

**National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Pain and Palliative care**

MEDICINE MOTIVATION:

1. Executive Summary

Date: 29 August 2017
Medicine (INN): Bisacodyl suppositories
Medicine (ATC): A06AB02
Indication (ICD10 code): Constipation in palliative care patients who cannot swallow; and opioid-induced constipation (K59.0 +(Z51.1))
Patient population: Adult palliative care patients who cannot swallow
Prevalence of condition: Local context unknown
Level of Care: Primary level of care
Prescriber Level: Nurse prescriber
Current standard of Care: n/a
Efficacy estimates: (preferably NNT)n/a
Motivator/reviewer name(s): Motivator: Dr S.R. Krause/ Reviewer(s): Pearl Lentsoane; Trudy Leong
PTC affiliation: n/a

2. Name of author(s)/motivator(s)

Pearl Lentsoane, Trudy Leong

3. Author affiliation and conflict of interest details

Pearl Lentsoane: Mankweng hospital, Limpopo province; No conflicts of interest

Trudy Leong: National Department of Health - Essential Drugs Programme; Secretariat to the Primary Health Care Committee; No conflicts of interest.

4. Introduction/ Background

Constipation is one of the most common problems in patients receiving palliative care and can cause extreme suffering and discomfort. The EML PHC ERC received a motivation for bisacodyl suppositories for this indication from the Palliative Care TWG. The rationale for bisacodyl suppositories is for use in patients suffering from constipation who are not able to swallow oral medication. This review reviews the evidence for bisacodyl suppositories in two clinical settings: A) constipation in adult palliative care patients who are unable to swallow; B) opioid-induced constipation.

A: BISACODYL SUPPOSITORIES FOR CONSTIPATION IN PALLIATIVE CARE

5. Search 1: PICO #1

Purpose/Objective i.e. PICO question 1

-P(*patient/population*): Adult palliative care patients

-I(*intervention*): Bisacodyl suppositories

-C(*comparator*): Placebo, no treatment

-O(*outcome*): 1. Efficacy (relief of constipation) 2. Adverse effects

(P) Amongst adult palliative care patients with constipation who cannot take oral medication is (I) **bisacodyl** compared to (C) placebo/no treatment (O) effective in terms of improvement in fatigue symptoms, with minimal/acceptable side effects?

6. Methods:

a. Data sources

Pubmed - searches conducted on 29 August 2017

Google and google scholar - search conducted on 30 October 2017

b. Searches

Study inclusion criteria:

Type of studies: RCTs and systematic reviews

i. Search strategy 1

systematic[sb] AND (("bisacodyl"[MeSH Terms] OR "bisacodyl"[All Fields]) AND ("constipation"[MeSH Terms] OR "constipation"[All Fields]))

Search retrieved 12 articles.:

- no RCTs that involved the use of bisacodyl;
- 4 systematic reviews not related to the clinical question;
- The remaining 8 studies were not related to the clinical question.

ii. Search strategy 2:

("bisacodyl"[MeSH Terms] OR "bisacodyl"[All Fields]) AND ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]))

The search retrieved 4 articles, of which 2 were relevant to the clinical question but are only available in French and Norwegian (English abstract available). The remaining 2 studies relate to opioid induced constipation.

iii. Search strategy 3:

("bisacodyl"[MeSH Terms] OR "bisacodyl"[All Fields]) AND ("suppositories"[MeSH Terms] OR "suppositories"[All Fields] OR "suppository"[All Fields] OR "pessaries"[MeSH Terms] OR "pessaries"[All Fields]) AND ("terminally ill"[MeSH Terms] OR ("terminally"[All Fields] AND "ill"[All Fields]) OR "terminally ill"[All Fields])

The search retrieved 4 articles: Two Systematic reviews relating to the clinical question and two relating to opioid-induced constipation.

iv. Search strategy 4 (google and google scholar):

"health technology" and "constipation "and "palliative care"

The search retrieved no health technology assessments, but a rapid response report by the Canadian Agency for Drugs and Technologies in Health (CADTH) was of interest and has been added to the evidence table, below.

c. Excluded studies: *Describes briefly which you have rejected and why*

Author, date	Type of study	Reason for exclusion
P Paré, RN Fedorak, 2014	Systematic review	The studies did not include subjects who had known medical conditions.
Goodman et al , 2005	Prospective survey	Other stimulant laxatives were investigated.

d. Evidence synthesis

<i>Author, date</i>	<i>Type of study</i>	<i>n</i>	<i>Population</i>	<i>Intervention</i>	<i>Comparators</i>	<i>Primary outcome</i>	<i>Effect sizes</i>	<i>Comments</i>
Candy et al, 2015	Systematic review	280	Patients with constipation, receiving palliative care	laxatives	Placebo	Number and frequency of bowel movements	n/a	Laxatives were of similar effectiveness but the evidence remains limited due to insufficient data from a few small RCTs. None of the studies evaluated polyethylene glycol or any intervention given rectally.
Larkin et al, 2008	Clinical Guidelines		Palliative care patients	laxatives	There is minimal evidence that suggests superiority of one laxative over the other. Bisacodyl suppositories (10mg/day) are recommended as second line therapy.			
CADTH, 7 Dec 2015	Guidelines: Routine Bowel Care for Patients in Long-Term or Palliative Care		Long-term care for seniors and palliative care	laxatives	No HTAs, systematic reviews, meta-analyses could be identified for the development of these guidelines. Statement made as follows: "There is a lack of evidence to recommend the use of one pharmacological therapy over another. A softening and a stimulating agent may need to be prescribed together and the choice of laxative should be guided by the patient's situation and preferences. Where there is no difference in tolerability or effectiveness, the lowest cost option should be used". The report recommends the Department of Health, Ireland guideline that is mentioned below.			
National Clinical Guideline no.10, Ireland (2015)	Guidelines: Management of Constipation in Adult Patients Receiving Palliative Care		Palliative care patients: adults	laxatives	Stepwise approach recommended of non-pharmacological and pharmacological treatment; recommended as 2nd/3rd line option.			

e. Evidence quality:

There is very limited evidence on the use of bisacodyl suppositories. No health technology assessments, systematic reviews, meta-analyses or RCTs could be identified in the literature. However, guidelines recommend bisacodyl suppositories as second line treatment, based on clinical practice recommendations and expert opinion.

B: BISACODYL SUPPOSITORIES FOR OPIOID INDUCED CONSTIPATION

7. Search 1: PICO #2

Purpose/Objective i.e. PICO question 2

- P** (*patient/population*): Patients with opioid-induced constipation
- I** (*intervention*): Bisacodyl suppositories
- C** (*comparator*): Placebo, no treatment
- O** (*outcome*): 1. Efficacy (relief of constipation) 2. Adverse effects

(P) Amongst patients with opioid induced constipation who cannot take oral medication is **(I) bisacodyl**suppositories compared to **(C)** placebo/no treatment **(O)** effective in terms of improvement in symptoms, with minimal/acceptable side effects?

8. Methods:

a. Data sources

Pubmed - searches conducted on 29 August 2017

b. Searches

Study inclusion criteria:

Type of studies: RCTs and systematic reviews

c. Search terms

i. Strategy 1:

("bisacodyl"[MeSH Terms] OR "bisacodyl"[All Fields]) AND ("suppositories"[MeSH Terms] OR "suppositories"[All Fields] OR "pessaries"[MeSH Terms] OR "pessaries"[All Fields]) AND ("constipation"[MeSH Terms] OR "constipation"[All Fields])

filter: systematic

MeSH Terms: analgesics, opioid; constipation

This search strategy retrieved 20 articles. Two of which were relevant to the clinical question.

ii. Strategy 2:

MeSH Terms: suppositories; constipation; pessaries; bisacodyl

MeSH Terms: constipation; pessaries; bisacodyl; suppositories; analgesics, opioid

MeSH Terms: therapeutics; analgesics, opioid; constipation

Subheading: therapy

MeSH Terms: analgesics, opioid; laxatives; constipation

Retrieved 1 article already mentioned in the above search strategy.

Author, date	Type of study	Reason for exclusion
Friezel and Barclay ,2006	Systematic review	The RCT was done in patients with idiopathic constipation
Candy et al , 2006	Systematic review	The studies included all patients receiving palliative care, cause of constipation was not specific to opioid use.

<i>Author, date</i>	<i>Type of study</i>	<i>n</i>	<i>Population</i>	<i>Intervention</i>	<i>Comparators</i>	<i>Primary outcome</i>	<i>Effect sizes</i>	<i>Comments</i>
Kumar et al, 2014	Narrative review	Patients with opioid induced constipation	Patients with opioid induced constipation	laxatives	Other laxatives	Improvement of symptoms		Bisacodyl is recommended for use in combination with a stool softer. However no dose recommendations were outlined.
Ahmedzai et al, 2009	Systematic review		Patients with opioid induced constipation				No systematic reviews, RCTs or cohort studies of sufficient quality could be sourced.	Clinical experience suggests that they should ideally be combined with an osmotic or bulk-forming agent. Oral laxatives and rectal suppositories can only palliate the symptoms of opioid-induced constipation and do not relieve other aspects of opioid-induced bowel dysfunction such as delayed gastric emptying and abdominal cramps.
Twycross et al 2012	Narrative review		Patients with opioid induced constipation	Bisacodyl suppositories				Recommended dose in this group of patients is 10 to 20 mg PR once daily. It is also recommended when patient has not had bowel movement ≥ 3 days of using other laxatives e.g. senna

d. Evidence synthesis:

There is limited data on the use of bisacodyl suppositories in opioid-induced constipation; no RCTs or meta-analyses were found during the search.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS				
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>					
BENEFITS & HARMS	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>					
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group.</p> <p>List specific exclusion from the group:</p>	<p>Rationale for therapeutic alternatives included:</p> <p>References:</p> <p>Rationale for exclusion from the group:</p> <p>References:</p>				
VALUES & PREFERENCES ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>					
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)*</th> </tr> </thead> <tbody> <tr> <td>Bisacodyl suppository, 10 mg</td> <td></td> </tr> </tbody> </table> <p>*Price not listed on the SEP database or on contract circulars.</p> <p>Additional resources:</p>	Medicine	Cost (ZAR)*	Bisacodyl suppository, 10 mg	
Medicine	Cost (ZAR)*					
Bisacodyl suppository, 10 mg						

EQUITY	Would there be an impact on health inequity? Yes No Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	
FEASIBILITY	Is the implementation of this recommendation feasible? Yes No Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	

Type of recommendation	We recommend against the option and for the alternative <input checked="" type="checkbox"/>	We suggest not to use the option or to use the alternative <input type="checkbox"/>	We suggest using either the option or the alternative <input type="checkbox"/>	We suggest using the option <input type="checkbox"/>	We recommend the option <input type="checkbox"/>
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Recommendation:Based on this evidence review, the Primary Health Care Committee recomemnded that bisacodyl suppositories not be included in the EML for primary level of care. However, this medicine could be considered for use at hospital level where short-term use would be restricted specifically in patients who cannot swallow. The Committee was of the opinion that it was not appropriate to initiate management at primary level of care, but should be initiated by palliative care teams and accessed at primary level of care should down-referral mechanism if required.

Rationale:Use of bisacodyl suppositories for constipation in palliative care would be limited to a small population of patients: adult palliative care patients who cannot swallow. There is no evidence of superiority to alternate laxatives that are currently included in the primary health care EML.

Level of Evidence: III Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Monitoring and evaluation considerations

Research priorities

References:

1. Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev*. 2015 May 13;(5):CD003448. <https://www.ncbi.nlm.nih.gov/pubmed/25967924>
2. Larkin,PJ ,Sykes,NP,Centeno,C,Ellershaw,JE, Elsner,F, Eugene,B.Gootjes,JRG,Naba,M,Noguera,IA,Ripamonti,C, Zucco,F, ,Zuurmond, WWA .The management of constipation in palliative care: clinical practice recommendations *Palliative Medicine*. Vol 22, Issue 7, pp. 796 – 807. <http://dx.doi.org/10.1177%2F0269216308096908>
3. Twycross R, Sykes N, Mihalyo M, Wilcock A. Stimulant laxatives and opioid-induced constipation. *J Pain Symptom Manage*. 2012 Feb;43(2):306-13. <https://www.ncbi.nlm.nih.gov/pubmed/22248790>
4. Ahmedzai SH, Boland JW. Constipation: opioid antagonists in people prescribed opioids. *BMJ Clin Evid*. 2015 Sep 11;2015. pii: 2407. <https://www.ncbi.nlm.nih.gov/pubmed/26360669>
5. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Gastroenterol Res Pract*. 2014;2014:141737. <https://www.ncbi.nlm.nih.gov/pubmed/24883055>
6. Canadian Agency for Drugs and Technologies in Health (CADTH). Rapid response report - Routine Bowel Care for Patients in Long-Term or Palliative Care: Guidelines; 2015 Dec 7. [Internet]. Canadian [cited 2017 October 30]. Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/dec-2015/RB0940%20Bowel%20Care%20in%20LTC%20Final.pdf>
7. Management of constipation in adult patients receiving palliative care [Internet]. Dublin: Department of Health, Ireland; 2015 Nov. [cited 2017 October 30]. (National clinical guideline no. 10). Available from: <http://health.gov.ie/wp-content/uploads/2015/11/Mgmt-ofConstipation-Guideline.pdf>