



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



TITLE: Diocetyl Sulfosuccinate or Docusate (Calcium or Sodium) for the Prevention or Management of Constipation: A Review of the Clinical Effectiveness

DATE: 26 June 2014

CONTEXT AND POLICY ISSUES

Constipation has many definitions and is often described differently depending on the population queried. Many physicians define constipation as a reduction in the frequency of bowel movements to fewer than three times per week while patients identify more with the symptoms associated with constipation such as difficulty passing stool, hard stool consistency, feelings of abdominal cramping, and feelings of incomplete stool passage.¹ Causes of constipation may be primary (idiopathic) or secondary to other factors such as diet, medication, or medical conditions.² Constipation can affect anyone as a minor annoyance but up to a quarter of the population experiences it chronically or severely.² It can substantially affect quality of life and be debilitating.² It is estimated that between 2% to 27% of the population are affected depending upon the definition of constipation used.¹

Chronic constipation is a significant problem in the elderly,^{1,3} in patients with chronic conditions,³⁻⁵ and in patients receiving opioids as part of a treatment regimen.⁵⁻⁷ Up to 20% suffer from chronic constipation in the community-dwelling elderly population while this number increases to approximately 50%¹ to 75%³ in institutionalized elderly patients. Approximately 90% of patients treated with opioids for non-cancer pain suffer from constipation with this number rising to 95% in patients treated for cancer pain.⁶ Chronic constipation can be defined using any one of three options: the Rome III criteria for functional constipation, the American College of Gastroenterology definition, or the American Gastroenterological Association definition.¹

Current treatment options include dietary or bulking agents (i.e. psyllium seed husk), osmotic laxatives (i.e. lactulose, sorbitol, polyethylene glycol [PEG]), stimulant laxatives (i.e. sennosides, bisacodyl, sodium picosulfate), and stool softeners (i.e. docusate sodium or calcium).^{1,2} In North America, docusate and a stimulant laxative such as sennosides are commonly used in bowel treatment protocols associated with institutionalized elderly⁴ and oncology treatments.⁵ A paucity of evidence is available to support the use of the stool softener docusate yet it continues to be prescribed in everyday clinical practice for the aforementioned populations.⁴⁻⁶ While the

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actual cost of docusate is low, additional costs associated with its administration (i.e. nursing time) and its widespread use can be significant. Therefore, this review was undertaken to determine the clinical effectiveness of docusate for the prevention or management of constipation.

RESEARCH QUESTION

1. What is the clinical effectiveness of dioctyl sulfosuccinate or docusate (calcium or sodium) for the prevention or management of constipation?

KEY FINDINGS

There remains a paucity of good quality evidence to support the use of docusate for the prevention or management of constipation in hospitalized patients or long-term care residents. Docusate appears to be no more effective than placebo for increasing stool frequency or softening stool consistency. Furthermore, it does not appear to lessen symptoms associated with constipation (i.e. abdominal cramps) or affect the perceptions associated with completeness of or difficulties with stool evacuation. More robust, high quality primary studies are required to definitively ascertain the clinical effectiveness of docusate for the prevention and management of constipation, no matter what its cause.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and May 27, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adult patients with constipation and/or for whom prevention of constipation is desired (in hospital and/or long-term care settings)
Intervention	Dioctyl sulfosuccinate or docusate (provided in either a calcium or sodium salt)
Comparator	<ul style="list-style-type: none"> • Placebo • Other management methods
Outcomes	Measurable clinical changes in bowel function
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to January 1, 2004. Health technology assessments, meta-analyses, and systematic reviews (SR) were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The AMSTAR⁸ tool was used to guide the critical appraisal of the methodological quality of the SRs included in this report. Emphasis was placed upon the methods used to conduct the literature search, study selection, quality assessment, data extraction, and data summarization. Using the Downs and Black Checklist,⁹ an assessment of the study design, reporting, representativeness of populations, and sample size were included for the non-randomized studies. The randomized controlled trial (RCT) was also appraised using the Downs and Black Checklist⁹ and included assessments of, but not limited to, allocation concealment and blinding.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified a total of 367 citations. Of these, 352 citations were excluded during the title and abstract screening and 15 potentially relevant articles were retrieved for full-text review. In addition, 3 potentially relevant reports were retrieved by a literature search from other sources (i.e. grey literature). Five studies were included in the review including two SRs, one RCT, and two non-randomized studies.

A PRISMA diagram demonstrating the study selection process is presented in Appendix 1.

Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

Two SRs,^{6,7} one RCT,⁴ and two non-randomized studies^{3,5} were included in this review. Detailed study characteristics are provided in Appendix 3.

The SRs originated in Canada⁶ and the United Kingdom.⁷ Both aimed to examine the management of constipation in patients prescribed opioids for either chronic-non cancer pain or cancer pain, with Ahmedzai and Boland⁷ observing the effectiveness and harms of many laxative regimens (including docusate) and Ruston et al.⁶ primarily focusing on the efficacy and harms of docusate sodium, sennosides, and lactulose compared to PEG.⁷ The SR by Ahmedzai and Boland,⁷ which included prospective and retrospective RCTs, SRs, and comparative cohort studies, identified one SR that met their inclusion criteria. This SR included four RCTs on docusate calcium compared to placebo; however, further data was not reported from three of the four RCTs due to weak methodology (reasons included: no definition of constipation or evaluation of constipation prior to start of study, no statement on how randomization was performed, and no analysis by intention-to-treat).⁷ Therefore, they included data from only one RCT (N=22).¹⁰ The other SR by Ruston et al. did not identify any relevant evidence.⁶

Two of the primary studies examined the management of constipation^{3,4} and the other observed both the prevention and management of constipation.⁵ Two of the three primary research studies originated in Canada^{4,5} while the other originated in Norway.³ Two primary studies observed elderly populations in either a hospice⁴ or nursing home³ setting while the other examined patients that had been admitted to a cancer center for treatment.⁵ Patients in the hospice setting were close to the end of life (mean age of approximately 72 to 75 years),⁴ those in the nursing home had various chronic co-morbidities (mean age of 85.6 years),³ and those in the Hawley and Byeon study had many different types of cancer (mean age of approximately 59 to 63 years).⁵ In addition, all of these studies had a certain proportion of their populations receiving opioids for either chronic non-cancer pain^{3,4} or cancer pain.³⁻⁵ The RCT by Tarumi et al.⁴ observed patients receiving oral docusate sodium with sennosides versus sennosides alone for the management of constipation (N=74) while the sequential cohort study by Hawley and Byeon⁵ examined either orally administered sennosides alone or sennosides plus docusate sodium treatment regimen for the prevention and management of constipation (N=60). Fosnes et al.³ observed a cross-section of elderly patients admitted to a nursing home treated with one of a number of different laxatives administered regularly or on demand (N=197). These laxatives were categorized according to the Anatomical Therapeutic Chemical Classification System (ATC) level five and included softeners/emollients (liquid paraffin), contact laxatives (bisacodyl, senna glycosides, and sodium picosulphate), bulk laxatives (ispaghula), osmotic laxatives (lactulose and macrogol combinations), and enemas (docusate sodium and laurilsulfate suppositories were included in this category).

Summary of Critical Appraisal

Details of the critical appraisal are provided in Appendix 4.

Both SRs^{6,7} reported rigorous methodology that included descriptions of comprehensive literature searches, with Ruston et al.⁶ additionally performing prescoping searches and Ahmedzai and Boland⁷ obtaining numerous alerts regarding harms data. In addition, both had clearly defined *a priori* research questions and inclusion criteria. Ruston et al.⁶ also clearly described the data selection and extraction methods using a two-author system and the statistical analysis that would have been used if any evidence had fit their inclusion criteria. The SR by Ahmedzai and Boland⁷ included grading of their evidence; an interesting caveat to this being that the grading was performed on the outcomes and populations of interest only and not necessarily on the methodological quality of the included studies themselves. The one study that provided information on the effectiveness of docusate for their SR was an RCT.⁷ Authors from both reviews declared their conflicts of interest.^{6,7}

All three of the primary studies had clearly defined objectives, outcomes of interest, and reported baseline patient characteristics.³⁻⁵ Standardized or specified tools that recorded stool frequency,⁴ consistency,^{3,4} and volume⁴ were used in two of the three studies^{3,4} while the third study used a chart review.⁵ The Tarumi et al.⁴ study included a sample size calculation in order to ascertain appropriate statistical power;⁴ however, an important limitation to note included the lack of a specified allocation concealment in this RCT.⁴ Two non-randomized studies had inadequate sample sizes^{3,5} while all three involved numerous healthcare providers which could have potentially introduced confounding into the administration of the laxatives or the accurate reporting of symptoms or outcomes.³⁻⁵ Docusate use was not observed in many patients in the Fosnes et al. study³ and, therefore, not much could be determined regarding its effectiveness. Hawley and Byeon reported discrepancies between their two cohorts whereby the second cohort had a larger population of those with one specific type of cancer thus potentially

confounding the results.³ Authors in two of the studies declared conflicts of interest.^{3,4} Conflict interests were not declared in the Hawley and Byeon study,⁵ however, specifics in funding were declared.

Summary of Findings

Detailed findings are provided in Appendix 5.

Four of the five citations identified for this review did not report any increased clinical effectiveness at either reducing symptoms associated with or for the prevention of constipation upon the administration of docusate sodium³⁻⁵ or docusate calcium.⁷ The fifth review was unable to identify RCTs that examined the use of docusate sodium, sennosides, or lactulose compared to PEG for the management of opioid-induced constipation.⁶

The included publications focused on the management of constipation in populations (or subsets of the populations) that were either being treated with opioids for malignancy pain^{3-5,7} or for pain associated with other chronic non-malignant disease.^{3,4,7} In addition, the management of constipation in some patients not taking opioids was included in the analysis of two primary studies.^{3,4} In patients prescribed opioids, docusate (calcium⁷ or sodium⁴) appeared no more effective than placebo⁷ or sennosides alone (when observing a sennosides plus docusate sodium versus sennosides alone protocol⁴) at increasing stool frequency, softening stool consistency,^{4,7} in lessening perceptions of difficulty associated with evacuation,⁴ in perceptions of evacuation completeness,⁴ or for relieving others characteristics associated with opioid-induced bowel dysfunction (e.g. abdominal cramps or delayed gastric emptying).⁷ In one of the primary studies involving a stepwise (increased dosing) schedule involving either sennosides and docusate sodium or sennosides alone in cancer patients, the frequency of bowel movements increased in those taking the sennosides alone protocol⁵. In addition, a sub-analysis involving symptom control / supportive care showed that patients following the sennosides alone protocol had statistically significantly more bowel movements and had bowel movements on more than 50% of days when compared to those following the docusate and sennosides protocol (62.5% versus 31.6%, respectively).⁵ Normalization of stool frequency or consistency was not achieved in 41% of nursing home residents that were treated with one of numerous laxatives regimens in the cross sectional study; however, this examined many laxatives and the results for those treated with docusate were not specified.³

Bowel care interventions, whereby rescue medications were provided to induce bowel movements if the laxative regimens were not successful, were either reported in the included studies^{4,5,10} or not specified (due to the cross sectional study design which observed numerous laxative regimens).³ The Tarumi et al. study⁴ did not observe any statistical significance in these reported interventions when comparing the docusate plus sennosides to the sennosides alone groups in hospice patients (68.6% versus 74.4%, respectively). In contrast to this, Hawley and Byeon⁵ reported a statistically significant 57% of cancer patients in the docusate plus sennosides protocol requiring additional interventions (lactulose, suppositories, or enemas) when compared to cancer patients following the sennosides alone protocol (40%) in their symptom control/supportive care subanalysis.⁵

Limitations

While the number of reviews included in the Ahmedzai and Boland⁷ SR was large, only one RCT (that was part of the SR they included in their analysis) informed their conclusions

regarding the use of docusate for the prevention or management of constipation. This RCT¹⁰ was determined to be of lower quality and included only 22 patients, many of which received additional interventions apart from their laxative protocol.

Sample sizes were also an issue in two of the three primary studies included in this review.^{3,5} In the study by Fosnes et al.³ there was a large cohort of patients included in the study; however, only five patients were actively using docusate to manage their constipation. Another aspect similar to other studies included in this review, was the fact that patients were able to access additional bowel interventions if necessary.^{4,5,10} While these interventions were primarily provided to those whose treatment regimens appeared insufficient, this still may have introduced confounding as, perhaps, the treatments had not yet had enough time to work or the effect was due to the rescue medications and not the docusate.

As previously stated, Fosnes et al.³ observed numerous laxative regimens and did not focus on one specific laxative; therefore, little can be inferred with regard to the clinical effectiveness of docusate from this study. Information from this cross sectional observation appeared to be representative of the nursing home population (e.g. various underlying medical conditions, elderly bedridden and ambulatory) yet its incorporation of the frail and mentally reduced most likely reduced the data quality (as some patients themselves provided information on their bowel movements).³ Furthermore, this study primarily observed laxative “types” (i.e. osmotic, stimulant, etc.) and categorized them according the ATC level five criteria. Therefore, according to these criteria, docusate (administered as a suppository) was classified in the enema category³ and thus this may reduce its generalizability in a population taking oral docusate.

The RCT by Tarumi et al.⁴ compared the clinical effectiveness of docusate and sennosides to sennosides and placebo. While there was no clear benefit of the addition of docusate to sennosides for the management of constipation, one must take into account the potential issues associated with this hospice population. These patients were primarily at the end of their life (as the RCT reported that the median length of stay was 16 days and most were discharged at death⁴) and their bodies may have been in the process of shutting down. Numerous items to consider would have been whether the patients were eating and, if they were, what the consistency of their food was like. These aspects, along with disease-stage, could all have played a role in the state of constipation or in the clinical effectiveness of the aforementioned treatments. The authors did note that the lack of statistical significance between the groups may not definitively indicate that docusate was no better than placebo for the treatment of constipation as there was an inability to control for additional interventions, other medication use, and there was no internal measure of the assay sensitivity.⁴

Another additional issue relating to all three of the primary studies³⁻⁵ was that observations of the treatments were done at numerous settings. This introduces variation in how nurses and researchers attain information (even in the presence of standardized or validated tools). Hawley and Byeon⁵ specifically mentioned the diversity in the healthcare providers and how, being an un-funded study, the investigators could not be continually present to ensure consistency in reporting. In addition, even though all staff were alerted to the ongoing study, many healthcare providers would have been unaware that their patients were involved; thus increasing the possibility that the reporting of bowel movements may not have been accurately ascertained.⁵ In addition, two of the primary studies reported the use of standardized or specified tools used to analyze various aspects of the stool frequency, consistency, and volume.^{3,4} However, none of these types of tools were specified in the Hawley and Byeon study; alternately, they assessed

outcome data by nursing chart review.⁵ Therefore, it is uncertain whether inconsistencies may have been introduced by reporting this way.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The lack of clinical evidence supporting the use of docusate for the prevention or management of constipation is problematic in determining its clinical efficacy, particularly as it is prescribed as a part of many bowel protocols in North America.⁵ While more rigorous and larger RCTs are required to definitively ascertain the clinical effectiveness of docusate, the available evidence suggests that docusate is no more effective than placebo in the prevention or management of constipation. The primary³⁻⁵ and secondary⁷ studies included in this review all indicated that docusate did not increase stool frequency or soften stool consistency. Furthermore, many of the other characteristics associated with opioid-induced bowel dysfunction (i.e. abdominal cramps) and the perceptions surrounding the difficulties and the completeness of evacuation were unchanged with the use of docusate. The studies were limited by inadequate sample sizes, the use of additional bowel medications (rescue medications) which may have confounded the results, and the potential lack of consistent data capture involving multiple health care providers. Furthermore, the study results are mostly generalizable to patients with opioid induced constipation. Until further evidence is available, decision-makers need to determine if the status quo is suitable for their patients and their budgets with regard to prescribing docusate for the management or prevention of constipation.

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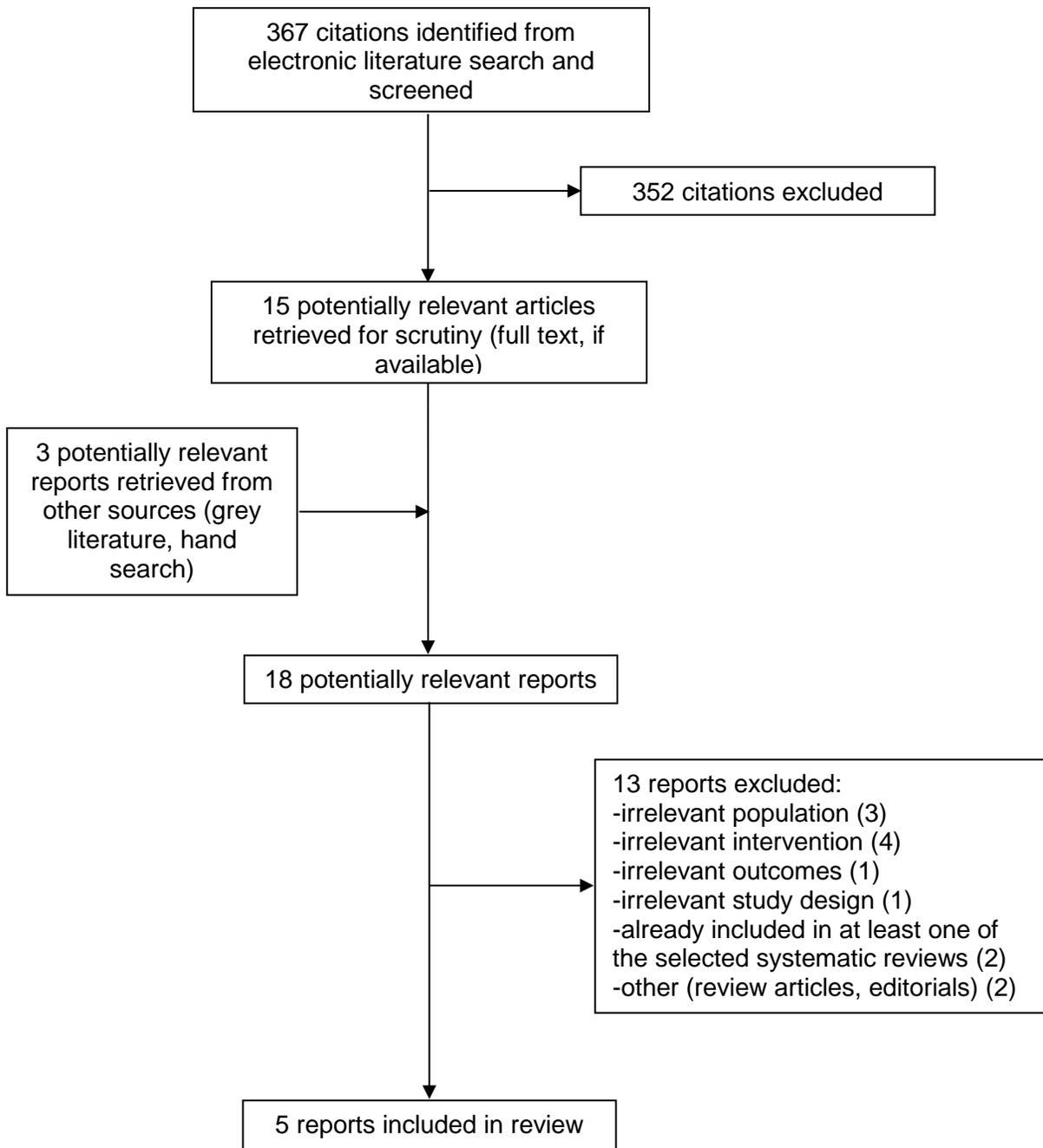
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REFERENCES

1. Gallagher PF, O'Mahony D, Quigley EM. Management of chronic constipation in the elderly. *Drugs Aging*. 2008;25(10):807-21.
2. Tack J, Muller-Lissner S, Stanghellini V, Boeckstaens G, Kamm MA, Simren M, et al. Diagnosis and treatment of chronic constipation--a European perspective. *Neurogastroenterol Motil* [Internet]. 2011 Aug [cited 2014 Jun 2];23(8):697-710. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170709/pdf/nmo0023-0697.pdf>
3. Fosnes GS, Lydersen S, Farup PG. Effectiveness of laxatives in elderly--a cross sectional study in nursing homes. *BMC Geriatr* [Internet]. 2011 [cited 2014 Jun 2];11:76. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3226585/pdf/1471-2318-11-76.pdf>
4. Tarumi Y, Wilson MP, Szafran O, Spooner GR. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *J Pain Symptom Manage*. 2013 Jan;45(1):2-13.
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):575-81.
6. Ruston T, Hunter K, Cummings G, Lazarescu A. Efficacy and side-effect profiles of lactulose, docusate sodium, and sennosides compared to PEG in opioid-induced constipation: a systematic review. *Can Oncol Nurs J*. 2013;23(4):236-46.
7. Ahmedzai SH, Boland J. Constipation in people prescribed opioids. *Clin Evid* (Online) [Internet]. 2010 [cited 2014 Jun 2];2010. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907601/pdf/2010-2407.pdf>
8. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2014 Jun 24];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>
9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* [Internet]. 1998 Jun [cited 2014 Jun 24];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>
10. Castle SC, Cantrell M, Israel DS, Samuelson MJ. Constipation prevention: empiric use of stool softeners questioned. *Geriatrics*. 1991 Nov;46(11):84-6.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Potentially Relevant Additional References

Pitlick M, Fritz D. Evidence about the pharmacological management of constipation, part 2: implications for palliative care. *Home Healthc Nurse*. 2013 Apr;31(4):207-18.

[PubMed: PM23549252](#)

Connolly M, Larkin P. Managing constipation: a focus on care and treatment in the palliative setting. *Br J Community Nurs*. 2012 Feb;17(2):60, 62-0, 67.

[PubMed: PM22306597](#)

Mueller-Lissner SA, Wald A. Constipation in adults. *Clin Evid (Online)* [Internet]. 2010 Jul [cited 2014 Jun 24]; 2010. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217654>

[PubMed: PM21418672](#)

See: Option Docusate, page 16

Patel M, Schimpf MO, O'Sullivan DM, LaSala CA. The use of senna with docusate for postoperative constipation after pelvic reconstructive surgery: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol*. 2010 May;202(5):479-5.

[PubMed: PM20207340](#)

Khaja M, Thakur CS, Bharathan T, Baccash E, Goldenberg G. 'Fiber 7' supplement as an alternative to laxatives in a nursing home. *Gerodontology*. 2005 Jun;22(2):106-8.

[PubMed: PM15934353](#)

APPENDIX 3: Characteristics of Included Studies

Table 2: Summary of Clinical Review and Trial Characteristics			
Author(s), Publication Year, Country	Trial Design, Population, N	Intervention, Dosing Regimen	Outcomes
<i>Systematic Reviews</i>			
Ahmedzai and Boland, ⁷ 2010 UK	<ul style="list-style-type: none"> Search period up to July 2009 <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Published SRs, RCTs, open, and blinded studies (max. loss to follow-up of 30% / year), prospective and retrospective comparative cohort studies (harms only) People prescribed opioids 	<ul style="list-style-type: none"> Oral laxatives Rectally applied medications Opioid Antagonists 	<ul style="list-style-type: none"> BM frequency Stool consistency Abdominal pain and discomfort Completeness of evacuation AEs (nausea, vomiting) Small bowel transit time
Ruston et al., ⁶ 2013, Canada	<ul style="list-style-type: none"> Search period up to September 2012 <p>Inclusion criteria:</p> <ul style="list-style-type: none"> RCTs Adults ≥18 years of age, constipation associated with chronic opioid use (for cancer and non-cancer pain or substance withdrawal), in- or out-patients or palliative care 	PEG compared to one of the following: <ul style="list-style-type: none"> Lactulose DS S 	<p>Primary outcomes of interest:</p> <ul style="list-style-type: none"> Efficacy (frequency of BM) Quality of stool (hard, soft, or loose) <p>Secondary outcomes of interest:</p> <ul style="list-style-type: none"> AEs Drug interactions Additional laxative use Relief of constipation associated symptoms

Table 2: Summary of Clinical Review and Trial Characteristics

Author(s), Publication	Trial Design, Population,	Intervention, Dosing Regimen	Outcomes
<i>Randomized Controlled Trial</i>			
Tarumi et al., ⁴ 2013, Canada	<ul style="list-style-type: none"> Prospective, multicentre, DB, PL- controlled RCT (10 day trial) Adults ≥ 18 years of age with cancer, newly admitted hospice residents, able to take oral meds, no gastrointestinal stoma, PPS score of ≥ 20%, Folstein MMSE score of > 23; expanded criteria to include patients with non-malignant disease and those not taking opioids N = 74 	<p>DS Group (n=35):</p> <ul style="list-style-type: none"> 2 x 100 mg DS BID capsules (morning and late afternoon) plus, 1 to 3 S (8.6 mg) tablets QD to TID <p>PL Group (n=39):</p> <ul style="list-style-type: none"> 2 x PL BID in addition to 1 to 3 S (8.6 mg) tablets QD to TID 	<p>Primary outcomes:</p> <ul style="list-style-type: none"> Stool frequency Stool volume Stool consistency <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Type/frequency of additional bowel care interventions Difficulty/completeness of evacuation Symptoms possibly related to constipation^f
<i>Non-Randomized Studies</i>			
Fosnes et al., ³ 2011, Norway	<ul style="list-style-type: none"> Cross-sectional study Adults ≥ 60 years of age; nursing home residents; some mobile, some bedridden; using laxatives regularly or on demand N = 197 	<p>Laxative Interventions:</p> <ul style="list-style-type: none"> Osmotic (lactulose, macrogol combinations) Contact(bisacodyl, senna glycosides, sodium pico sulphate) Bulk (ispaghula [psylla seeds]) Enemas^a (docusate sodium, laurilsulfate) Softeners/Emollients (liquid paraffin) <p>Dosing Schedules:</p> <ul style="list-style-type: none"> On demand Regular use (standard dose) – this was the dosing schedule for docusate Regular use (high dose^b) 	<ul style="list-style-type: none"> Normalization of bowel function^c

Table 2: Summary of Clinical Review and Trial Characteristics

Author(s), Publication	Trial Design, Population,	Intervention, Dosing Regimen	Outcomes
Hawley and Byeon, ⁵ 2008, Canada	<ul style="list-style-type: none"> • Nonrandomized, nonblinded sequential cohort study (total of 488 days of observation) • Hospitalized cancer patients (80% taking opioids); 8.4 ± 2.5 days vs 7.8 ± 2.7 days on bowel protocol in the DS+S vs S protocol, respectively • N = 60 	<p>DS+S Protocol:^d (n=30) Step 1: DS 200 mg po BID Step 2: DS 200 mg po BID + S 17.2 mg po q hs Step 3: DS 200 mg po TID + S 17.2 mg po BID (if no BM in past 48 hrs) Step 4: DS 200 mg po TID + S 17.2 mg po TID (if no BM in next 24 hrs) Step 5: DS 200mg po TID + S 25.8 mg po TID (if no BM after a further 24 hrs)</p> <p>S-only Protocol:^e (n=30) Step 1: S 17.2 mg po qhs Step 2: S 17.2 mg po BID (if no BM in past 48 hrs) Step 3: S 17.2 mg po TID (if no BM in next 24 hrs) Step 4: S 25.8 mg po TID (if no BM after a further 24 hrs)</p> <ul style="list-style-type: none"> • DS administered as a capsule • S administered as a tablet 	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Proportion of total days with at least 1 BM/day • Proportion of patients with BM at least 40% or at least 50% of days <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Use of enemas, suppositories, or lactulose • Reported cramping and/or diarrhea

AE = adverse events; BID = twice daily; BM = bowel movement; DS+S = docusate-plus-sennosides; DB = double blind; DS = docusate sodium; hrs = hours; MMSE = Mini-Mental Status Examination; PEG = polyethylene glycol; PL = placebo; po = orally; PPS = Palliative Performance Scale; QD = once daily; qhs = at bedtime; RCT = randomized controlled trial; S = sennosides; SR = systematic review; TID = three times daily.

^a Enema defined according to the Anatomic Therapeutic Chemical Classification System (ATC); route of entry was suppository.³

^b Defined as, "liquid paraffin >15 ml/day; bisocodyl >10 mg/day; senna glycosides >24 mg/day; sodium pico sulphate >10 drops (5 mg)/day; lactulose >30 ml/day; macrogol combinations 26.2 (2 sachets); docusate sodium >1 suppository/day; and laurilsulfate >1 suppository/day."³

^c Defined as, "...defecation frequency from three defecations/week to three defecations/day and stool consistency 3-5 on Bristol Stool Form Scale."³

^d Starting dose (step) was determined by admitting physician; was based on opioid use and past bowel history. Opioid naïve patients started at Step 1, patients on opioids started at Step 2, patients on opioids (with no bowel movement in 48 hours prior to assessment) started at Step 3, patients switched to closest equivalent step if they were already taking laxatives.⁵

^e Opioid naïve patients started at Step 1, patients on opioids started at Step 1, patients on opioids (with no bowel movement in the 48 hours prior to assessment) started at Step 2, patients switched to closest equivalent step if they were already taking laxatives.⁵

^f Including, "pain, tiredness, nausea, drowsiness, anxiety, depression, appetite loss, well-being, and shortness of breath."

APPENDIX 4: Summary of Critical Appraisal

Table 3: Summary of Critical Appraisal of Clinical Reviews and Studies		
Author, Year	Strengths	Limitations
<i>Systematic Reviews</i>		
Ahmedzai and Boland, ⁷ 2009	<ul style="list-style-type: none"> • Clear definition of constipation and supportive care used. • Research questions and inclusion criteria established <i>a priori</i>. • Comprehensive literature search with no language restrictions. • Included alerts for harms data. • GRADE evaluation included for the outcomes and populations of Interest. • Scientific quality of the included study was used appropriately in forming conclusions. • Conflicts of interest declared. 	<ul style="list-style-type: none"> • Quality of evidence (high, moderate, low, very low) reflects available evidence for outcomes and populations of interest only, not necessarily the overall methodological quality of the individual included studies. • Clinical findings based on 1 RCT included in the 1 SR they found; opioid dose was unclear, sample size (N=22) with even less completing the trial; results were presented without P values. • Open-label studies were included. • No grey literature search was specified. • List of excluded studies not provided.
Ruston et al., ⁶ 2013	<ul style="list-style-type: none"> • Completed unpublished scoping review prior to formulating research questions. • Research questions and inclusion criteria established <i>a priori</i>. • Comprehensive literature search (including grey literature search) with no language restrictions. • Rigorous study selection. • Data extraction and validity assessment were outlined and would have been rigorous if any studies had been identified. • Conflicts of interest declared. 	<ul style="list-style-type: none"> • Inclusion criteria may have been too stringent. • Lack of clear definition for opioid-induced constipation. • List of excluded studies not provided but PRISMA diagram provided.

Table 3: Summary of Critical Appraisal of Clinical Reviews and Studies

Author, Year	Strengths	Limitations
<i>Randomized Controlled Trial</i>		
Tarumi et al., ⁴ 2013	<ul style="list-style-type: none"> • Prospective DB design with clearly stated objective. • Baseline characteristics reported. • Sample size calculation included and appropriate; sufficient power to detect clinical effects. • Specific tool (Bowel Movement Record) was used to maintain consistency in recording stool frequency, consistency, volume, ease, and completeness of defecation. • Conflicts of interest declared. 	<ul style="list-style-type: none"> • Allocation concealment and ITT not specified; (10 [40%] and 8 [21%] patients did not complete study in DS and PL groups, respectively). • Inclusion criteria expanded ~5 months after start of trial to include patients with non-malignant disease and those not taking opioids. • Randomization code could be broken at the request of the physician or patient; occurrence of this not specified.
<i>Non-Randomized Studies</i>		
Fosnes et al., ³ 2011	<ul style="list-style-type: none"> • Clearly stated objective. • In depth patient baseline characteristics provided. • Patients with gastrointestinal disease excluded; therefore, removing some potential confounding. • Standardized tool for assessing stool consistency used (Bristol Stool Form Scale). • Patients and treatments representative of population in nursing homes (including those with and without normal bowel function). • Conflicts of interest declared. 	<ul style="list-style-type: none"> • Inclusion of frail and mentally reduced participants; may reduce data quality for patients self-reported symptoms. • Differing sites may have alternate methods of reporting and the use of laxatives may have been imprecisely registered as they may not have been handled as accurately as other drugs. • Only a small number of patients used DS (n=5) and it was only one of many treatment regimens examined.

Table 3: Summary of Critical Appraisal of Clinical Reviews and Studies

Author, Year	Strengths	Limitations
Hawley and Byeon, ⁵ 2008	<ul style="list-style-type: none"> • Primary and secondary outcomes clearly stated. • Patient characteristics reported. • Stepwise treatment (determined by admitted physician) based on patient’s past bowel history and opioid requirements. • Other laxative use recorded. • Observation duration balanced by observing first 12 days on the bowel protocol (even if patients maintained this regimen further). • Subgroup analysis observing either symptom control or supportive care. • Funding declared. 	<ul style="list-style-type: none"> • Sequential cohort study with no matching or adjustments for co-founders. • Sample size included 60 patients only. • Many different healthcare providers were involved in patient care and were not all aware of their patient’s participation in the study. • Patients could take an enema, lactulose, or a suppository as required; therefore potentially confounding results. • More patients with GU cancer were enrolled in the second (S only) cohort, while GU was least common cancer diagnosis in the first (DS + S) cohort. • Conflicts of interest not declared.

DS = docusate sodium; GU = genitourinary; ITT = intention-to-treat; RCT = randomized controlled trial; S = sennosides; SR = systematic review.

APPENDIX 5: Summary of Clinical Findings

Table 4: Summary of Findings and Authors' Conclusions		
Author, Year	Main Study Findings	Authors' Conclusions
<i>Systematic Reviews</i>		
Ahmedzai and Boland, ⁷ 2009	<ul style="list-style-type: none"> • Management of constipation. • One SR of 4 RCTs comparing docusate to placebo was found; three of the four RCTs had weak methods and were excluded from their analysis. Findings were based on one RCT (N=22). Patients received Docusate 240 mg BID x 3 weeks compared to PL in a cross-over design. • RCT found no significant difference between Docusate and PL in stool frequency or consistency at 8 weeks after crossover in 15/22 (68%) in those who completed trial <ul style="list-style-type: none"> ○ mean number of BM/week: <ul style="list-style-type: none"> ▪ D 4.25 ▪ PL 4.12, (not significant; P values not reported). ○ percentage of soft and normal stools: <ul style="list-style-type: none"> ▪ D 97% ▪ PL 93% (not significant; P values not reported). 	<ul style="list-style-type: none"> • <i>“Compared with placebo Docusate may be no more effective than placebo at increasing stool frequency in people prescribed opioids (very low-quality evidence).”</i> (page 6) • <i>“Although docusate is prescribed in people taking opioids, there is no good evidence to support its use.”</i> (page 6) • <i>“Further RCTs assessing all the currently available treatments are needed.”</i> (page 2)
Ruston et al., ⁶ 2013	<ul style="list-style-type: none"> • Management of constipation. • No studies met the inclusion criteria; hence, no conclusion can be drawn. 	<ul style="list-style-type: none"> • <i>“Insufficient evidence exists to determine the efficacy and side effect profiles of lactulose, docusate sodium, sennosides, and PEG in the treatment of OIC.”</i> (page 240)

Table 4: Summary of Findings and Authors' Conclusions

Author, Year	Main Study Findings	Authors' Conclusions
<i>Randomized Controlled Trial</i>		
Tarumi et al., ⁴ 2013	<ul style="list-style-type: none"> • Management of constipation. • BM mean difference 0.05 (95% CI: -0.09, 0.19) <p>Responder Analysis:</p> <ul style="list-style-type: none"> • BM on 50% or more days: <ul style="list-style-type: none"> ○ DS 56% ○ PL 71% • 1 BM every 3 consecutive days: <ul style="list-style-type: none"> ○ DS 70.8% ○ PL 80.6% • Mean stool frequency (± SD): <ul style="list-style-type: none"> ○ DS 1.0 (0.5) ○ PL 0.88 (0.30) • No significant differences between stool volume in DS vs PL • Difficult BM: <ul style="list-style-type: none"> ○ DS 32.5% ○ PL 25.0%, (P=0.57) • Sense of complete evacuation: <ul style="list-style-type: none"> ○ DS 73.5% ○ PL 78.6, (P=0.77) • Bowel care interventions: <ul style="list-style-type: none"> ○ DS 68.6% ○ PL 74.4%, (P=0.77) 	<ul style="list-style-type: none"> • "...docusate plus sennosides was not more efficacious than sennosides alone (placebo plus sennosides) in the management of constipation in hospice patients." (pg. 8) • "...RCT showed no statistically significant difference in stool frequency, volume, or consistency between docusate and placebo..." (pg. 8) • "...general standing orders/policies for the use of docusate in the management of constipation on hospice units should be reviewed in light of this study." (pg. 11)
<i>Non-Randomized Studies</i>		
Fosnes et al., ³ 2011	<ul style="list-style-type: none"> • Management of constipation. • No results were provided specifically for docusate sodium. • No conclusion could be reached as only five patients were reported to have used this treatment 	<ul style="list-style-type: none"> • "All laxatives used in this study have been proven to be superior to placebo" (page 5)

Table 4: Summary of Findings and Authors' Conclusions

Author, Year	Main Study Findings	Authors' Conclusions
<p>Hawley and Byeon,⁵ 2008</p>	<ul style="list-style-type: none"> • Prevention and management of constipation. • Percent of days with at least 1 BM: <ul style="list-style-type: none"> ○ DS+S 49% ○ S 50%, (P=0.86) • BM at least 50% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 13 (43.3) ○ S 19 (63.3), (P=0.12) • BM at least 40% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 18 (60) ○ S 24 (80), (P=0.09) • Use of rescue medications:^a <ul style="list-style-type: none"> ○ DS+S 17 (56.7) ○ S 12 (40), (P=0.19) <p><i>Subanalysis of patients admitted for symptom control or supportive care, DS+S (n=19) and S (n=24):</i></p> <ul style="list-style-type: none"> • BM at least 50% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 6 (31.6) ○ S 15 (62.5), (P=0.04) • BM at least 40% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 9 (47.4) ○ S 19 (79.2), (P=0.09) <p><i>Subanalysis of patients admitted for symptom control or supportive care and on opioids, DS+S (n=19) and S (n=24):</i></p> <ul style="list-style-type: none"> • BM at least 50% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 5 (31.3) ○ S 12 (57.1), (P=0.12) • BM at least 40% of days, n (%): <ul style="list-style-type: none"> ○ DS+S 8 (50.0) ○ S 16 (76.2), (P=0.1) 	<ul style="list-style-type: none"> • <i>“A docusate-containing five-step bowel protocol was not as effective as a four-step sennosides-only protocol over a period of 5–12 days in a population of hospitalized cancer patients.”</i> (pg. 580) • <i>“Further research is needed into the optimal laxative agents to use in this population at high risk of constipation and with the possibility of serious morbidity, and into the optimal protocol format.”</i> (pg. 580)

BID = twice a day; BM = bowel movement; DB = double blind; D = docusate; DS = docusate sodium; OIC = opioid-induced constipation; PEG = polyethylene glycol; PL = placebo; vs = versus.

^a Use of lactulose, suppository, or enema.