation, 3) requirements for additional milk of magnesia or dulcolax, 4) abdominal pain, 5) cramping, and 6) nausea. No other differences between groups, but only gas and cramping are reported on the results table.	Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR	YES NO UNCLEAR
Other sources of bias	Actual dose of methadone received by patients- is constipation or improvement of constipation related to this? Actual length of each treatment is not reported.	Was the study apparently free of other problems that could put it at a high risk of bias? YES / NO / UNCLEAR	YES NO UNCLEAR
Overall risk of bias	More than two domains are scored as not clear or not done	HIGH / MODERATE/LOW	HIGH MODERATE LOW

References

[1] Caraccia-Economou D. Bowel management: constipation, diarrhea, obstruction, and ascites. In: Ferrell B, Coyle N, editors. Textbook of Palliative Nursing. 2nd ed. New York, NY: Oxford University Press, Inc.; 2006. p. 219-238.

[2] Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 2007 Jul;61(7):1181-1187.

[3] Woolery M, Bisanz A, Lyons HF *et al*. Putting evidence into practice: evidence-based interventions for the prevention and management of constipation in patients with cancer. *Clin J Oncol Nurs* 2008 Apr;12(2):317-337.

[4] World Health Organization. WHO's pain ladder. 2011; Available at: http://www.who.int/cancer/palliative/painladder/en/index.html. Accessed Nov 17, 2011.

[5] Hjalte F, Berggren AC, Bergendahl H *et al*. The direct and indirect costs of opioid-induced constipation. *J Pain Symptom Manage* 2010 Nov;40(5):696-703.

[6] Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med* 2008 May;11(4):575-581.

[7] Rome Foundation. Appendix A: Rome III diagnostic criteria for functional gastrointestinal disorders. 2006; Available at: http://www.romecriteria.org/criteria/. Accessed Nov 17, 2011.

[8] Lee-Robichaud H, Thomas K, Morgan J *et al*. Lactulose versus Polyethylene Glycol for Chronic Constipation. *Cochrane Database Syst Rev* 2010(7):007570.

[9] Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg* 2001 Nov;182(5A Suppl):11S-18S.

[10] Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol* 2011 quiz 843; May;106(5):835-842.

[11] Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil* 2004 Oct;16(Suppl 2):17-28.

[12] Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage* 2002 Jul;24(1):71-90.

[13] Annunziata K, Bell T. Impact of opioid-induced constipation on healthcare resource utilisation and patient functioning. *Eur J Pain* 2006;10(suppl S1):S172.

[14] McNicol E, Boyce DB, Schumann R *et al*. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials. *Pain Med* 2008 Sep;9(6):634-659.

[15] Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician* 2006 Oct 15;74(8):1347-1354.

[16] Higgins J, Altman D. Chapter 8: assessing risk of bias in included studies. In: Higgins J, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.0) Chichester, UK: John Wiley & Sons, Ltd.; 2008.
[17] PRISMA. Transparent reporting of systematic reviews and meta-analyses. 2009; Available at: http://www.prisma-statement.org/. Accessed Nov 17, 2011.
[18] Freedman MD, Schwartz HJ, Roby R *et al*. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. *J Clin Pharmacol* 1997 Oct;37(10):904-907.
[19] STARD. STARD Statement. 2008; Available at: http://www.stard-statement.org/. Accessed Nov 17, 2011.
[20] Intelliware Development Inc. Shoppers Drug Mart: Health Watch. 2011;6.0.

Appendix A

Systematic Review Data Extraction Elements Form

Efficacy and Side-Effect Profiles of Lactulose, Docusate Sodium, and Sennosides compared to PEG in Opioid Induced Constipation

**Note:
Where the following information is not applicable to the study design, state: *Not applicable*
Where the following information is not reported, state: *Not reported*
Where the following information is unclear, state: *Unable to determine*

Table 2-3

- Identification
    - Refworks ID
    - Year
    - Country
    - Language
- Author information
    - Authors: Names of all authors in the following format – Author, A.B. - Last name, First Initial (or two initials if application)
    - Published
    - Unpublished
    - Contact Information
- Title
- Objective
    - Objective of study or research question
- Funding Organization
- Sample Setting- where the study occurred (i.e. oupatient, inpatient)
- Fidelity
    - Same dose?
    - Same time?
    - Same instruction given?
    - Any other notes about study intervention
- Definition of Constipation- use stated definition from authors
- Description of Interventions and Controls
    - Non-PEG intervention- state dose, route, timing
    - PEG intervention- state dose, route, timing
- Description of Co-Intervention(s)
    - Name of co-intervention(s) and dose, route, timing

Table 2-4

- Inclusion/Exclusion Criteria
    - Inclusion- as described by study authors
    - Exclusion- as described by study authors

- Recruitment Procedures Used:
    - Randomized- explain randomization procedures under 'describe'
    - Single blind- was only the research team or only the subject blinded?
    - Double blind- were both the subjects and researchers blinded?
        - Explain blinding procedures under 'describe'
- Characteristics of participants
    - Mean age- included mean age ± standard deviation (if present)
    - Gender- % of Males and % of Females (if not listed, calculate)
    - Ethnicity
    - Socioeconomic Status
    - Baseline characteristics-
        - Were patients treated previously for opioid induced constipation?
        - How long were patients on opioids?
        - What is their disease status (e.g. palliative)?
    - Co-morbidities
        - Why were they on opioids (e.g. post-op, cancer pain)?
        - Any other disease states that may affect constipation
- Opioid medication
    - List medication and dose, route, timing
    - Use morphine equivalency table if drug is not morphine
- Unit of Allocation/Number of Participants
    - Unit of Allocation
        - E.g. participant vs. GP office vs. other
        - What was the unit of allocation that was randomized?
    - Number of participants
- Participants included in analysis
    - Included in analysis- report N=, and calculate % (if not included in study)
    - Withdrawals/losses to follow up- report N=, and calculate % (if not included in study)
    - Report reasons for withdrawals/loss to follow up
- Type of analysis use
    - Report analysis used to account for loss of participants
    - ITT or other

Table 2-5

- Outcome and Follow Up
    - Outcome Unit of Analysis- How were bowel movements measured?
    - Length of follow up
- Instruments
    - What instruments were used?
    - What is their reliability/validity?

    - Expect instruments that measure associated symptoms of constipation or quality of stools
- Subgroup analysis or additional outcomes
    - Subgroups analysis- if done, describe:
- Outcomes
    - Were outcomes pre-specified?
    - Measurement Tool
- Statistical Techniques
    - Report statistical tests used for analysis
- Results of Study
    - How are results reported?
    - Are results dichotomous (expect- OR, RR, CI, p-values) or continuous (expect) mean difference with a CI
- Adverse events
    - Report side effects and drug interactions of non-PEG and PEG medication
    - Report any other adverse events
- Comments
    - Report any comments i.e. additional study limitations or important aspects to note

Appendix B

General information- identification/interventions

Identification	Author Information	Title	Objective of Study	Funding Organization	Sample Setting	Definition of Constipation	Description of Interventions and Controls	Descriptions of Co-Intervention(s)
RefWorks ID: Year: 1997 Country: USA Language: English Contact Information: Michael D. Freedman, M.D., F.A.C.P., F.C.P. Department of Medicine New Children's Hospital and Center for Reconstructive Surgery 3825 Greenspring Ave Baltimore, MD 21211-1398	Authors: Freedman, M., Schwartz, J., Roby, R. & Fleisher, S. X Published ☐ Unpublished	Tolerance and efficacy of polyethylene glycol 3350/ electrolyte solution versus lactulose in relieving opiate induced constipation: A double-blinded placebo-controlled trial	To study PEG with electrolytes in treating non-organic constipation in methadone maintenance patients with constipation despite the use of lactulose	☐ Pharmaceutical Company X Other (describe): Not reported	Outpatients on a methadone drug maintenance program	Not reported	1st week=control period; patients received no interventions Non PEG: Placebo Dose: 240mL Route: PO Timing: Every night Non-PEG: Lactulose Dose: 30 mL Route: PO Timing: Every night PEG 3350 WITH ELECTROLYTES Dose: Not reported Route: PO Timing: Every night	Co-Intervention: Milk of magnesia Dose: Not reported Route: Not reported- but PO is most common Timing: as needed Co-Intervention: Dulcolax Dose: Not reported Route: Not reported Timing: as needed

Appendix C

Participant characteristics

Inclusion/Exclusion Criteria	Recruitment Procedures Used	Characteristics of Participants	Opioid Medication	Unit of Allocation/ Number of Paticipants	Patricipants Included in Analysis /Withdrawals	Type of Analysis Used
Inclusion: *On methadone maintenance with constipation; plan to continue the methadone program for another 7 weeks *Previous use of laxatives *≥18 years of age Exclusion: *Women who were pregnant or lactating *Patients with elevated TSH, history of colonic surgery, childhood constipation requiring more than 1 purgative procedure per month, adult onset constipation predating methadone use, heme positive stool of unknown etiology, those with unreliable follow up examination, those with a history of rectal bleeding	X Randomized ☐ Single Blind X Double Blind Describe: Randomized to all three treatment regimens; used Latin square assignment Study described as double blind (drug preparation was not mentioned) patients received all 3 identically flavored treatments	Mean age: Not reported; range = 18-50 Gender: %M; %F- Not reported Ethnicity: Not reported SES: Not reported Baseline characteristics: Physical exam prior to study- see exclusion criteria Co-morbidities: Patients were healthy prior to entering study- see exclusion criteria	Opioid Medication: Methadone Dose: Not reported Route: Not reported, but likely PO Timing: Not reported Morphine equivalency table conversion: Unable to convert as methadone dose not reported	Unit of Allocation: Participant Number of Participants: N= 57	Included in Analysis: N=57; 100 % Withdrawals/Lost to Follow-up: N=0; 0% Reasons:	☐ Intention-to-treat X Other (describe): Not applicable

Appendix D

Outcomes

Outcome and Follow Up	Instruments	Subgroup Analysis or Additional Outcomes	Outcomes	Statistical Techniques	Results of Study	Adverse Events	Comments
Outcome Unit of Analysis: Weekly stools (hard, soft, or loose) Length of Follow Up: 7 weeks; but length of time on each treatment not reported.	Instrument Used: Self-reported diary Reliability/ Validity: Reliability and validity not tested	☐ Sub-group analysis If yes, describe: Not applicable Drug interactions: Not reported Relief of Associated Symptoms: Lactulose and PEG appeared to be just as potent in reducing the number of hard stools induced by the use of methadone	X Yes- outcomes were pre-specified Outcomes: 1) total number/ consistency of stool (hard, loose, or soft) 2) completeness of evacuation 3) requirements for additional milk of magnesia or dulcolax 4) abdominal pain 5) cramping 6) nausea *Vital signs, CBC, and electrolytes done at the conclusion *Gas was also reported, but ? how measured	*Frequency of stools, adverse effects, and effectiveness were tabulated for each treatment and control periods *Differences in the treatment periods= independent Student's t-test *Data were expressed as mean $\pm$ SEM *All p values $\leq$0.05 were accepted as significant *Equivalence between the material was concluded if 90% of confidence intervals overlapped	*Lactulose (0.98$\pm$0.23) and PEG (1.06$\pm$0.18)- fewer hard stools than placebo (1.75$\pm$0.24; $p<0.01$) and control (2.08$\pm$0.27; <0.03) *No significant differences between lactulose or PEG *All three treatments- fewer hard stools than during the 1st week without treatment (except placebo) *Increased frequency of loose/diarrheal stools with PEG (2.24$\pm$0.34) compared to control (0.09$\pm$0.04; $p<0.01$); no change in electrolytes between groups	Side Effects for Non-PEG: Reported adverse effects not significant compared to control (Frequency of excess gas= 3.60$\pm$0.41 compared to 2.83$\pm$0.42) Side Effects for PEG: *Increased frequency of loose stools compared with control ($p<0.01$); but no change in electrolytes resulted	*Study used PEG 3350 with electrolytes; changes in electrolytes may have been prevented by the PEG electrolytes *Dose of PEG was not reported *Only 2 weeks on each treatment arm *Dose of methadone was not reported- so it will be difficult to compare to other studies *Gas not on the diary items- how was it measured?

			Measurement Tool: Self-reported symptom diary-recording all of the above		*Increased co-interventions only during control period *Constipation reduction with placebo not statistically significant	Other: *No drug-related adverse reactions that resulted in withdrawal from study	