

## Bijlage Zoekverantwoording

### Onderzoeksvragen 1, 2 en 3: diagnostiek

#### Onderzoeksvraag 1: lichamelijk onderzoek

Wat zijn de voor- en nadelen van lichamelijk onderzoek ten opzichte van alleen zelfrapportage bij het vaststellen van obstipatie in de palliatieve fase?

What are the advantages and disadvantages of physical examination compared to self-report in the determination of constipation in the palliative phase?

|              |   |
|--------------|---|
| Patients     | patients in the palliative phase with (suspected) constipation                                      |
| Intervention | physical examination  |
| Comparator   | self-report   |
| Outcome      | diagnostic accuracy, patient satisfaction, negative consequences of the physical examination, costs |

#### Onderzoeksvraag 2: laboratoriumonderzoek

Wat zijn de voor- en nadelen van laboratoriumonderzoek ten opzichte van lichamelijk onderzoek of alleen zelfrapportage bij het vaststellen van obstipatie in de palliatieve fase?

What are the advantages and disadvantages of laboratory tests compared to physical examination or self-report in the determination of constipation in the palliative phase?

|              |   |
|--------------|---|
| Patients     | patients in the palliative phase with (suspected) constipation                                  |
| Intervention | laboratory tests (calcium (hypercalcemia) and thyroid function (hypothyroidism))                |
| Comparator   | physical examination or self-report   |
| Outcome      | diagnostic accuracy, patient satisfaction, negative consequences of the laboratory tests, costs |

#### Onderzoeksvraag 3: beeldvormend onderzoek

Wat zijn de voor- en nadelen van een buikoverzichtsfoto of CT-scan ten opzichte van lichamelijk onderzoek of zelfrapportage bij het vaststellen van obstipatie in de palliatieve fase?

What are the advantages and disadvantages of a x-ray of the abdomen or CT-scan compared to physical examination or self-report in the determination of constipation in the palliative phase?

|              |  |
|--------------|--|
| Patients     | patients in the palliative phase with (suspected) constipation   |
| Intervention | x-ray of the abdomen or CT-scan  |
| Comparator   | physical examination or self-report  |
| Outcome      | diagnostic accuracy, patient satisfaction, negative consequences of a x-ray of the abdomen or CT-scan, costs |

#### Search strategy research question 1, 2 and 3

The search of research question 1, 2 and 3 was combined.

On November 6, 2020 the scientific literature is searched in databases Medline, Embase and the Cochrane Library. The search strings are shown in this appendix.

The literature has been selected systematically based on the following predefined criteria:

- Design: randomized clinical trials (RCT's), controlled clinical trials (CCT's) and observational studies
- Publication dates: from inception to search date
- The outcomes are reported

Literature was excluded when no quantitative data was presented and when no comparison was made between the different diagnostic tools.

### Search results research question 1, 2 and 3

The selection criteria were applied on the references yielded from the search. 157 unique hits were screened on title and abstract (Table 1). Of these, 150 were excluded. Of the remaining seven papers, the full-text was retrieved. Based on the full-text, no papers were included for research questions 1 and 2 and two papers were included for research question 3. The included papers for research question 3 are:

- Clark K, Lam LT, Talley NJ, Quinn J, Blight A, Byfieldt N, et al. Assessing the Presence and Severity of Constipation with Plain Radiographs in Constipated Palliative Care Patients. *J Palliat Med.* 2016;19(6):617–21.
- Nagaviraj K, Yong WC, Fassbender K, Zhu G, Oneschuk D. Comparison of the constipation assessment scale and plain abdominal radiography in the assessment of constipation in advanced cancer patients. *J Pain Symptom Manage.* 2011;42(2):222–8.

Table 2 provides an overview of the excluded studies with reasons.

Table 1. Overall search results of research question 1, 2 and 3.

| Database                          | Number of hits |
|-----------------------------------|----------------|
| Medline                           | 105            |
| Embase                            | 13             |
| Cochrane Library                  | 39             |
| <b>Total hits</b>                 | <b>157</b>     |
| n excluded (language, duplicates) | 0              |
| <b>Total unique eligible hits</b> | <b>157</b>     |

Table 2. Overview of excluded studies based on full-text evaluation of research question 1, 2 and 3.

| Reference   | Reason for exclusion  |
|---|---|
| Abernethy, A. P., et al. (2009). "Detailing of gastrointestinal symptoms in cancer patients with advanced disease: new methodologies, new insights, and a proposed approach." <i>Current Opinion in Supportive &amp; Palliative Care</i> 3(1): 41-49. | Narrative review, no comparison of relevant diagnostic methods.                       |
| Bruera, E., et al. (1994). "The assessment of constipation in terminal cancer patients admitted to a palliative care unit: a retrospective review." <i>Journal of Pain &amp; Symptom Management</i> 9(8): 515-519.                                    | No comparison or correlation analysis between diagnostic methods.                     |
| Clark, K. and D. C. Currow (2012). "Assessing constipation in palliative care within a gastroenterology framework." <i>Palliative Medicine</i> 26(6): 834-841.  | Narrative review, no detailed information available on different diagnostic measures. |
| Clark, K. et al. (2016) 'Assessing the Presence and Severity of Constipation with Plain Radiographs in Constipated Palliative Care Patients', <i>Journal of Palliative Medicine</i> . Mary Ann Liebert Inc., 19(6), pp. 617–621.                      | No relevant diagnostic intervention for research question 1 and 2                     |
| Mancini, I. and E. Bruera (1998). "Constipation in advanced cancer patients." <i>Supportive Care in Cancer</i> 6(4): 356-364.   | Narrative review, no detailed information available on different diagnostic measures. |

|   |   |
|---|---|
| Nagaviroj, K. et al. (2011) 'Comparison of the constipation assessment scale and plain abdominal radiography in the assessment of constipation in advanced cancer patients', <i>Journal of Pain and Symptom Management</i> . <u>J Pain Symptom Manage</u> , 42(2), pp. 222–228. | No relevant diagnostic intervention for research question 1 and 2 |
| Zhe, H. (2016). "The assessment and management of constipation among patients with advanced cancer in a palliative care ward in China: A best practice implementation project." <i>JBI Database of Systematic Reviews and Implementation Reports</i> 14(5): 295-309.            | Implementation study, does not look at accuracy of tests.         |

### Search strings research question 1, 2 and 3

#### OID MEDLINE

- 1 "Constipation in palliative care".ti. (0)
- 2 Constipation/ (14129)
- 3 Defecation/ (7152)
- 4 Fecal Incontinence/ (9947)
- 5 Feces/ (92512)
- 6 Diarrhea/ (48122)
- 7 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\* adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or (fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or faeces).ti,kw. (52839)
- 8 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*)).ti,kw. (4893)
- 9 Fecal Impaction/ (1062)
- 10 or/2-9 (173840)
- 11 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\* adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or (fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or faeces).tw,kw. (181916)
- 12 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*) or (irritable adj bowel adj syndrome)).tw,kw. (36857)
- 13 Gastrointestinal Motility/ (21256)
- 14 **or/2-13 (298215)=constipation**
- 15 Palliative Care/ (54813)
- 16 Terminal Care/ (28534)
- 17 Terminally Ill/ (6553)
- 18 Hospice Care/ (6568)
- 19 (palliat\* or terminal\* or endstage or hospice\* or (end adj2 life) or (care adj3 dying) or ((advanced or late or last or end or final) adj2 (stage\* or phase\*))).tw,kw. (748871)
- 20 "advanced disease\*".tw,kw. (20570)
- 21 ("end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage").tw,kw. (69274)
- 22 (terminal\* adj6 care\*).tw,kw. (4150)
- 23 (terminal\* adj6 (ill\* or disease)).tw,kw. (11194)
- 24 terminal?stage\*.tw,kw. (12)
- 25 (dying or (close adj6 death)).tw,kw. (36006)

**26 or/15-25 (817134)=palliative**  
**27 14 and 26 (7531)= constipation + palliative**  
 28 Constipation/dg (489)  
 29 Constipation/di (1717)  
 30 exp Radiography, Abdominal/ (42028)  
 31 ((abdominal adj3 radiogr\*) or (plain adj3 radiogra\*)).tw,kw. (14509)  
 32 exp Tomography, X-Ray Computed/ (437598)  
 33 (ct or (computer adj3 tomograp\*)).tw,kw. (353397)  
 34 hypercalciemi\*.tw,kw. (9)  
 35 Hypercalcemia/bl [Blood] (1431)  
 36 hypercalc\*.tw,kw. (22201)  
 37 exp clinical laboratory techniques/ or exp medical history taking/ or exp physical examination/  
 or early diagnosis/ (3930904)  
 38 (physical adj3 exam\*).tw,kw. (72755)  
 39 thyroid diseases/ or exp hypothyroidism/ (48394)  
 40 dg.fs. (1203366)  
**41 or/28-40 (5363775)=research variants**  
 42 27 and 41 (1589)  
 43 or/2-9,11-12 (282604)  
**44 26 and 43 (7160)=palliative +constipation more specific**  
**45 41 and 44 (1520)= palliative +constipation more specific + research variants**  
 46 ((patient adj3 report\*) or mortalit\* or accura\* or adverse or cost? or (patient adj3  
 satisfact\*)).tw,kw. (2621664)  
 47 45 and 46 (232)  
 48 "filter systematic reviews".ti. (0)  
 49 meta analysis.pt. (121698)  
 50 (meta-anal\$ or metaanal\$).tw,kf. (186448)  
 51 (quantitativ\$ adj10 (review\$ or overview\$)).tw. (9767)  
 52 (systematic\$ adj10 (review\$ or overview\$)).tw. (205051)  
 53 (methodologic\$ adj10 (review\$ or overview\$)).tw. (12336)  
 54 (quantitativ\$ adj10 (review\$ or overview\$)).kf. (79)  
 55 (systematic\$ adj10 (review\$ or overview\$)).kf. (21659)  
 56 (methodologic\$ adj10 (review\$ or overview\$)).kf. (79)  
 57 medline.tw. and review.pt. (80341)  
 58 (pooled adj3 analy\*).tw. (20830)  
 59 (pooled adj3 analy\*).kf. (282)  
 60 "cochrane\$.fc\_jour. (15058)  
**61 or/49-60 (374878)= SR**  
 62 "medline rct filter".ti. (0)  
 63 controlled-clinical-trial.pt. (93908)  
 64 randomized-controlled-trial.pt. (516213)  
 65 randomized controlled trial/ (516213)  
 66 randomi?ed controlled trial?.tw. (184514)  
 67 randomi?ed controlled trial?.kf. (11901)  
 68 random-allocation.tw,kf. (1747)  
 69 double-blind-method.tw,kf. (501)  
 70 single-blind-method.tw,kf. (90)  
 71 (random adj8 (selection? or sample?)).kf,tw. (46306)  
 72 random\*.tw,kf. (1172025)  
**73 or/63-72 (1382184)=rct**  
**74 45 and 61 (17)= palliative +constipation more specific + research variants + SR**  
 75 "diagnose filter".ti. (0)  
 76 exp "Sensitivity and Specificity"/ (591081)

77 sensitivity.tw. (813566)  
78 sensitivity.kf. (18179)  
79 specificity.tw. (470125)  
80 specificity.kf. (7932)  
81 ((pre-test or pretest) adj probability).tw. (2295)  
82 ((pre-test or pretest) adj probability).kf. (69)  
83 ((post-test or posttest) adj probability).tw. (896)  
84 ((post-test or posttest) adj probability).kf. (18)  
85 predictive value\$.tw. (111068)  
86 predictive value\$.kf. (1361)  
87 likelihood ratio\$.tw. (15928)  
88 likelihood ratio\$.kf. (598)  
89 or/76-88 (1502902)  
90 45 and 89 (105)  
91 73 and 90 (7)  
**92 45 and 73 (119)= palliative +constipation more specific + research variants + rct**  
93 (palliat\* or terminal\* or endstage or hospice\* or (end adj2 life) or (care adj3 dying) or  
((advanced or late or last or end or final) adj2 (stage\* or phase\*))).ti,kw. (137173)  
94 "advanced disease\*".ti,kw. (745)  
95 ("end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage").ti,kw.  
(13496)  
96 (terminal\* adj6 care\*).ti,kw. (1742)  
97 (terminal\* adj6 (ill\* or disease)).ti,kw. (2947)  
98 terminal?stage\*.ti,kw. (11)  
99 (dying or (close adj6 death)).ti,kw. (8537)  
**100 15 or 16 or 17 or 18 or 93 or 94 or 95 or 96 or 97 or 98 or 99 (184306)=palliative more  
specific**  
**101 92 and 100 (27)= palliative specific +constipation more specific + research variants + rct**  
**102 74 and 100 (8)= )= palliative specific +constipation more specific + research variants +  
SR**  
103 "Filter observationele studies".ti. (0)  
104 epidemiologic studies/ (8445)  
105 exp case-control studies/ (1115022)  
106 exp cohort studies/ (2048881)  
107 cross-sectional studies/ (341944)  
108 (case adj3 control).tw,kf. (135508)  
109 (cohort adj5 (study or studies or analy\$)).tw,kf. (283429)  
110 (follow-up adj5 (study or studies)).tw,kf. (92432)  
111 (longitudinal or retrospective or prospective or (cross adj5 sectional)).tw,kf. (1629212)  
112 (observational adj5 (study or studies)).tw,kf. (152635)  
113 or/104-112 (3286558)  
**114 45 and 100 and 113 (84)= palliative specific +constipation more specific + research  
variants + observant**

#### EMBASE

1 "obstipatie palliatieve behandeling of preventie".ti. (0)  
2 "embase AvE constipation in palliative care".ti. (0)  
3 exp constipation/ (92332)  
4 defecation/ (13553)  
5 defecation disorder/ (2610)  
6 defecation measurement/ (85)  
7 feces incontinence/ (20999)  
8 feces/ (59916)

9 hard feces/ (599)  
10 diarrhea/ (235533)  
11 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\*  
adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or  
(fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or  
faeces).ti,kw. (65299)  
12 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or  
(evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3  
symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or  
(void\* adj3 bowel\*) or (strain\* adj3 bowel\*)).ti,kw. (7938)  
13 feces impaction/ (1734)  
14 or/3-13 (395027)  
15 exp palliative therapy/ (113165)  
16 exp terminal care/ (70588)  
17 terminally ill patient/ or hospice patient/ (8731)  
18 (palliat\* or terminal\* or endstage or hospice\* or (end adj3 life) or (care adj3 dying) or  
((advanced or late or last or end or final) adj3 (stage\* or phase\*))).ti,kw. (190624)  
19 or/15-18 (294360)  
20 14 and 19 (6471)  
21 practice guideline/ (436517)  
22 guideline?.ti. (105364)  
23 21 or 22 (467556)  
24 20 and 23 (332)  
25 exp \*constipation/ (14175)  
26 9 or 11 or 12 or 13 or 25 (75811)  
27 23 and 26 (1151)  
28 19 and 27 (34)  
29 "filter systematic reviews & meta-analyses Embase ".ti. (0)  
30 meta analysis/ (200850)  
31 "systematic review"/ (270009)  
32 (meta-analy\$ or metaanaly\$).tw. (243564)  
33 (meta-analy\$ or metaanaly\$).kw. (59154)  
34 (systematic\$ adj4 (review\$ or overview\$)).tw. (254189)  
35 (systematic\$ adj4 (review\$ or overview\$)).kw. (32311)  
36 (quantitativ\$ adj5 (review? or overview?)).tw,kw. (5731)  
37 (methodologic adj5 (overview? or review?)).tw,kw. (392)  
38 (review\$ adj3 (database? or medline or embase or cinahl)).tw,kw. (29620)  
39 (pooled adj3 analy\$).tw,kw. (32185)  
40 (extensive adj3 review\$ adj3 literature).tw,kw. (3908)  
41 (meta or synthesis or (literature adj8 database?) or extraction).tw,kw. (1515386)  
42 review.pt. (2657180)  
43 41 and 42 (170154)  
44 or/30-40,43 (602667)  
45 19 and 26 and 44 (43)  
46 exp abdominal radiography/ (31584)  
47 ((abdominal adj3 radiogr\*) or (plain adj3 radiogra\*)).tw,kw. (18706)  
48 exp x-ray computed tomography/ (60916)  
49 (ct or (computer adj3 tomograp\*)).tw,kw. (615944)  
50 hypercalcemia/di [Diagnosis] (2299)  
51 hypercalc\*.tw,kw. (28954)  
52 laboratory technique/ or exp laboratory test/ (169617)  
53 anamnesis/ (120411)  
54 exp physical examination/ (252915)

55 early diagnosis/ (108873)  
 56 (physical adj3 exam\*).tw,kw. (129767)  
 57 thyroid disease/ or exp hypothyroidism/ (90036)  
 58 hypothyroid\*.tw,kw. (51525)  
 59 or/46-58 (1371256)  
 60 20 and 59 (776)  
 61 44 and 60 (20)  
 62 25 or 26 (75811)  
 63 \*defecation/ (2125)  
 64 62 or 63 (76562)  
 65 61 and 64 (2)  
 66 "filter randomised controlled trials Embase".ti. (0)  
 67 randomization/ (88986)  
 68 exp randomized controlled trial/ (632118)  
 69 exp controlled clinical trial/ (819657)  
 70 Major Clinical Study/ (3929257)  
 71 random\$.tw. (1600284)  
 72 random\$.kw. (50911)  
 73 Double Blind Procedure/ (178442)  
 74 or/67-73 (5335138)  
 75 60 and (44 or 74) and 64 (14)  
 76 "filter observational studies emb sign".ti. (0)  
 77 Clinical study/ (156336)  
 78 Case control study/ (163460)  
 79 Family study/ (26156)  
 80 Longitudinal study/ (147316)  
 81 Retrospective study/ (988360)  
 82 Prospective study/ (640967)  
 83 Randomized controlled trials/ (190422)  
 84 82 not 83 (634005)  
 85 Cohort analysis/ (634518)  
 86 (Cohort adj (study or studies)).tw,kw. (324113)  
 87 (Case control adj (study or studies)).tw,kw. (140522)  
 88 (follow up adj (study or studies)).tw,kw. (68099)  
 89 (observational adj (study or studies)).tw,kw. (178159)  
 90 (epidemiologic\$ adj (study or studies)).tw,kw. (111404)  
 91 (cross sectional adj (study or studies)).tw,kw. (234993)  
 92 77 or 78 or 79 or 80 or 81 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 (2862700)  
 93 (60 and 64 and 92) not (44 or 74) (5)

#### COCHRANE LIBRARY

#1 MeSH descriptor: [Palliative Care] explode all trees  
 #2 MeSH descriptor: [Terminal Care] this term only  
 #3 palliative:ti,ab  
 #4 MeSH descriptor: [Constipation] this term only  
 #5 constipat\*:ti,ab,kw  
 #6 (#1 OR #2 OR #3) AND (#4 OR #5)  
 #7 (bowel next2 dysfunction\*):TI,kw  
 #8 palliat\* or terminal\* or endstage or hospice\*:ti,kw  
 #9 #1 OR #2 OR #3 OR #8  
 #10 #4 OR #5 OR #7  
 #11 #9 AND #10

- #12 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [diagnostic imaging - DG, diagnosis - DI]
- #13 MeSH descriptor: [Radiography, Abdominal] explode all trees
- #14 ((abdominal next3 radiogra\*) or (plain next3 radiogra\*)):ti,ab,kw
- #15 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
- #16 (ct or (computer next tomograp\*)):ti,ab,kw
- #17 hypercalc\*:ti,ab,kw
- #18 MeSH descriptor: [Hypercalcemia] explode all trees
- #19 MeSH descriptor: [Clinical Laboratory Techniques] explode all trees
- #20 MeSH descriptor: [Medical History Taking] explode all trees
- #21 MeSH descriptor: [Physical Examination] this term only
- #22 (physic\* next3 exam\*):ti,ab,kw
- #23 hypothyroid\*:ti,ab,kw
- #24 MeSH descriptor: [Hypothyroidism] explode all trees
- #25 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
- #26 #11 and #25
- #27 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
- #28 #11 and #27
- #29 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [diagnostic imaging - DG, diagnosis - DI]
- #30 #13 or #15 or #18 or #19 or #20 or #21 or #24
- #31 #11 and #27 and #30
- #32 ((abdominal next3 radiogra\*) or (plain next3 radiogra\*)):ti
- #33 (ct or (computer next tomograp\*)):ti
- #34 hypercalc\*:ti
- #35 (physic\* next3 exam\*):ti
- #36 hypothyroid\*:ti
- #37 #32 or #33 or #34 or #35
- #38 #11 and #27 and (#30 or #37)
- #39 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [drug therapy - DT]
- #40 MeSH descriptor: [Magnesium Sulfate] explode all trees
- #41 MeSH descriptor: [Phosphates] explode all trees
- #42 MeSH descriptor: [Bisacodyl] explode all trees
- #43 MeSH descriptor: [Senna Extract] this term only
- #44 MeSH descriptor: [Benzofurans] this term only
- #45 (linaclotide or Linzess):ti
- #46 prucaloprid\*:ti
- #47 sennoside:ti
- #48 bisacodyl:ti
- #49 MeSH descriptor: [Magnesium Sulfate] explode all trees
- #50 sodium next phosph\*:ti
- #51 MeSH descriptor: [Lactulose] explode all trees
- #52 (lactulose or lactitol):ti
- #53 MeSH descriptor: [Magnesium Hydroxide] explode all trees
- #54 magnesium next hydroxide:ti
- #55 MeSH descriptor: [Dietary Fiber] explode all trees
- #56 MeSH descriptor: [Plant Extracts] this term only
- #57 MeSH descriptor: [Psyllium] explode all trees
- #58 MeSH descriptor: [Senna Extract] this term only
- #59 MeSH descriptor: [Laxatives] this term only
- #60 (laxant\* or laxati\*):ti
- #61 #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60

#62 #11 and #61

## Onderzoeksvragen 4, 5, 6, 7 en 9: preventie en behandeling

### Onderzoeksvraag 4: preventie bij patiënten die niet behandeld worden met opioïden

Wat zijn de (on)gunstige effecten van (niet-)medicamenteuze behandeling ter preventie van obstipatie bij patiënten in de palliatieve fase die niet behandeld worden met opioïden?

What are the (un)favourable effects of (non)pharmacological therapy to prevent constipation in patients in the palliative phase who are not treated with opioids?

|              |  |
|--------------|--|
| Patients     | patients in the palliative phase   |
| Intervention | dietary fibers (psyllium seed or sterculiagom), fluid intake, mobilisation and or laxatives (movicolon, magnesium(hydr)oxide, lactulose or lactitol, magnesium sulfate, sodium phosphate, bisacodyl and sennosides, prucalopride, linaclotide) |
| Comparator   | no treatment, placebo or other of the interventions  |
| Outcome      | symptom relief, patient satisfaction, adverse effects  |

### Onderzoeksvraag 5: preventie bij patiënten die behandeld worden met opioïden

Wat zijn de (on)gunstige effecten van (niet-)medicamenteuze behandeling ter preventie van obstipatie bij patiënten in de palliatieve fase, die behandeld worden met opioïden?

What are the (un)favourable effects of (non)pharmacological therapy to prevent constipation in patients in the palliative phase who are treated with opioids?

|              |  |
|--------------|--|
| Patients     | patients in the palliative phase who are treated with opioids  |
| Intervention | dietary fibers (psyllium seed or sterculiagom), fluid intake, mobilisation and or laxatives (movicolon, magnesium(hydr)oxide, lactulose or lactitol, magnesium sulfate, sodium phosphate, bisacodyl and sennosides, prucalopride, linaclotide, methylnaltrexone, naloxegol (moventig)) |
| Comparator   | no treatment, placebo or other of the interventions  |
| Outcome      | symptom relief, patient satisfaction, adverse effects  |

### Onderzoeksvraag 6: niet-medicamenteuze behandeling bij patiënten die opioïden krijgen

Wat zijn de (on)gunstige effecten van niet-medicamenteuze behandeling ter behandeling van obstipatie bij patiënten in de palliatieve fase?

What are the (un)favourable effects of non-pharmacological therapy to treat constipation in patients in the palliative phase?

|              |  |
|--------------|--|
| Patients     | patients in the palliative phase that have constipation                    |
| Intervention | dietary fibers (psyllium seed or sterculiagom), fluid intake, mobilisation |
| Comparator   | no treatment, placebo or other of the interventions                        |
| Outcome      | symptoms relief, patient satisfaction, adverse effects                     |

### Onderzoeksvraag 7: medicamenteuze behandeling

Wat zijn de (on)gunstige effecten van behandeling met laxantia van obstipatie bij patiënten in de palliatieve fase die geen opioïden ontvangen?

What are the (un)favourable effects of treatment with laxatives to treat constipation in patients in the palliative phase who are not treated with opioids?

|              |  |
|--------------|--|
| Patients     | patients in the palliative phase that have constipation and are not treated with opioids   |
| Intervention | laxatives (movicolon, magnesium(hydr)oxide, lactulose or lactitol, magnesium sulfate, sodium phosphate, bisacodyl and sennosides, prucalopride, linaclotide, (micro) enema, docusate sodium) |
| Comparator   | no treatment, placebo, other of the interventions  |
| Outcome      | symptom relief, patient satisfaction, adverse effects  |

### Onderzoeksvraag 9: medicamenteuze behandeling

Wat zijn de (on)gunstige effecten van opioïdantagonisten op obstipatie bij patiënten in de palliatieve fase die opioïden gebruiken?

What are the (un)favourable effects of opioidantagonists on constipation in patients in the palliative phase who are treated with opioids?

Patients patients in the palliative phase that have constipation and are treated with opioids  
Intervention methylnaltrexone, naloxegol, naloxone, naldemedine, alvimopan  
Comparator no treatment, placebo, other of the interventions  
Outcome symptom relief, patient satisfaction, adverse effects

#### Search strategy research question 4, 5, 6, 7 and 9

The search of research question 4, 5, 6, 7 and 9 was combined.

On November 6, 2020 the scientific literature is searched in databases Medline, Embase, Cinahl and the Cochrane Library. The search strings are shown in this appendix.

The literature has been selected systematically based on the following predefined criteria:

- Design: randomized clinical trials (RCT's), controlled clinical trials (CCT's) and systematic reviews assessing RCT's and CCT's
- Publication dates: from inception to search date
- The outcomes are reported

Literature was excluded when it concerned a conference abstract, when the study examined interventions in a non-palliative patient population, when no quantitative data was presented or when no comparison was made.

#### Search results research question 4, 5, 6, 7 and 9

The selection criteria were applied on the references yielded from the search. 280 unique hits were screened on title and abstract (Table 3). Of these, 213 were excluded. Of the remaining 67 papers, the full-text was retrieved. Based on the full-text, no papers were included for research questions 4 and 6, two papers were included for research question 5, 1 paper was included for research question 7 and 1 paper was included for research question 9.

The included papers for research question 5 are:

- Agra Y, Sacristan A, Gonzalez M, Ferrari M, Portugués A, Calvo MJ. 'Efficacy of senna versus lactulose in terminal cancer patients treated with opioids', J Pain Symptom Manage. 1998;15(1):1–7.
- Ramesh PR, Kumar KS, Rajagopal MR, Blachandran P, Warriar PK. Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna. J Pain Symptom Manage. 1998;16(4):240–244.

The included paper for research questions 7 is:

- Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Vol. 2015, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2015.

The included paper for research questions 9 is:

- Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Database Syst Rev. 2018;6(6):CD006332.

Table 4 provides an overview of the excluded studies with reasons.

Table 3. Overall search results of research question 4, 5, 6, 7 and 9.

| Database | Number of hits |
|----------|----------------|
| Medline  | 87             |
| Embase   | 106            |

|                                   |            |
|-----------------------------------|------------|
| Cinahl                            | 223        |
| Cochrane Library                  | 39         |
| <b>Total hits</b>                 | <b>455</b> |
| n excluded (language, duplicates) | 175        |
| <b>Total unique eligible hits</b> | <b>280</b> |

Table 4. Overview of excluded studies based on full-text evaluation of research question 4, 5, 6, 7 and 9.

| Reference  | Reason for exclusion  |
|--|---|
| Agra, Y., et al. (1998). "Efficacy of senna versus lactulose in terminal cancer patients treated with opioids." <i>Journal of Pain &amp; Symptom Management</i> 15(1): 1-7   | Included for research question 5, wrong population for other research questions         |
| Ahmedzai, S. H. and J. W. Boland (2015). "Constipation: opioid antagonists in people prescribed opioids." <i>Clinical Evidence</i> 11: 11  | Wrong patient population  |
| Bader, S., et al. (2012). "[Is the pharmacological treatment of constipation in palliative care evidence based? : a systematic literature review]." <i>Der Schmerz</i> 26(5): 568-586.   | Review. Primary studies are included  |
| Becker, G., et al. (2007). "Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review." <i>Journal of Pain &amp; Symptom Management</i> 34(5): 547-565   | Wrong patient population  |
| Boyle, D. J., et al. (2014). "Electrically stimulated gracilis neosphincter for end-stage fecal incontinence: The long-term outcome." <i>Diseases of the Colon and Rectum</i> 57(2): 215-222.  | Wrong patient population  |
| Bui, K., et al. (2014). "The effects of mild or moderate hepatic impairment on the pharmacokinetics, safety, and tolerability of naloxegol." <i>Journal of Clinical Pharmacology</i> 54(12): 1368-1374   | Pharmacokinetic study in healthy volunteers   |
| Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Vol. 2015, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2015.                           | Included for research question 7, wrong patient population for other research questions |
| Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018. | Included for research question 9, wrong patient population for other                    |

|   |   |
|---|---|
|   | research questions                            |
| Chamberlain, B. H., et al. (2009). "Methylnaltrexone treatment of opioid-induced constipation in patients with advanced illness." <i>Journal of Pain &amp; Symptom Management</i> 38(5): 683-690  | Posthoc study of already included study       |
| Chau, D. L., et al. (2008). "Opiates and elderly: Use and side effects." <i>Clinical Interventions in Aging</i> 3(2): 273-278.  | Narrative review, Wrong patient population    |
| Cheng, C. W., et al. (2013). "A cross-sectional study of constipation and laxative use in advanced cancer patients: insights for revision of current practice." <i>Supportive Care in Cancer</i> 21(1): 149-156   | No comparative study                          |
| Cherny, N. I. (2004). "Taking care of the terminally ill cancer patient: Management of gastrointestinal symptoms in patients with advanced cancer." <i>Annals of Oncology</i> 15 (SUPPL. 4): iv205-iv213  | Narrative review                              |
| Clark, K. (2016). "Assessing the presence and severity of constipation with plain radiographs in constipated palliative care patients." <i>Palliative Medicine</i> 30 (6): NP14-NP15  | No intervention study                         |
| Clark, K., et al. (2012). "A retrospective pilot study to explore the timing of cessation of laxatives before death in a palliative care unit." <i>International Journal of Palliative Nursing</i> 18(7): 326-330                                       | Full-text not available                       |
| Clark, K., et al. (2011). "Exploring the relationship between the frequency of documented bowel movements and prescribed laxatives in hospitalized palliative care patients." <i>American Journal of Hospice and Palliative Medicine</i> 28(4): 258-263 | No comparative study                          |
| Clark, K. and N. Byfieldt (2014). "A study to explore which constipation symptoms predict satisfaction with management of constipation and which exacerbate the impact of the problem on the individual." <i>Palliative Medicine</i> 28 (6): 672        | Conference abstract                           |
| Clark, K., et al. (2010). "The impact of opioids, anticholinergic medications and disease progression on the prescription of laxatives in hospitalized palliative care patients: a retrospective analysis." <i>Palliative Medicine</i> 24(4): 410-418   | No comparative study                          |
| Clemens, K. E., et al. (2013). "Pharmacological treatment of constipation in palliative care." <i>Current Opinion in Supportive &amp; Palliative Care</i> 7(2): 183-191   | Selective review                              |
| Crowther, A. G. O. (1978). "Management of constipation in terminally ill patients." <i>Journal of International Medical Research</i> 6(4): 348-35   | No comparative study                          |
| Davis, M. (2016). "Managing constipation without laxatives: What is new? is it possible? Should we?" <i>Journal of Pain and Symptom Management</i> 51 (2): 346-347  | Conference abstract                           |
| Dickerson, D. and M. Nunnally (2010). "Methylnaltrexone relieves opioid-induced constipation and undiagnosed c. difficile septic ileus in a critically ill patient." <i>Critical Care Medicine</i> 12): A274  | Single case study                             |
| Earnshaw, S. R., et al. (2010). "Methylnaltrexone bromide for the treatment of opioid-induced constipation in patients with advanced illness--a cost-effectiveness analysis." <i>Alimentary Pharmacology &amp; Therapeutics</i> 31(8): 911-921          | Cost effectiveness analysis of included study |

|  |  |
|--|--|
| Elsner, F. and T. Pastrana (2011).<br>"Chronic constipation in patients receiving palliative care: Current treatment options and challenges." <i>Onkologie</i> 6): 52  | Conference abstract                      |
| Emmanuel, A., et al. (2017). "Constipation in older people: A consensus statement." <i>International Journal of Clinical Practice</i> 71 (1) (no pagination)(e12920)   | Consensus statement                      |
| Erichsen, E., et al. (2016). "Constipation in specialized palliative care: factors related to constipation when applying different definitions." <i>Supportive Care in Cancer</i> 24(2): 691-698   | No intervention study                    |
| Falbo, P. T., et al. (2019). "[Analysis of the European Consensus on the treatment of opioid-induced constipation analgesic drugs.]." <i>Recenti Progressi in Medicina</i> 110(7): 338-342   | Full-text not available                  |
| Ferrell, B. (2008). "Polyethylene glycol laxative for chronic constipation." <i>Journal of Pain and Palliative Care Pharmacotherapy</i> 22(2): 149-150   | Conference abstract?                     |
| Flerlage, J. E. and J. N. Baker (2015). "Methylnaltrexone for Opioid-Induced Constipation in Children and Adolescents and Young Adults with Progressive Incurable Cancer at the End of Life." <i>Journal of Palliative Medicine</i> 18(7): 631-633                   | Case series, No comparative study        |
| Foss, J. (2009). "How safe and effective is methylnaltrexone for the treatment of opioid-induced constipation in advanced illness?" <i>Nature Clinical Practice Gastroenterology and Hepatology</i> 6(1): 12-13  | Commentary                               |
| Gandara Del Castillo, A., et al. (2018). "Prevalence of the need for sodium intake restriction and the use of laxatives in palliative patients." <i>Revista Espanola de Enfermedades Digestivas</i> 110(11): 712-717   | No intervention study                    |
| Ginex, P., et al. (2020). "Prevention and Treatment of Chronic and Opioid-Induced Constipation in Patients with Cancer: A Systematic Review and Meta-Analysis (RP511)." <i>Journal of Pain and Symptom Management</i> 60 (1): 235                                    | Conference abstract                      |
| Goodman, M., et al. (2005). "Constipation management in palliative care: A survey of practices in the United Kingdom." <i>Journal of Pain and Symptom Management</i> 29(3): 238-244  | No comparative study                     |
| Halabi, I. M. (1999). "Cisapride in management of chronic pediatric constipation." <i>Journal of Pediatric Gastroenterology &amp; Nutrition</i> 28(2): 199-20  | Wrong patient population                 |
| Hasson, F., et al. (2020). "'Take more laxatives was their answer to everything': A qualitative exploration of the patient, carer and healthcare professional experience of constipation in specialist palliative care." <i>Palliative Medicine</i> 34(8): 1057-1066 | Focus group study, no intervention study |
| Herndon, C. M., et al. (2002). "Management of opioid induced gastrointestinal effects in patients receiving palliative care." <i>Pharmacotherapy: The Journal of Human Pharmacology &amp; Drug Therapy</i> 22(2 I): 240-250  | Narrative review                         |
| Hurdon, V., et al. (2000). "How useful is docusate in patients at risk for constipation? A systematic review of the evidence in the chronically ill." <i>Journal of Pain &amp; Symptom Management</i> 19(2): 130-136   | Wrong population                         |
| Iskedjian, M., et al. (2011). "Methylnaltrexone in the treatment of opioid-induced constipation in cancer patients receiving palliative care: Willingness-to-pay and cost-benefit analysis." <i>Journal of Pain and Symptom Management</i> 41(1): 104-115            | Survey                                   |
| Janku, F., et al. (2016). "Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer." <i>Annals of Oncology</i> 27(11): 2032-2038  | Posthoc analysis of                      |

|   | included studies                                |
|---|---|
| Kawubiri, W. (2018). "Assessment of practice of managing constipation in patients on oral morphine at initial three subsequent visits at J.O.Y hospice mbale Uganda in 2014." Supportive Care in Cancer 26 (2 Supplement 1): S318   | Conference abstract                             |
| Kot, T. V. and N. A. Pettit-Young (1992). "Lactulose in the management of constipation: a current review." Annals of Pharmacotherapy 26(10): 1277-1282  | Narrative review                                |
| Kraus, D., et al. (2016). "Constipation in Duchenne Muscular Dystrophy: Prevalence, Diagnosis, and Treatment." Journal of Pediatrics 171: 183-188   | No intervention study, wrong patient population |
| Larkin, P. J., et al. (2008). "The management of constipation in palliative care: Clinical practice recommendations." Palliative Medicine 22(7): 796-807  | Review. Primary studies are included            |
| Laubisch, J. E. and J. N. Baker (2013). "Methylnaltrexone use in a seventeen-month-old female with progressive cancer and rectal prolapse." Journal of Palliative Medicine 16(11): 1486-1488  | Single case study                               |
| Laval, G., et al. (2000). "The use of steroids in the management of inoperable intestinal obstruction in terminal cancer patients: Do they remove the obstruction?" Palliative Medicine 14(1): 3-10   | Wrong patient population                        |
| Lu, C. Y., et al. (2019). "Association of Constipation with risk of end-stage renal disease in patients with chronic kidney disease." BMC Nephrology 20 (1) (no pagination)(304)  | No intervention study                           |
| McIlfratrick, S., et al. (2019). "Examining constipation assessment and management of patients with advanced cancer receiving specialist palliative care: A multi-site retrospective case note review of clinical practice." BMC Palliative Care 18 (1) (no pagination)(57) | No intervention study                           |
| Miles, C. L., et al. (2006). "Laxatives for the management of constipation in palliative care patients." Cochrane Database of Systematic Reviews (4) (no pagination)(CD003448)  | Review. Primary studies are included            |
| Moore, J., et al. (2018). "Physician practices surrounding constipation management in hospitalized older adults." Journal of Hospital Medicine. Conference: Hospital Medicine, HM 13(4 Supplement 1)  | Conference abstract                             |
| Mori, M., et al. (2017). "Phase II trial of subcutaneous methylnaltrexone in the treatment of severe opioid-induced constipation (OIC) in cancer patients: an exploratory study." International Journal of Clinical Oncology 22(2): 397-404                                 | No comparative study                            |
| Mozaffari, S., et al. (2018). "Methylnaltrexone bromide for the treatment of opioid-induced constipation." Expert Opinion on Pharmacotherapy 19(10): 1127-1135  | Narrative review                                |
| Muldrew, D. H. L., et al. (2018). "Assessment and management of constipation for patients receiving palliative care in specialist palliative care settings: A systematic review of the literature." Palliative Medicine 32(5): 930-938                                      | No comparative study                            |
| Radbruch, L., et al. (2000). "Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine." Palliative Medicine 14(2): 111-119   | No intervention study                           |

|   |   |
|---|---|
| Ramesh, P. R., et al. (1998). "Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna." <i>Journal of Pain &amp; Symptom Management</i> 16(4): 240-244.  | Included for research question 5, wrong population for other research questions |
| Rauk, R. L. (2013). "Treatment of opioid-induced constipation: Focus on the peripheral mu-opioid receptor antagonist methylnaltrexone." <i>Drugs</i> 73(12): 1297-1306  | Narrative review  |
| Sawh, S. B., et al. (2012). "Use of methylnaltrexone for the treatment of opioid-induced constipation in critical care patients." <i>Mayo Clinic Proceedings</i> 87(3): 255-259   | Wrong patient population  |
| Schoorl, J. and Z. Zyllicz (1997). "Laxative policy for terminal patients ineffective. [Dutch]." <i>Nederlands Tijdschrift voor Geneeskunde</i> 141(17): 823-826  | Full-text not available   |
| Shoop, C. and Y. Hu (2016). "Naloxegol for treating opioid-induced constipation n patients with non-cancer pain." <i>Journal of Pain and Symptom Management</i> 51 (2): 412   | Conference abstract   |
| Skollerud, L. M., et al. (2013). "Laxative prescriptions to cancer outpatients receiving opioids: a study from the Norwegian prescription database." <i>Supportive Care in Cancer</i> 21(1): 67-73  | No intervention study   |
| Slatkin, N., et al. (2009). "Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients." <i>The Journal of Supportive Oncology</i> 7(1): 39-46   | No prevention   |
| Sumida, K., et al. (2020). "Constipation in CKD." <i>Kidney International Reports</i> 5(2): 121-134   | Narrative review  |
| Sykes, N. P. (1996). "A volunteer model for the comparison of laxatives in opioid-related constipation." <i>Journal of Pain and Symptom Management</i> 11(6): 363-369   | Wrong patient population  |
| Sykes, N. P. (1996). "An investigation of the ability of oral naloxone to correct opioid-related constipation in patients with advanced cancer." <i>Palliative Medicine</i> 10(2): 135-144  | No prevention   |
| Tack, J., et al. (2013) "Efficacy and safety of naloxegol in patients with opioidinduced constipation (OIC): Results from 2 identical phase 3, prospective, randomized, multicenter, double-blind, controlled trials." <i>Supportive Care in Cancer</i> 1): S260    | Conference abstract   |
| Thomas, J., et al. (2008). "Methylnaltrexone for opioid-induced constipation in advanced illness." <i>New England Journal of Medicine</i> 358(22): 2332-2343  | No prevention   |
| Zhe, H. (2016). "The assessment and management of constipation among patients with advanced cancer in a palliative care ward in China: A best practice implementation project." <i>JBI Database of Systematic Reviews and Implementation Reports</i> 14(5): 295-309 | No intervention study   |

#### Search strings research question 4, 5, 6, 7 and 9

#### OVID MEDLINE

- 1 normacol.af. (11)
- 2 movicolon.af. (1)
- 3 Sugar Alcohols/ (2386)
- 4 Magnesium Sulfate/ (5157)

- 5 Phosphates/ (63100)  
6 exp Bisacodyl/ (422)  
7 senna extract/ or sennosides/ (644)  
8 Benzofurans/ (12512)  
9 Constipation/dt [Drug Therapy] (2356)  
10 Linzess.af. (18)  
11 (linaclotide or Linzess).tw,rn,kw. (305)  
12 prucaloprid\*.tw,rn,kw. (387)  
13 senna extract/ or sennosides/ (644)  
14 sennoside\*.tw,rn,kw. (485)  
15 bisacodyl.tw,rn,kw. (653)  
16 Magnesium Sulfate/ (5157)  
17 sodium phospho\*.tw,rn,kw. (6059)  
18 LACTULOSE/ (2165)  
19 lactulose.tw,rn,kw. (3980)  
20 lactitol.tw,rn,kw. (322)  
21 magnesium hydroxide/ (1148)  
22 magnesium hydroxide.tw,rn,kw. (1497)  
23 movicolon.tw,rn,kw. (1)  
24 "Polyethylene Glycols"/ (55042)  
25 sterculiagom.tw,rn,kw. (0)  
26 plant extracts/ or psyllium/ or exp senna extract/ (116013)  
27 exp Laxatives/ (5334)  
**28 or/1-27 (267913)=treatment options**  
29 "AvE constipation in palliative care".ti. (0)  
30 Constipation/ (14129)  
31 Defecation/ (7152)  
32 Fecal Incontinence/ (9947)  
33 Feces/ (92512)  
34 Diarrhea/ (48122)  
35 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\*  
adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or  
(fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or  
faeces).ti,kw. (52839)  
36 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or  
(evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3  
symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or  
(void\* adj3 bowel\*) or (strain\* adj3 bowel\*)).ti,kw. (4893)  
37 Fecal Impaction/ (1062)  
38 or/30-37 (173840)  
39 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\*  
adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or  
(fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or  
faeces).tw,kw. (181916)  
40 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or  
(evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3  
symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or  
(void\* adj3 bowel\*) or (strain\* adj3 bowel\*) or (irritable adj bowel adj syndrome)).tw,kw.  
(36857)  
41 Gastrointestinal Motility/ (21256)  
**42 or/30-41 (298215)=constipation**  
43 Palliative Care/ (54813)  
44 Terminal Care/ (28534)

45 Terminally Ill/ (6553)  
46 Hospice Care/ (6568)  
47 (palliat\* or terminal\* or endstage or hospice\* or (end adj2 life) or (care adj3 dying) or  
((advanced or late or last or end or final) adj2 (stage\* or phase\*))).tw,kw. (748871)  
48 "advanced disease\*".tw,kw. (20570)  
49 ("end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage").tw,kw.  
(69274)  
50 (terminal\* adj6 care\*).tw,kw. (4150)  
51 (terminal\* adj6 (ill\* or disease)).tw,kw. (11194)  
52 terminal?stage\*.tw,kw. (12)  
53 (dying or (close adj6 death)).tw,kw. (36006)  
**54 or/43-53 (817134)= palliative phase**  
55 42 and 54 (7531)  
56 Constipation/dg (489)  
57 Constipation/di (1717)  
58 exp Radiography, Abdominal/ (42028)  
59 ((abdominal adj3 radiogr\*) or (plain adj3 radiogra\*)).tw,kw. (14509)  
60 exp Tomography, X-Ray Computed/ (437598)  
61 (ct or (computer adj3 tomograp\*)).tw,kw. (353397)  
62 hypercalciemi\*.tw,kw. (9)  
63 Hypercalcemia/bl [Blood] (1431)  
64 hypercalc\*.tw,kw. (22201)  
65 exp clinical laboratory techniques/ or exp medical history taking/ or exp physical examination/  
or early diagnosis/ (3930904)  
66 (physical adj3 exam\*).tw,kw. (72755)  
67 thyroid diseases/ or exp hypothyroidism/ (48394)  
68 dg.fs. (1203366)  
69 or/56-68 (5363775)  
70 55 and 69 (1589)  
71 or/30-37,39-40 (282604)  
72 54 and 71 (7160)  
73 69 and 72 (1520)  
74 ((patient adj3 report\*) or mortalit\* or accura\* or adverse or cost? or (patient adj3  
satisfact\*)).tw,kw. (2621664)  
75 73 and 74 (232)  
76 "filter systematic reviews".ti. (0)  
77 meta analysis.pt. (121698)  
78 (meta-anal\$ or metaanal\$).tw,kf. (186448)  
79 (quantitativ\$ adj10 (review\$ or overview\$)).tw. (9767)  
80 (systematic\$ adj10 (review\$ or overview\$)).tw. (205051)  
81 (methodologic\$ adj10 (review\$ or overview\$)).tw. (12336)  
82 (quantitativ\$ adj10 (review\$ or overview\$)).kf. (79)  
83 (systematic\$ adj10 (review\$ or overview\$)).kf. (21659)  
84 (methodologic\$ adj10 (review\$ or overview\$)).kf. (79)  
85 medline.tw. and review.pt. (80341)  
86 (pooled adj3 analy\*).tw. (20830)  
87 (pooled adj3 analy\*).kf. (282)  
88 "cochrane\$.fc\_jour. (15058)  
89 or/77-88 (374878)  
90 "medline rct filter".ti. (0)  
91 controlled-clinical-trial.pt. (93908)  
92 randomized-controlled-trial.pt. (516213)  
93 randomized controlled trial/ (516213)

94 randomi?ed controlled trial?.tw. (184514)  
 95 randomi?ed controlled trial?.kf. (11901)  
 96 random-allocation.tw,kf. (1747)  
 97 double-blind-method.tw,kf. (501)  
 98 single-blind-method.tw,kf. (90)  
 99 (random adj8 (selection? or sample?)).kf,tw. (46306)  
 100 random\*.tw,kf. (1172025)  
 101 or/91-100 (1382184)  
 102 73 and 89 (17)  
 103 "diagnose filter".ti. (0)  
 104 exp "Sensitivity and Specificity"/ (591081)  
 105 sensitivity.tw. (813566)  
 106 sensitivity.kf. (18179)  
 107 specificity.tw. (470125)  
 108 specificity.kf. (7932)  
 109 ((pre-test or pretest) adj probability).tw. (2295)  
 110 ((pre-test or pretest) adj probability).kf. (69)  
 111 ((post-test or posttest) adj probability).tw. (896)  
 112 ((post-test or posttest) adj probability).kf. (18)  
 113 predictive value\$.tw. (111068)  
 114 predictive value\$.kf. (1361)  
 115 likelihood ratio\$.tw. (15928)  
 116 likelihood ratio\$.kf. (598)  
 117 or/104-116 (1502902)  
 118 73 and 117 (105)  
 119 101 and 118 (7)  
 120 73 and 101 (119)  
 121 (palliat\* or terminal\* or endstage or hospice\* or (end adj2 life) or (care adj3 dying) or  
 ((advanced or late or last or end or final) adj2 (stage\* or phase\*))).ti,kw. (137173)  
 122 "advanced disease\*".ti,kw. (745)  
 123 ("end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage").ti,kw.  
 (13496)  
 124 (terminal\* adj6 care\*).ti,kw. (1742)  
 125 (terminal\* adj6 (ill\* or disease)).ti,kw. (2947)  
 126 terminal?stage\*.ti,kw. (11)  
 127 (dying or (close adj6 death)).ti,kw. (8537)  
 128 43 or 44 or 45 or 46 or 121 or 122 or 123 or 124 or 125 or 126 or 127 (184306)  
 129 120 and 128 (27)  
 130 102 and 128 (8)  
 131 "Filter observationele studies".ti. (0)  
 132 epidemiologic studies/ (8445)  
 133 exp case-control studies/ (1115022)  
 134 exp cohort studies/ (2048881)  
 135 cross-sectional studies/ (341944)  
 136 (case adj3 control).tw,kf. (135508)  
 137 (cohort adj5 (study or studies or analy\$)).tw,kf. (283429)  
 138 (follow-up adj5 (study or studies)).tw,kf. (92432)  
 139 (longitudinal or retrospective or prospective or (cross adj5 sectional)).tw,kf. (1629212)  
 140 (observational adj5 (study or studies)).tw,kf. (152635)  
 141 or/132-140 (3286558)  
 142 73 and 128 and 141 (84)  
**143 28 and 55 (292)= treatment options + constipation + palliative phase**  
 144 128 and 141 and 143 (32)

145 opioid\*.tw. (92076)  
 146 144 not 145 (14)  
 147 42 and 54 and 28 and (89 or 101) (56)  
 148 147 not 145 (31)  
 149 exp Morphine Derivatives/ (50940)  
 150 exp Fentanyl/ (15956)  
 151 (fentanyl or morphine or opioid\*).tw,rn,kw. (147877)  
 152 or/149-151 (158133) opioden  
 153 144 and 152 (21)  
 154 42 and 54 and 28 and 152 and (89 or 101) (27)= sr of rct  
 155 from 146 keep 1-14 (14)  
 156 from 153 keep 1-21 (21)  
 157 from 154 keep 1-27 (27)  
 158 exp Analgesics, Opioid/ (117527)  
**159 152 or 158 (186740)= opioids**  
 160 42 and 54 and 28 and 159 and (89 or 101) (29) def SR or rct for question 3  
 161 (42 and 54 and 28 and 152 and 141) not (89 or 101) (23) def observat  
 162 42 and 54 and 28 and (89 or 101) (56)= question 2 rct or sr but incl treatment with opioids  
 163 162 not 160 (27)= question 2 rct or SR no opioids  
 164 (42 and 54 and 28 and 141) not (89 or 101) (43)= question 2 observat but incl treatment met  
 opioids  
 165 164 not 161 (20)= )= question 2 observat but no treatment with opioids  
 166 from 160 keep 1-29 (29)  
 167 from 161 keep 1-23 (23)  
 168 from 165 keep 1-20 (20)  
 169 (42 and 54 and 28 and 159 and 141) not (89 or 101) (24)= slot def observat question 3  
 170 42 and 54 and 28 and (89 or 101) (56)  
 171 162 not 159 (27)  
 172 "thomas\$.fc\_auts. and "methyl".fc\_titl. and "2008".fc\_pubyr. (14)  
 173 from 169 keep 1-24 (24)  
 174 from 172 keep 8 (1)  
 175 "candy\$.fc\_auts. and "laxatives for the manag".fc\_titl. and "2015".fc\_pubyr. (1)  
 176 42 and 54 and 28 and 159 and 174 (1)  
 177 170 and 174 (1)  
 178 162 and 175 (1)

#### EMBASE

1 "obstipatie palliatieve behandeling of preventie".ti. (0)  
 2 "embase constipation in palliative care".ti. (0)  
 3 exp constipation/ (92332)  
 4 defecation/ (13553)  
 5 defecation disorder/ (2610)  
 6 defecation measurement/ (85)  
 7 feces incontinence/ (20999)  
 8 feces/ (59916)  
 9 hard feces/ (599)  
 10 diarrhea/ (235533)  
 11 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\*  
 adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or  
 (fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or  
 faeces).ti,kw. (65299)  
 12 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or  
 (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3

symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or  
 (void\* adj3 bowel\*) or (strain\* adj3 bowel\*).ti,kw. (7938)

13 feces impaction/ (1734)  
 14 or/3-13 (395027)  
 15 exp palliative therapy/ (113165)  
 16 exp terminal care/ (70588)  
 17 terminally ill patient/ or hospice patient/ (8731)  
 18 (palliat\* or terminal\* or endstage or hospice\* or (end adj3 life) or (care adj3 dying) or  
 ((advanced or late or last or end or final) adj3 (stage\* or phase\*))).ti,kw. (190624)  
 19 or/15-18 (294360)  
 20 14 and 19 (6471)  
 21 practice guideline/ (436517)  
 22 guideline?.ti. (105364)  
 23 21 or 22 (467556)  
 24 20 and 23 (332)  
 25 exp \*constipation/ (14175)  
 26 9 or 11 or 12 or 13 or 25 (75811)  
 27 23 and 26 (1151)  
 28 19 and 27 (34)  
 29 "filter systematic reviews & meta-analyses Embase ".ti. (0)  
 30 meta analysis/ (200850)  
 31 "systematic review"/ (270009)  
 32 (meta-analy\$ or metaanaly\$).tw. (243564)  
 33 (meta-analy\$ or metaanaly\$).kw. (59154)  
 34 (systematic\$ adj4 (review\$ or overview\$)).tw. (254189)  
 35 (systematic\$ adj4 (review\$ or overview\$)).kw. (32311)  
 36 (quantitativ\$ adj5 (review? or overview?)).tw,kw. (5731)  
 37 (methodologic adj5 (overview? or review?)).tw,kw. (392)  
 38 (review\$ adj3 (database? or medline or embase or cinahl)).tw,kw. (29620)  
 39 (pooled adj3 analy\$).tw,kw. (32185)  
 40 (extensive adj3 review\$ adj3 literature).tw,kw. (3908)  
 41 (meta or synthesis or (literature adj8 database?) or extraction).tw,kw. (1515386)  
 42 review.pt. (2657180)  
 43 41 and 42 (170154)  
 44 or/30-40,43 (602667)  
 45 19 and 26 and 44 (43)  
 46 exp abdominal radiography/ (31584)  
 47 ((abdominal adj3 radiogr\*) or (plain adj3 radiogra\*)).tw,kw. (18706)  
 48 exp x-ray computed tomography/ (60916)  
 49 (ct or (computer adj3 tomograp\*)).tw,kw. (615944)  
 50 hypercalcemia/di [Diagnosis] (2299)  
 51 hypercalc\*.tw,kw. (28954)  
 52 laboratory technique/ or exp laboratory test/ (169617)  
 53 anamnesis/ (120411)  
 54 exp physical examination/ (252915)  
 55 early diagnosis/ (108873)  
 56 (physical adj3 exam\*).tw,kw. (129767)  
 57 thyroid disease/ or exp hypothyroidism/ (90036)  
 58 hypothyroid\*.tw,kw. (51525)  
 59 or/46-58 (1371256)  
 60 20 and 59 (776)  
 61 44 and 60 (20)  
 62 25 or 26 (75811)

63 \*defecation/ (2125)  
64 62 or 63 (76562)  
65 61 and 64 (2)  
66 "filter randomised controlled trials Embase".ti. (0)  
67 randomization/ (88986)  
68 exp randomized controlled trial/ (632118)  
69 exp controlled clinical trial/ (819657)  
70 Major Clinical Study/ (3929257)  
71 random\$.tw. (1600284)  
72 random\$.kw. (50911)  
73 Double Blind Procedure/ (178442)  
74 or/67-73 (5335138)  
75 60 and (44 or 74) and 64 (14)  
76 "filter observationele studies emb sign".ti. (0)  
77 Clinical study/ (156336)  
78 Case control study/ (163460)  
79 Family study/ (26156)  
80 Longitudinal study/ (147316)  
81 Retrospective study/ (988360)  
82 Prospective study/ (640967)  
83 Randomized controlled trials/ (190422)  
84 82 not 83 (634005)  
85 Cohort analysis/ (634518)  
86 (Cohort adj (study or studies)).tw,kw. (324113)  
87 (Case control adj (study or studies)).tw,kw. (140522)  
88 (follow up adj (study or studies)).tw,kw. (68099)  
89 (observational adj (study or studies)).tw,kw. (178159)  
90 (epidemiologic\$ adj (study or studies)).tw,kw. (111404)  
91 (cross sectional adj (study or studies)).tw,kw. (234993)  
92 77 or 78 or 79 or 80 or 81 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 (2862700)  
93 (60 and 64 and 92) not (44 or 74) (5)  
94 from 75 keep 1-14 (14)  
95 from 93 keep 1-5 (5)  
96 exp normacol/ (133)  
97 movicolon.tw,kw. (7)  
98 "movicolon"/ (9)  
99 dietary fiber/ (22473)  
100 ispagula/ (2885)  
101 laxative/ or lactitol/ or lactulose/ or magnesium hydroxide/ or magnesium oxide/ or magnesium  
sulfate/ or senna extract/ or sennoside/ or sennoside a/ or sennoside b/ or sodium dihydrogen  
phosphate/ (50531)  
102 benzofuran derivative/ (5443)  
103 prucalopride/ (1141)  
104 linaclotide/ (957)  
105 exp laxative/dt [Drug Therapy] (21461)  
106 or/96-105 (85172)  
107 20 and 106 (583)  
108 exp opiate/ (88294)  
109 exp morphine derivative/ (202005)  
110 exp fentanyl derivative/ (83571)  
111 (fentanyl or morphine or opioid\*).tw,rm,kw. (251260)  
112 or/108-111 (351015)  
113 107 and (44 or 74) (135)

- 114 107 and (44 or 74) and 112 (98)= question 3 treatment prevention SR or rct  
 115 113 not 114 (37)= question 2 treatment prevention SR or rct  
 116 107 and 92 (68)  
 117 107 and 92 and 112 (48) = question 3 treatment prevention observat  
 118 116 not 117 (20) question 2 treatment prevention observat

CINAHL

- S1 (MH "Constipation+") (6,192)  
 S2 (MH "Defecation") (1,427)  
 S3 (MH "Fecal Incontinence") (3,030)  
 S4 (MH "Feces+") (9,194)  
 S5 (MH "Diarrhea") (10,686)  
 S6 TI ( (constipat\* or (hard N3 stool\*) or (bowel N3 symptom\*) or (impact\* N3 stool\*) or (impact\* N3 feces) or (impact\* N3 faeces) or (fecal\* N3 incontin\*) or (faecal\* N3 incontin\*) or (fecal\* N3 impact\*) or (faecal\* N3 impact\*) or (loose N3 stool\*) or diarrh\* or feces or faeces) ) OR AB ( (constipat\* or (hard N3 stool\*) or (bowel N3 symptom\*) or (impact\* N3 stool\*) or (impact\* N3 feces) or (impact\* N3 faeces) or (fecal\* N3 incontin\*) or (faecal\* N3 incontin\*) or (fecal\* N3 impact\*) or (faecal\* N3 impact\*) or (loose N3 stool\*) or diarrh\* or feces or faeces) ) (29,194)  
 S7 TI ( (defecat\* or (bowel\* N3 function\*) or (bowel\* N3 habit\*) or (bowel\* N3 symptom\*) or (evacuat\* N3 feces) or (evacuat\* N3 feces) or (evacuat\* N3 bowel\*) or (bowel\* N3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*)). ) AND AB ( 36 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*)). ) (1)  
 S8 S1 or S2 or S3 or S4 or S5 or S6 or S7 (43,492)  
 S9 (MH "Palliative Care") OR (MH "Hospice and Palliative Nursing") (40,649)  
 S10 (MH "Terminal Care+") (65,517)  
 S11 (MH "Terminally Ill Patients+") (11,944)  
 S12 (MH "Hospice Care") (9,008)  
 S13 TI ( (palliat\* or terminal\* or endstage or hospice\* or (end N2 life) or (care N3 dying) or ((advanced or late or last or end or final) N2 (stage\* or phase\*))) ) OR AB ( (palliat\* or terminal\* or endstage or hospice\* or (end N2 life) or (care N3 dying) or ((advanced or late or last or end or final) N2 (stage\* or phase\*))) ) (109,512)  
 S14 TI ( "end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage" ) OR AB ( "end-stage disease\*" or "end stage disease\* or end-stage illness" or "end stage" ) (15,245)  
 S15 TI terminal\* N6 care AND AB terminal\* N6 care (227)  
 S16 TI ( (terminal\* N6 (ill\* or disease)) ) AND AB ( (terminal\* N6 (ill\* or disease)) ) (823)  
 S17 TI ( dying or (close N6 death) ) OR AB ( dying or (close N6 death) ) (16,541)  
 S18 S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 (143,750)  
 S19 S8 and S18 (1,407)  
 S20 (MH "Constipation+/PC/TH/DH/DT") (3,274)  
 S21 (MH "Magnesium Sulfate") (1,580)  
 S22 (MH "Dietary Fiber") (7,417)  
 S23 (MH "Cathartics+") (6,234)  
 S24 TI ( lactulose or lactitol or psyllium\* or sterculiagom or movicolon or sennosi\* ) OR AB ( psyllium\* or sterculiagom or movicolon or sennosi\* ) (363)  
 S25 (MH "Fluid Intake") (3,105)  
 S26 TI ( fluid or movement or exercis\* or laxativ\* or fiber\* ) OR AB ( fluid or movement or exercis\* or laxativ\* or fiber\* ) (251,096)  
 S27 S20 or S21 or S22 or S23 or S24 or S25 or S26 (264,447)  
 S28 S19 and S27 (313)  
 S29 S19 and S27 (223)

## COCHRANE LIBRARY

- #1 MeSH descriptor: [Palliative Care] explode all trees
- #2 MeSH descriptor: [Terminal Care] this term only
- #3 palliative:ti,ab
- #4 MeSH descriptor: [Constipation] this term only
- #5 constipat\*:ti,ab,kw
- #6 (#1 OR #2 OR #3) AND (#4 OR #5)
- #7 (bowel next2 dysfunction\*):TI,kw
- #8 palliat\* or terminal\* or endstage or hospice\*:ti,kw
- #9 #1 OR #2 OR #3 OR #8
- #10 #4 OR #5 OR #7
- #11 #9 AND #10
- #12 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [diagnostic imaging - DG, diagnosis - DI]
- #13 MeSH descriptor: [Radiography, Abdominal] explode all trees
- #14 ((abdominal next3 radiogra\*) or (plain next3 radiogra\*)):ti,ab,kw
- #15 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
- #16 (ct or (computer next tomograp\*)):ti,ab,kw
- #17 hypercalc\*:ti,ab,kw
- #18 MeSH descriptor: [Hypercalcemia] explode all trees
- #19 MeSH descriptor: [Clinical Laboratory Techniques] explode all trees
- #20 MeSH descriptor: [Medical History Taking] explode all trees
- #21 MeSH descriptor: [Physical Examination] this term only
- #22 (physic\* next3 exam\*):ti,ab,kw
- #23 hypothyroid\*:ti,ab,kw
- #24 MeSH descriptor: [Hypothyroidism] explode all trees
- #25 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
- #26 #11 and #25
- #27 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
- #28 #11 and #27
- #29 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [diagnostic imaging - DG, diagnosis - DI]
- #30 #13 or #15 or #18 or #19 or #20 or #21 or #24
- #31 #11 and #27 and #30
- #32 ((abdominal next3 radiogra\*) or (plain next3 radiogra\*)):ti
- #33 (ct or (computer next tomograp\*)):ti
- #34 hypercalc\*:ti
- #35 (physic\* next3 exam\*):ti
- #36 hypothyroid\*:ti
- #37 #32 or #33 or #34 or #35
- #38 #11 and #27 and (#30 or #37)
- #39 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [drug therapy - DT]
- #40 MeSH descriptor: [Magnesium Sulfate] explode all trees
- #41 MeSH descriptor: [Phosphates] explode all trees
- #42 MeSH descriptor: [Bisacodyl] explode all trees
- #43 MeSH descriptor: [Senna Extract] this term only
- #44 MeSH descriptor: [Benzofurans] this term only
- #45 (linaclotide or Linzess):ti
- #46 prucaloprid\*:ti
- #47 sennoside:ti
- #48 bisacodyl:ti
- #49 MeSH descriptor: [Magnesium Sulfate] explode all trees

- #50 sodium next phosphat\*:ti
- #51 MeSH descriptor: [Lactulose] explode all trees
- #52 (lactulose or lactitol):ti
- #53 MeSH descriptor: [Magnesium Hydroxide] explode all trees
- #54 magnesium next hydroxide:ti
- #55 MeSH descriptor: [Dietary Fiber] explode all trees
- #56 MeSH descriptor: [Plant Extracts] this term only
- #57 MeSH descriptor: [Psyllium] explode all trees
- #58 MeSH descriptor: [Senna Extract] this term only
- #59 MeSH descriptor: [Laxatives] this term only
- #60 (laxant\* or laxati\*):ti
- #61 #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
- #62 #11 and #61
- #63 MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [prevention & control - PC]
- #64 #63 and #9
- #65 ((feeding or nutrition) NEAR/3 (tube or enteral)):ti,ab,kw
- #66 MeSH descriptor: [Nutritional Support] explode all trees
- #67 #65 or #66
- #68 #11 and #6**

## Onderzoeksvraag 8: bijwerkingen

### Onderzoeksvraag 8: bijwerkingen van behandeling met laxantie

Wat is het verschil in bijwerkingen tussen lactulose, lactitol (importal) en macrogol bij patiënten met obstipatie (in de palliatieve fase)?

What is the difference in side effects between lactulose, lactitol (importal) and macrogol in patients with constipation (in the palliative phase)?

|              |                                 |
|--------------|---------------------------------|
| Patients     | patients that have constipation |
| Intervention | lactulose                       |
| Comparator   | lactitol, macrogol              |
| Outcome      | adverse effects                 |

### Search strategy research question 8

On March 24, 2021 the scientific literature is searched in databases Medline and Embase. The search strings are shown in this appendix.

The literature has been selected systematically based on the following predefined criteria:

- Design: randomized clinical trials (RCT's), controlled clinical trials (CCT's) and observational studies
- Publication dates: from inception to search date
- The outcomes are reported

Literature was excluded when no quantitative data was presented or when no comparison was made.

### Search results research question 8

The selection criteria were applied on the references yielded from the search. 306 unique hits were screened on title and abstract (Table 5). Of these, 299 were excluded. Of the remaining 8 papers, the full-text was retrieved. Based on the full-text, 3 papers were included:

- Chassagne P, Ducrotte P, Garnier P, Mathiex-Fortunet H. Tolerance and long-term efficacy of polyethylene glycol 4000 (Forlax®) compared to lactulose in elderly patients with chronic constipation. *Journal of Nutrition, Health and Aging*. 2017;21(4):429–439.
- Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus Polyethylene Glycol for Chronic Constipation. *Cochrane Database Syst Rev* 2010;7(7):CD007570.
- Mueller-Lissner SA, Wald A. Constipation in adults. *BMJ clinical evidence*. 2010;2010:0413.

Table 6 provides an overview of the excluded studies with reasons.

Table 5. Overall search results of research question 8.

| Database                          | Number of hits |
|-----------------------------------|----------------|
| Medline                           | 122            |
| Embase                            | 184            |
| <b>Total hits</b>                 | <b>306</b>     |
| n excluded (language, duplicates) | -              |
| <b>Total unique eligible hits</b> | <b>306</b>     |

Table 6. Overview of excluded studies based on full-text evaluation of research question 8.

| Reference   | Reason for exclusion    |
|---|-------------------------|
| Ahmedzai, S.H. & Boland, J. "Constipation in people prescribed opioids." <i>Clinical Evidence</i> 2010;04:2407. | Better review available |

|   |                   |
|---|-------------------|
| Attar, A., Lémann, M., Ferguson, A., et al. "Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic obstipation." Gut 1999;44:226-230.   | Wrong populataion |
| Christie, A.H., Culbert, P., Guest, J.F. "Economic impact of low dose polyethylene glycol 3350 plus electrolytes compared with lactulose in the management of idiopathic constipation in the UK." Pharmacoeconomics 2002;20(1):49-60. | Wrong population  |

### Search strings research question 8

#### OID MEDLINE

- 1 Hypercalcemia/ (12995)
- 2 Constipation/ (14340)
- 3 Defecation/ (7237)
- 4 Fecal Incontinence/ (10049)
- 5 Feces/ (94193)
- 6 Diarrhea/ (48736)
- 7 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\* adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or (fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or faeces).ti,kw. (53890)
- 8 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*)).ti,kw. (5010)
- 9 Fecal Impaction/ (1066)
- 10 or/2-9 (176812)=P obstipatie
- 11 1 and 10 (88)
- 12 (hypercalcemia\* or (milk adj1 alkali adj2 syndrome?)).tw,kw. (14033)
- 13 exp Calcium/bl [Blood] (29834)
- 14 1 or 12 or 13 (46208)
- 15 10 and 14 (449)
- 16 (dutch or english or german or french).la. (29282067)
- 17 15 and 16 (429)
- 18 "filter medline systematic reviews".ti. (0)
- 19 meta analysis.pt. (128585)
- 20 (meta-anal\$ or metaanal\$).tw,kf. (198922)
- 21 (systematic\$ adj10 (review\$ or overview\$)).tw,kf. (222443)
- 22 (quantitativ\$ adj10 (review\$ or overview\$)).tw,kf. (10316)
- 23 (methodologic\$ adj10 (review\$ or overview\$)).tw,kf. (12886)
- 24 medline.tw. and review.pt. (82099)
- 25 (pooled adj3 analy\*).tw,kf. (22125)
- 26 "cochrane\$.fc\_jour. (15277)
- 27 or/19-26 (396628)
- 28 17 and 27 (0)
- 29 "medline filter observationele studies".ti. (0)
- 30 epidemiologic studies/ (8592)
- 31 exp case-control studies/ (1152475)
- 32 exp cohort studies/ (2105407)
- 33 cross-sectional studies/ (357779)
- 34 (case adj3 control).tw,kf. (139586)
- 35 (cohort adj5 (study or studies or analy\$)).tw,kf. (300614)

36 (follow-up adj5 (study or studies)).tw,kf. (94881)  
37 (longitudinal or retrospective or prospective or (cross adj5 sectional)).tw,kf. (1699242)  
38 (observational adj5 (study or studies)).tw,kf. (162421)  
39 or/30-38 (3395907)  
40 17 and 39 (28)  
41 hypercalci\*.tw,kw. (4678)  
42 from 40 keep 3 (1)  
43 (metabolic adj3 analys\*).tw,kw. (8591)  
44 (metabolic adj3 abnormalit\*).tw,kw. (10591)  
45 me.fs. (5677345)  
46 10 and 45 (33223)  
47 1 or 12 or 13 or 41 (49812)  
48 46 and 47 (284)  
49 39 and 48 (9)  
50 43 or 44 or 45 (5686585)  
51 47 and 50 (17709)  
52 10 and 51 (284)  
53 exp Calcium Phosphates/ (35104)  
54 Calcium, Dietary/ (14167)  
55 1 or 12 or 13 or 53 or 54 (93484)=calcium  
56 10 and 16 and 45 and 55 (556)  
57 Prognosis/ (528576)  
58 incidence/ or prevalence/ (551516)  
59 (progn\* or inciden\* or prevale\*).tw,kw. (1435919)  
60 57 or 58 or 59 (1968044)  
61 56 and 60 (3)  
62 (predictive adj3 valu\*).tw,kw. (117118)  
63 60 or 62 (2052006)  
64 10 and 55 and 63 (16)=P + calcium + prognose  
65 sn.fs. (984478)  
66 60 or 62 or 65 (2837327)  
67 10 and 16 and 55 and 66 (15)=P + talen + calcium + voorspelling  
68 Lactulose/ (2191)  
69 L2B0WJF7ZY.rn. (181)  
70 lactitol.tw,kw. (5)  
71 68 or 69 or 70 (2315)  
72 Polyethylene Glycols/ (55938)  
73 macrogol?.tw,kw. (276)  
74 macrogol?.ti. (61)  
75 3WJQ0SDW1A.rn. (55938)  
76 (clensia or colofort or klean?prep or molaxol\* or movicolon\* or moviprep\* or pleinvu\* or ple?nvu\*).tw,kw. (40)  
77 Laxatives/ (1548)  
78 72 or 73 or 74 or 75 or 76 (56120)  
79 10 and 16 and 71 and 78 (51)=P + talen + lactilose + overige  
80 exp Gastrointestinal Agents/tu [Therapeutic Use] (96272)  
81 exp Gastrointestinal Agents/ae (32063)  
82 10 and 80 and 81 (757)  
83 82 and (78 or 71) (67)  
84 10 and 16 and 27 (2357)  
85 84 and (78 or 71) (41)  
86 from 79 keep 1-51 (51)  
87 from 83 keep 1-67 (67)

- 88 10 and 16 and 39 and (78 or 71) (184)= P + talen + observat + medicatie
- 89 88 (184)
- 90 limit 89 to yr="1990 -Current" (175)= P + talen + observat + medicatie na 1990
- 91 comment/ (900614)
- 92 90 not 91 (171)= P + talen + observat + medicatie geen comments
- 93 Palliative Care/ (55823)
- 94 Terminal Care/ (28978)
- 95 Terminally Ill/ (6612)
- 96 Hospice Care/ (6702)
- 97 (palliat\* or terminal\* or endstage or hospice\* or (end adj3 life) or (care adj3 dying) or ((advanced or late or last or end or final) adj3 (stage\* or phase\*))).ti,kw. (140722)
- 98 or/93-97 (183572)
- 99 92 and 98 (3)
- 100 81 and 90 (27)= P + talen + observat + medicatie adverse effects

#### EMBASE

- 1 "obstipation en hypercalcemie".ti. (0)
- 2 exp constipation/ (95194)
- 3 defecation/ (14212)
- 4 defecation disorder/ (2706)
- 5 defecation measurement/ (89)
- 6 feces incontinence/ (21528)
- 7 feces/ (62690)
- 8 hard feces/ (625)
- 9 diarrhea/ (242541)
- 10 (constipat\* or (hard adj3 stool\*) or (bowel adj3 symptom\*) or (impact\* adj3 stool\*) or (impact\* adj3 feces) or (impact\* adj3 faeces) or (fecal\* adj3 incontin\*) or (faecal\* adj3 incontin\*) or (fecal\* adj3 impact\*) or (faecal\* adj3 impact\*) or (loose adj3 stool\*) or diarrh\* or feces or faeces).ti,kw. (67108)
- 11 (defecat\* or (bowel\* adj3 function\*) or (bowel\* adj3 habit\*) or (bowel\* adj3 symptom\*) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 f#eces) or (evacuat\* adj3 bowel\*) or (bowel\* adj3 symptom\*) or (bowel adj3 movement\*) or (intestin\* adj3 motility) or (colon adj3 transit\*) or (void\* adj3 bowel\*) or (strain\* adj3 bowel\*)).ti,kw. (8211)
- 12 feces impaction/ (1774)
- 13 or/2-12 (407612)
- 14 hypercalcemia/ (28114)
- 15 (hypercalcemia\* or (milk adj1 alkali adj2 syndrome?)).tw,kw. (18789)
- 16 calcium/ (290189)
- 17 calcium blood level/ (31902)
- 18 calcium phosphate/ (22215)
- 19 calcium intake/ (15442)
- 20 (calcium adj3 blood).tw,kw. (4157)
- 21 or/14-20 (347598)
- 22 13 and 21 (6378)
- 23 (dutch or english or german or french).la. (32736072)
- 24 "filter observationele studies emb sign".ti. (0)
- 25 Clinical study/ (157129)
- 26 Case control study/ (170558)
- 27 family study/ (26222)
- 28 Longitudinal study/ (153317)
- 29 Retrospective study/ (1055232)
- 30 Prospective study/ (675384)
- 31 Randomized controlled trials/ (200321)

32 30 not 31 (667864)  
 33 Cohort analysis/ (689122)  
 34 (Cohort adj (study or studies)).tw,kw. (344501)  
 35 (Case control adj (study or studies)).tw,kw. (145144)  
 36 (follow up adj (study or studies)).tw,kw. (69479)  
 37 (observational adj (study or studies)).tw,kw. (189085)  
 38 (epidemiologic\$ adj (study or studies)).tw,kw. (113615)  
 39 (cross sectional adj (study or studies)).tw,kw. (249713)  
 40 25 or 26 or 27 or 28 or 29 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (3014189)  
 41 "emb SR filter".ti. (0)  
 42 meta analysis/ (212799)  
 43 "systematic review"/ (291282)  
 44 (meta-analy\$ or metaanaly\$).tw,kw. (261908)  
 45 (systematic\$ adj4 (review\$ or overview\$)).tw,kw. (275263)  
 46 (quantitativ\$ adj5 (review? or overview?)).tw,kw. (5984)  
 47 (methodologic adj5 (overview? or review?)).tw,kw. (404)  
 48 (review\$ adj3 (database? or medline or embase or cinahl)).tw,kw. (30979)  
 49 (pooled adj3 analy\$).tw,kw. (33958)  
 50 (extensive adj3 review\$ adj3 literature).tw,kw. (4049)  
 51 (meta or synthesis or (literature adj8 database?) or extraction).tw,kw. (1557774)  
 52 review.pt. (2723208)  
 53 51 and 52 (178746)  
 54 or/42-50,53 (636349)  
 55 22 and 23 and 54 (311)= calcium + talen + SR  
 56 (metabolic adj3 analys\*).tw,kw. (11417)  
 57 (metabolic adj3 abnormalit\*).tw,kw. (15261)  
 58 prediction/ or exp "prediction and forecasting"/ (1407478)  
 59 55 and 58 (31)= calcium + talen + SR + prediction  
 60 40 and 55 (31)  
 61 22 and 23 and 40 and 58 (49)  
 62 61 (49)  
 63 limit 62 to yr="1990 -Current" (48)  
 64 56 or 57 (26517)  
 65 13 and 21 and 23 and 64 (19)  
 66 65 not 63 (19)  
 67 conference abstract/ (1176786)  
 68 66 not 67 (17)= prediction  
 69 Palliative Care/ (76527)  
 70 (palliat\* or terminal\* or endstage or hospice\* or (end adj3 life) or (care adj3 dying) or  
 ((advanced or late or last or end or final) adj3 (stage\* or phase\*))).ti,kw. (195114)  
 71 hospice care/ or exp terminal care/ (72439)  
 72 from 63 keep 1-48 (48)  
 73 from 68 keep 1-17 (17)  
 74 69 or 70 or 71 (275352)=palliatief  
 75 21 and 23 and 74 (3232)  
 76 13 and 75 (170)  
 77 exp comparative study/ (1469262)  
 78 76 and 77 (12)  
 79 exp \*constipation/ (14580)  
 80 21 and 23 and 79 (144)= calcium + talen + focus obstipatie  
 81 77 and 80 (8)  
 82 80 and (54 or 40) (20)= calcium + talen + focus obstipatie + SR of observat

- 83 lactulose/ae, cb, cm, cr, it, to, pv, tm [Adverse Drug Reaction, Drug Combination, Drug Comparison, Drug Concentration, Drug Interaction, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment] (1146)
- 84 lactulose/ (9536)
- 85 lactitol/ae, cb, cm, cr, do, it, to, pv [Adverse Drug Reaction, Drug Combination, Drug Comparison, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Special Situation for Pharmacovigilance] (210)
- 86 exp macrogol/ae, cb, cm, cr, it, to, pv, tm [Adverse Drug Reaction, Drug Combination, Drug Comparison, Drug Concentration, Drug Interaction, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment] (2386)
- 87 exp macrogol/ (56353)
- 88 laxative/ae, cb, cm, cr, do, it, to, pv, tm [Adverse Drug Reaction, Drug Combination, Drug Comparison, Drug Concentration, Drug Dose, Drug Interaction, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment] (2060)
- 89 clensia.tw. (7)
- 90 "clensia"/ (3)
- 91 colofort.tw. (3)
- 92 bicarbonate plus macrogol 3350 plus potassium chloride plus sodium chloride plus sodium sulfate/ (90)
- 93 klean-prep.tw,kw. (117)
- 94 from 93 keep 1 (1)
- 95 exp bicarbonate plus macrogol 3350 plus potassium chloride plus sodium chloride/ or exp macrogol/ or exp bicarbonate plus bisacodyl plus macrogol 3350 plus potassium chloride plus sodium chloride/ (56377)
- 96 (molaxol\* or movicolon\* or moviprep\* or pleinvu\*).tw,kw. (286)
- 97 "Adverse Reactions Titles ".ec. (1019760)
- 98 ascorbic acid plus polyethylene glycol 3350 plus potassium chloride plus sodium ascorbate plus sodium chloride plus sodium sulfate/ (79)
- 99 ple?nvu\*.tw,kw. (30)
- 100 84 or 87 or 89 or 90 or 91 or 92 or 93 or 95 or 96 or 98 or 99 (65205)
- 101 lactitol/ (799)
- 102 100 or 101 (65563)
- 103 97 and 102 (4289)
- 104 13 and 103 (1666)
- 105 54 and 104 (127)
- 106 105 (127)
- 107 limit 106 to yr="1990 -Current" (127)
- 108 84 or 101 (9909)
- 109 87 or 88 or 89 or 90 or 91 or 92 or 93 or 95 or 96 or 98 or 99 (58421)
- 110 13 and 23 and 108 and 109 (859)= obstipatie + talen + (lactitol of lactulose ) + overige macrogol varianten
- 111 cm.fs. (624606)
- 112 110 and 111 (203)
- 113 54 and 110 (85)= SR + obstipatie + talen + (lactitol of lactulose ) + overige macrogol varianten
- 114 74 and 13 and 23 and 108 and 109 (65)= palliatief + medicatiebijwerkingen
- 115 74 and 13 and 23 and (108 or 109) and (77 or 40) (32)= )=palliatief + obstipatie + talen + medicaties + drug comparison + observationele studies of comparative
- 116 (74 and 13 and 23 and (108 or 109) and 111) not 115 (26)=palliatief + obstipatie + talen + medicaties + drug comparison +not observationele studies of comparative in vorige set
- 117 from 113 keep 1-85 (85)
- 118 from 114 keep 1-65 (65)
- 119 from 115 keep 1-32 (32)
- 120 from 116 keep 1-26 (26)

- 121 22 and 23 and 54 and 58 (31)
- 122 exp risk factor/ (1109264)
- 123 22 and 23 and 58 and 122 (32)=obstipatie + calcium + talen + risk
- 124 \*prediction/ or exp \*"prediction and forecasting"/ (169755)
- 125 123 and 124 (1)
- 126 exp constipation/co, et, pc, si [Complication, Etiology, Prevention, Side Effect] (45598)