Bijlage Evidence tabellen

Evidence tabellen behorende bij de uitgangsvragen die via de GRADE-methodiek zijn uitgewerkt. Onderzoeksvragen 1, 2, 4, en 6 leverden geen resultaten op en zijn daarom niet opgenomen in deze bijlage.

Onderzoeksvraag 3: buikoverzichtsfoto of CT-scan

Wat is diagnostische waarde van een buikoverzichtsfoto of CT-scan ten opzichte van lichamelijk onderzoek of geen aanvullend onderzoek bij het vaststellen van obstipatie?

What is the diagnostic value of a x-ray of the abdomen or CT-scan compared to physical examination or no additional examination in the determination of constipation?

Patients	patients in the palliative phase that (appear to) have constipation
Intervention	x-ray of the abdomen or CT-scan
Comparator	physical examination
Outcome	accuracy, patient satisfaction, negative consequences of the diagnostic tool, costs

Evidence tables

Clark 2016						
Study characteristics	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Type of study: Prospective cross-sectional study Setting: Palliative care centers Country: Australia Source of funding: Not reported	Inclusion criteria: - Palliative patients with constipation and laxatives - Age over 18 years - An Australian-modified Karnofsky Performance Status of 40 or over - Not pregnant or wish to become pregnant - Be well enough to complete the study	1. Measurement of colon transit time: participants swallow a gelatin capsule containing 24 markers and then five days later have a plain abdominal radiograph. Retention of at least 20% of the markers is representative of prolonger colon transit times.	Patient Assessment of Constipation Symptom (PAC-SYM) tool.	Length of follow-up: n.a. Loss-to-follow-up: n.a.	36.7% had abnormal colon transit time. Overall poor levels of interobserver agreement on degree of fecal loading seen on plain radiographs. Lack of correlation between clinicians' assessment of the	

	Exclusion criteria: - Short-term reversible constipation attributable to specific etiologies such as hypercalcemia or chemotherapy-induced bowel dysfunction - Known bowel obstruction or previous bowel surgery that resulted in a reduction of the length of the GI-tract N total at baseline: 30 Baseline characteristics: Mean age: 69.9 (SD 10.1) Male: 63.3% Diagnosis of malignancy: 93.3%	2. Fecal shadowing on the abdominal radiograph.			degree of fecal loading and patient-reported symptoms of constipation, with the highest correlation being 0.32 (p=0.12). Only one of the four reviewers' scores assigned on clinical review correlated with an objective measure of whether colon transit times were grossly prolonged.	

Nagaviroj 2011						
Study characteristics	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Type of study: Prospective cross-sectional study Setting: Tertiary palliative care unit	Inclusion criteria: - Patients with advanced cancer - 18 years of age - Could complete a plain abdominal radiograph	Abdominal radiograph	Constipation Assessment Scale (CAS)	Length of follow-up: n.a. Loss-to-follow-up: n.a.:	There was no concordant correlation between the CAS score and each physician's radiographic constipation score.	

Country: Canada Source of funding: Not reported	Exclusion criteria: - Clinically suspected to have intestinal obstruction or peritonitis - Cognitive impairment - Were unable to have a flat plate of the abdomen completed because of pain or significantly decreased mobility - Severe psychosocial distress N total at baseline: 50 Baseline characteristics: Mean age: 62 (SD 11) Male: 42%				There also was no concordant correlation between the CAS score and the combined radiographic constipation scores of the three palliative medicine physicians (Kendall Tau coefficient=0.04; p=0.72).	

Risk of bias

Clark 2016				
Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Comments with respect to applicability**
Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? NA If a threshold was used, was it pre-specified? NA	Is the reference standard likely to correctly classify the target condition? NA Were the reference standard results interpreted without knowledge of the results of the index test? NA	Was there an appropriate interval between index test(s) and reference standard? NA Did all patients receive a reference standard? NA	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No

Yes			Did patients receive the same reference standard? No Were all patients included in the analysis? Yes	Are there concerns that the target condition as defined by the reference standard does not match the review question? No

Nagaviroj 2011				
Patient selection	**Index test**	**Reference standard**	**Flow and timing**	**Comments with respect to applicability**
Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes	Were the index test results interpreted without knowledge of the results of the reference standard? NA If a threshold was used, was it pre-specified? NA	Is the reference standard likely to correctly classify the target condition? NA Were the reference standard results interpreted without knowledge of the results of the index test? NA	Was there an appropriate interval between index test(s) and reference standard? NA Did all patients receive a reference standard? NA Did patients receive the same reference standard? No Were all patients included in the analysis? Yes	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No

References

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2. Nagaviroj 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 Aug;42(2):222-8.

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

Evidence tables

Candy 2015							
Included studies in the review	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
A. Agra 1998 B. Ramesh 1998	Type of study: RCT's Search date: September 9, 2014 Number of included studies: N=2 Country: A. Spain B. India	N total at baseline (n analysed): A. 91 (75) B. 36 Age, mean (SD): A. Intervention: 69.8 (12.2), control: 66.1 (11.0) B. Range 51-70 Gender, male: A. 63.7% B. 30.6%	A. Lactulose starting 15 mL (10g) twice daily for 27 days B. Misrakasneham starting at 2.5 mL for 2 weeks	A. Senna starting 0.4 mL (12mg) twice daily for 27 days B. Senna starting at 24 mg for 2 weeks	Length of follow-up: A. 27 days B. 14 days Loss-to-follow-up: A. 16 B. 5	**Misrakasneham versus senna** Satisfactory bowel movements with no adverse effects OR 7.67; 95% CI 0.37 to 158.01 Overall finding: No difference in laxation response **Senna versus lactulose** Mean number of defecation days:	The review included five studies. Only two studies were relevant for this question.

	Inclusion criteria: - Palliative patients or patients with advanced or end-stage disease - Any type of laxative					MD -0.10; 95% CI -0.60 to 0.40 Defecation-free days: MD 0.00; 95% CI -0.48 to 0.48 General state of health: MD -0.10; 95% CI -0.31 to 0.11 Overall finding: No difference in laxation response	

Risk of bias van geselecteerde studies

Author, publication year	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of patient and personell (performance bias)**	**Follow-up and ITT or per protocol analysis (attrition bias)**	**Selective reporting**	**Other bias**
Agra 1998	Unclear *"...Randomisation stratified by age and gender"*	Unclear *Not reported*	Low risk *Laxatives were supplied in closed opaque flasks to prevent prescribers from identifying them. Yet, as texture and taste could*	Low risk *18% loss to follow up. The authors stated that participants who dropped out were not particularly different from those who completed follow-up.*	Unclear *No registration prior publication*	Low risk *No other sources of bias were found.*

			not be homogenized, patients were able to differentiate between one and the other drug.			
Ramesh 1998	Low risk *Randomly allocated to the 2 study groups (25 each) by drawing lots (sampling with replacement)*	Unclear *Not reported*	High risk *The difference between the physical forms of the 2 drugs necessitated an open trial rather than a double-blind study.*	Unclear *Considarable number of drop outs. Unclear if used intention-to-treat analysis.*	Unclear *No registration prior publication*	Low risk *No other sources of bias were found.*

References

1. Agra Y, Sacristán A, González M, Ferrari M, Portugués A, Calvo MJ. Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. J Pain Symptom Manage. 1998 Jan;15(1):1-7.
2. 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;2015(5):CD003448.
3. Ramesh PR, Kumar KS, Rajagopal MR, Balachandran P, Warrier PK. Managing morphine-induced constipation: a controlled comparison of an Ayurvedic formulation and senna. J Pain Symptom Manage. 1998 Oct;16(4):240-4.

Onderzoeksvraag 7: medicamenteuze behandeling

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

What are the (un)favourable effects of treatment with laxatives to treat constipation in patients in the palliative phase?

Patients	patients in the palliative phase that have constipation
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

Evidence tables

Candy 2015							
Included studies in the review	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
A. Sykes 1991a B. Sykes 1991b C. Tarumi 2013	Type of study: RCT's Search date: September 9, 2014 Number of included studies: N=3 Country: A. UK B. UK C. Canada	N total at baseline (n analysed): A. 51 B. 118 C. 64 Age, mean (SD): A. n.r. B. n.r. C. Intervention: 75.3, control: 71.9 Gender, male: A. n.r. B. n.r. C. 64.0%	A. Senna with lactulose liquid twice daily for 1 week B. Magnesium hydroxide with liquid paraffin, mean dose 45 mL daily (week 1) and 49 mL daily (week 2) C. Docusate 100mg twice daily with sennosides (1-3 x 8.6mg tablets taken 1-3 times daily) for 10 days	A. Co-danthramer with poloxamer twice daily for 1 week B. Senna with lactulose, mean dose 38 mL daily (week 1) and 34 mL daily (week 2) C. Placebo twice daily with sennosides (1-3 x 8.6mg tablets taken 1-3 times daily) for 10 days	Length of follow-up: A. 7 days B. 7 days C. 10 days Loss-to-follow-up: A. 7 B. 74 C. 18	No differences in effectiveness were demonstrated in: - Lactulose compared with senna - Senna and lactulose compared with magnesium hydroxide met liquid paraffin - Misrakasneham compared with senna - Docusate and senna compared	

	Source of funding: Marie Curie Care fund Inclusion criteria: - Palliative patients or patients with advanced or end-stage disease - Any type of laxative - The reported outcomes included relief of constipation Exclusion criteria: - Studies including healthy volunteers, participants with constipation as a result of drug misuse and participants with constipation					with placebo with senna There was a significant difference in a subgroup of 17 participants receiving strong opioid analgesia that favoured senna with lactulose compared to co-danthramer with poloxamer. Few participants experienced adverse effects, e.g. nausea, vomiting, diarrhea, abdominal pain. Sykes 1991b showed a patient preference for senna with lactulose. Ramesh 1998 found no difference in patient preference between misrakasneham and senna.	

	arising from bowel obstruction						

Risk of bias

Candy 2015		
Item	**Yes, partial yes or no**	**Explanation**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Update of previous SR
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	
4. Did the review authors use a comprehensive literature search strategy?	Yes	
5. Did the review authors perform study selection in duplicate?	Yes	
6. Did the review authors perform data extraction in duplicate?	Unclear	Not reported
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	
8. Did the review authors describe the included studies in adequate detail?	Yes	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	
10. Did the review authors report on the sources of funding for the studies included in the review?	No	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	n.a.	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	n.a.	
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	n.a.	
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	

Referenties

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;2015(5):CD003448.
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4. Tarumi Y, Wilson MP, Szafran O, Spooner GR. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. J Pain Symptom Manage. 2013 Jan;45(1):2-13.

Onderzoeksvraag 8: medicamenteuze behandeling bij patiënten die behandeld worden met opioïden
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

Evidence tables
Systematic review

Mueller-Lissner 2010							
Included studies in the review	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
A. Attar 1999 B. Zhang 2003 C. Hammer 1992 D. Heitland 1988	Type of study: RCT's Search date: October 2009 Number of included studies: N=51 (4 relevant) Country: A. France, Scotland B. Unknown C. Germany D. Germany	N total at baseline (n analysed): A. 115 B. 85 C. 61 D. 60 Age: A. 18+ years B. Elderly C. Mean 54 years D. Mean 60 years Gender, male: A. 51.1%	A. Macrogol 3350 26 gr daily B. Macrogol 4000 10 gr daily C. Lactitol 20 gr daily for 3 days then 10 gr daily D. Lactitol 20 gr daily	A. Lactulose 20 gr daily B. Lactulose 15 mL daily C. Lactulose 30 mL daily for 3 days then 20 mL daily D. Lactulose 20 mL daily	Length of follow-up: A. 4 weeks B. 4 weeks C. 4 weeks D. 2 weeks	A. Two adverse effects with macrogols (diarrhea, abdominal pain) and one with lactulose (depression). B. 12% AE with macrogols vs 16% with lactulose (p>0.05). C. 31% AE with lactitol vs 62% with lactulose (p=0.02).	Details of studies not adequately described in SR.

	Source of funding: Not reported Inclusion criteria: - Published SR's and RCT's in any language and containing more than 20 individuals Exclusion criteria: Not applicable.	B. 51.3% C. 41.2% D. 59.0% E. 45.5% F. 54.5% G. 48.1% H. 43.3%				D. No significant differences between groups in AE and other symptoms.	

RCT's

Freedman, 1997						
Study characteristics	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Type of study: RCT, cross-over Setting: Outpatient methadone program Country: USA	Inclusion criteria: - Enrolled in methadone maintenance program - Complained of constipation - Previously sought laxatives Exclusion criteria: - Pregnant or lactating	Lactulose (30 mL)	Macrogol 3350 Placebo	Length of follow-up: 2 weeks per treatment (patients underwent all three treatment methods)	Frequency of excess gas/week: Lactulose: 3.6 (SD 0.4) Macrogol: 4.1 (SD 0.5) Placebo: 3.0 (SD 0.4) Difference not significant	

Source of funding: Not reported	- Elevated TSH - History of colon surgery - Childhood constipation requiring more than one bowel purging procedure per month - Onset before methadone use - Heme positive stool of unknown etiology N total at baseline: 57 Important prognostic factors: Age: between 18-50 years				Severe cramping/week: Lactulose: 1.5 (SD 0.3) Macrogol: 2.1 (SD 0.4) Placebo: 2.1 (SD 0.4) Difference not significant	

Bouhnik, 2004						
Study characteristics	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Type of study: RCT Setting: General practitioner Country: France Source of funding: Solvay Pharma	Inclusion criteria: - Patients with chronic idiopathic constipation - at least 6 months less than three stools per week and/or difficulty in defecation and/or straining on passage of stool Exclusion criteria:	Macrogol 4000	Lactulose	Length of follow-up: 4 weeks	No significant differences in side effects Borborygymi: I: 39% C: 46% Bloating: I: 43% C: 42%	

	- Taking concomitant medication which may modify bowel habit - Severe liver, renal or cardiac disease - Pregnant or lactating <u>N total at baseline:</u> I: 32 C: 33 <u>Important prognostic factors:</u> Age ± SD: I: 57 (19) C: 59 (18) Sex: I: 15.6% male C: 12.1% male				<u>Abdominal pain</u>: I: 26% C: 35% <u>Flatus in excess</u>: I: 65% C: 62%	

Chassagne, 2007						
Study characteristics	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
<u>Type of study</u>: RCT <u>Setting</u>: Ambulatory and institutionalized elderly care <u>Country</u>: France	<u>Inclusion criteria:</u> - At least 70 years - Chronic constipation (<3 stools/week for 3 months) <u>Exclusion criteria:</u> - Known organic intestinal disease	Macrogol 4000	Lactulose	<u>Length of follow-up:</u> 6 months	Fifteen patients (11.8%; 19 events) in the lactulose group and 20 patients in the macrogol group (16.9%; 28 events) presented at least one treatment-related adverse event (p=0,25).	

Source of funding: IPSEN (manufacturer of macrogol)	- History of abdominal or pelvic radiation or of intestinal surgery or severe hepatic or rental disease - Other comorbidities that could interfere with the study N total at baseline: I: 119 C: 127 Important prognostic factors: Age ± SD: I: 82.7 (7.4) C: 81.8 (7.9) Sex: I: 23.7% male C: 24.4% male				These principally concerned gastro-intestinal events, notably diarrhea and abdominal pain.	

Risk of bias

Systematic review

Mueller-Lissner, 2010		
Item	**Yes, partial yes or no**	**Explanation**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	

3. Did the review authors explain their selection of the study designs for inclusion in the review?	Partial yes	Rationale not clearly stated
4. Did the review authors use a comprehensive literature search strategy?	Partial yes	No reference lists or grey literature searched
5. Did the review authors perform study selection in duplicate?	No	“Selected by an information specialist”
6. Did the review authors perform data extraction in duplicate?	No	Method of data extraction not mentioned
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	Not even listed how many studies where found in the search
8. Did the review authors describe the included studies in adequate detail?	No	Details about the individual studies are lacking
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Not performed
10. Did the review authors report on the sources of funding for the studies included in the review?	No	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N.A.	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	N.A.	
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N.A.	
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	Not reported

RCT’s

Author, publication year	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of patient and personell (performance bias)**	**Blinding of outcome assessor (detection bias)**	**Follow-up and ITT or per protocol analysis (attrition bias)**	**Selective reporting**	**Other bias**
Freedman, 1997	Unclear	Low risk	Low risk *Double blinded*	Low risk *Double blinded*	Unclear *Not reported.*	Unclear *No protocol available.*	Medium risk *It seems no washout period was done.*

	Unclear who performed the randomization	*All participants would undergo all three treatments*					
Bouhnik, 2004	Low risk *Through sealed envelope through operator*	Unclear *Participants were enrolled prior to obtaining group assignment.*	High risk *Blinding is not mentioned*	High risk *Blinding is not mentioned*	Low risk *Analyses followed an ITT principle.*	Unclear *No protocol available.*	Low risk *No other sources of bias were found.*
Chassagne, 2007	Low risk *Randomization list kept by sponsor.*	Unclear *Participants were enrolled prior to obtaining group assignment.*	Low risk *Study was blinded.*	Low risk *Outcome assessor was blinded.*	Low risk *Analyses followed an ITT principle.*	Unclear *No protocol available.*	Low risk *No other sources of bias were found.*

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7. Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus Polyethylene Glycol for Chronic Constipation. Cochrane Database Syst Rev 2010;7(7):CD007570.
8. Mueller-Lissner SA. Wald A. Constipation in adults. BMJ clinical evidence. 2010;2010:0413.

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

Evidence tables

Candy 2018							
Included studies in the review	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
A. Ahmedzai 2012 B. Bull 2015 C. Dupoiron 2017 D. Katakami 2017 E. Portenoy 2008 F. Slatkin 2009 G. Sykes 1996 H. Thomas 2008	Type of study: RCT's Search date: August 28, 2017 Number of included studies: N=8 Country: A. International B. USA C. Unknown D. Korea / Japan E. USA	N total at baseline (n analysed): A. 184 B. 230 C. 243 D. 227 E. 33 F. 154 G. 27 H. 134 Age, mean (SD): A. Intervention: 61, Control: 64 B. Intervention: 65.3 (12.9), control: 65.7 (13.0)	A. Oxycodone/naloxone prolonged release up to 120 mg/day B. Subcutaneous methylnaltrexone 8mg or 12mg every other day C. Oxycodone/naloxone prolonged release up to 160 mg/80mg D. Group 1: naldemedine 0.1mg/day; Group 2: naldemedine 0.2mg/day; Group 3: naldemedine 0.4mg/day E. Group 1: subcutaneous methylnaltrexone 5mg 3 times per week; Group 2: subcutaneous methylnaltrexone 12.5mg 3	A. Oxycodone prolonged release up to 120 mg/day B. Placebo C. Oxycodone prolonged release D. Placebo E. Subcutaenous methylnaltrexone 1mg 3 times per week F. Placebo G. Placebo H. Placebo	Length of follow-up: A. 4 weeks B. 2 weeks C. 5 weeks D. 2 weeks E. 30 days F. 6 days G. 2 days H. 2 weeks Loss-to-follow-up: A. 51 B. 47 C. 33 D. 2 E. 11 F. 2 G. 15 H. 28	Naldemedine vs. placebo: Laxation response: RR 1.93 (95%CI 1.36-2.74) Adverse events: RR 1.36 (95%CI 1.04-1.79) Lower dose naldemedine 0.1mg/day vs higher dose (0.2-0.4mg/day): Laxation response: RR 0.73 (95%CI 0.55-0.95) and RR 0.69 (95%CI 0.53-0.89)	

	F. USA G. UK H. USA / Canada <u>Source of funding</u>: Marie Curie Care fund <u>Inclusion criteria</u>: - Patients with cancer or at a palliative stage - On a stable opioid regimen - Opioid-induced bowel dysfunction not responding to laxatives <u>Exclusion criteria</u>: - Studies including healthy volunteers, participants with constipation as a result of drug misuse and	C. Intervention: 57.9 (11.0), control: 57.5 (12.3) D. Range in mean: 63.4 – 65.8 E. 61 (19.0) F. 65.3 (14.96) G. 64 H. Intervention: median 70; Control: median 72 <u>Gender, male</u>: A. 51.1% B. 51.3% C. 41.2% D. 59.0% E. 45.5% F. 54.5% G. 48.1% H. 43.3%	times per week; Group 3: subcutaneous methylnaltrexone 20mg 3 times per week F. Group 1: single subcutaneous methylnaltrexone 0.15mg/kg; Group 2: single subcutaneous methylnaltrexone 0.3mg/kg G. Naloxone oral every 4 hours, different dosages H. Subcutaneous methylnaltrexone 0.15mg/kg			<u>Methylnaltrexone vs placebo</u>: Laxation response: RR 9.98 (95%CI 4.96-20.09) Adverse events: RR 1.17 (95%CI 0.94-1.45) <u>Low-dose methylnaltrexone vs high-dose methylnaltrexone</u>: Laxation response (at 5 days): RR 0.21 (95%CI 0.03-1.31) Adverse events: RR 1.00 (95%CI 1.00-1.00) <u>Naloxone vs. placebo</u>: Laxation response not reported. <u>OXN PR vs OXY PR</u>: OXN PR better scores on PAC-SYM (MD -5.10, 95%CI -8.08;--2.12).	

	participants with constipation arising from bowel obstruction					OXN PR better on Bowel Function Index (14.0, SD 8.1, p<0.05)	

Risk of bias

Candy 2018		
Item	**Yes, partial yes or no**	**Explanation**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Update of previous SR
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	
4. Did the review authors use a comprehensive literature search strategy?	Yes	
5. Did the review authors perform study selection in duplicate?	Yes	
6. Did the review authors perform data extraction in duplicate?	No	
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	
8. Did the review authors describe the included studies in adequate detail?	Yes	
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	

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