ONS CONSTIPATION SYSTEMATIC REVIEW

Supplementary Material

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1. PICO questions

Population	Intervention(s)	Comparator	Outcomes
Opioid-related constipation			
Adult patients with cancer receiving opioids who are not yet constipated or who are experiencing opioid-induced constipation	Bowel regimen and lifestyle education	Lifestyle education	Stool consistency Occurrence of constipation (y/n) Quality of life Adverse events that lead to treatment discontinuation
Adult patients with cancer with opioid-induced constipation	Osmotic PEG and lifestyle education	Lifestyle education	Stool consistency Occurrence of constipation (y/n) Quality of life Adverse events that lead to treatment discontinuation
Adult patients with cancer with opioid-induced constipation	Methylnaltrexone (subcutaneous or oral) and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life Adverse events that lead to treatment discontinuation Change in pain control/score

Adult patients with cancer with opioid-induced constipation	Naldemedine (0.2 mg) and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life Adverse events that lead to treatment discontinuation Change in pain control/score
Adult patients with cancer with opioid-induced constipation	Naloxegol and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life Adverse events that lead to treatment discontinuation Change in pain control/score
Adult patients with cancer with opioid-induced constipation	Lubiprostone and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life Adverse events that lead to treatment discontinuation Change in pain control/score
Adult patients with cancer with opioid-induced constipation	Linaclotide and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life

			Adverse events that lead to treatment discontinuation Change in pain control/score
Adult patients with cancer with opioid-induced constipation	Prucalopride and bowel regimen	Bowel regimen	More than 3 SBM/week or more than one SBM/week over baseline Rescue free bowel movements (RFBM) Quality of life Adverse events that lead to treatment discontinuation Change in pain control/score
Non-opioid related constipation			
Adult patients with cancer with non-opioid-related constipation	Osmotic or stimulant laxatives and lifestyle education	Lifestyle education	Duration of constipation Frequency of constipation Severity of constipation Resolution of constipation (y/n) Quality of life Adverse events (diarrhea, dehydration)
Adult patients with cancer with non-opioid-related constipation	Acupuncture and lifestyle education	Lifestyle education	Duration of constipation Frequency of constipation Severity of constipation Resolution of constipation (y/n) Quality of life

Adult patients with cancer with non-opioid-related constipation	Electroacupuncture and lifestyle education	Lifestyle education	Duration of constipation Frequency of constipation Severity of constipation Resolution of constipation (y/n) Quality of life

2. Search strategies

MEDLINE and Cochrane Library searches replicated from Hanson, Siddique, Scarlett, & Sultan, 2019

Ovid MEDLINE (limited 2018 to date):

No.	Searches
1	exp Analgesics, Opioid/ or exp Opiate/
2	(opioid* or opiate*).ti,ab.
3	1 or 2
4	exp Constipation/
5	(constipa* or colonic inertia).ti,ab.
6	4 or 5
7	3 and 6
8	((opioid* or opiate*) adj3 constipation).ti,ab.
9	7 or 8
10	exp Cathartics/ or exp Laxatives/ or exp Laxative/

11 (cathartic* or laxative* or bowel evacuant* or purgative*).ti,ab.

12 exp Polyethylene Glycols/ or exp macrogol 3350/

13 (PEG 3350 or Miralax or macrogol 3350).ti,ab.

14 exp Methylcellulose/

15 (methylcellulose or senna or Psyllium or metamucil or bisacodyl).ti,ab.

16 exp Lubiprostone/

17 (Amitiza or lubiprostone).ti,ab.

18 (linaclotide or linzess).mp.

19 exp Serotonin 5-HT4 Receptor Agonists/

20 exp serotonin 4 agonist/

21 exp prucalopride/

22 (prucalopride or resotran* or Resolor).mp.

23 exp mu opiate receptor antagonist/

24 (Peripherally-Acting Mu-Opioid Receptor Antagonist* or PAMORA*).mp.

25 exp naloxegol/

26 exp 17 methylnaltrexone/

27 (naloxegol or methylnaltrexone or Relistor or Movantik).mp.

28 exp alvimopan/

29 (alvimopam or Entereg).mp.

30 exp naloxone plus oxycodone/

31 (Targin or Targiniq or Targinact).mp.

32 exp Naloxone/

33 exp Oxycodone/

34 32 and 33

35 exp naldemedine/ or exp axelopran/

36 (TD-1211 or naldemedine or axelopran).mp.

37 or/10-31

38 or/34-37

39 9 and 38

40 limit 39 to english language

41 animals/ not (humans/ and animals/)

42 40 not 41

43 remove duplicates from 42

44 limit 43 to (editorial or letter or note or case reports or comment) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

45 Case Report/

46 43 not (44 or 45)

47 (Meta Analysis or Controlled Clinical Trial).pt.

48 Meta - Analysis/ or Meta - Analysis as Topic/ or exp Technology Assessment, Biomedical/

49 (meta analy* or metaanaly* or health technolog* assess*).mp.

50 Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/

51 exp Randomized Controlled Trial/

52 exp Random Allocation/ or exp Double - Blind Method/ or exp Control Groups/ or exp Placebos/

53 exp Randomization/ or exp RANDOM SAMPLE/ or Double Blind Procedure/ or exp Triple Blind Procedure/ or exp Control Group/ or exp PLACEBO/

54 (random* or RCT or RCTs or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.

55 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab.

56 or/47-55

57 46 and 56

Note: These terms were run as keywords instead of subject headings after receiving these notices:

The subject heading 'macrogol 3350' is invalid in this database.

The subject heading 'serotonin 4 agonist' is invalid in this database.

The subject heading 'prucalopride' is invalid in this database.

The subject heading 'mu opiate receptor antagonist' is invalid in this database.

The subject heading 'naloxegol' is invalid in this database.

The subject heading '17 methylnaltrexone' is invalid in this database.

The subject heading 'alvimopan' is invalid in this database.

The subject heading 'naloxone plus oxycodone' is invalid in this database.

The subject heading 'naldemedine' is invalid in this database.

Wiley Cochrane Library (limited 2018 to date):

#1 MeSH descriptor: [Analgesics, Opioid] explode all trees

#2 (opioid* or opiate*):ti,ab

#3 #1 or #2

#4 MeSH descriptor: [Constipation] explode all trees

#5 (constipa* or colonic inertia):ti,ab

#6 #4 or #5

#7 #3 and #6

#8 ((opioid* or opiate*) near/3 constipation):ti,ab

#9 #7 or #8

#10 MeSH descriptor: [Cathartics] explode all trees

#11 MeSH descriptor: [Laxatives] explode all trees

#12 (cathartic* or laxative* or bowel evacuant* or purgative*):ti,ab

#13 MeSH descriptor: [Polyethylene Glycols] explode all trees

#14 (PEG 3350 or Miralax or macrogol 3350):ti,ab

#15 MeSH descriptor: [Methylcellulose] explode all trees

#16 (methylcellulose or senna or Psyllium or metamucil or bisacodyl):ti,ab

#17 MeSH descriptor: [Lubiprostone] explode all trees

#18 (Amitiza or lubiprostone):ti,ab

#19 (linaclotide or linzess):ti,ab

#20 MeSH descriptor: [Serotonin 5-HT4 Receptor Agonists] explode all trees

#21 (prucalopride or resotran* or Resolor):ti,ab

#22 (Peripherally-Acting Mu-Opioid Receptor Antagonist* or PAMORA*):ti,ab

#23 (naloxegol or methylnaltrexone or Relistor or Movantik):ti,ab

#24 (alvimopam or Entereg):ti,ab

#25 (Targin or Targiniq or Targinact):ti,ab

#26 (TD-1211 or naldemedine or axelopran):ti,ab

#27 #10 or #11 or #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 or #25 or #26

#28 MeSH descriptor: [Naloxone] explode all trees

#29 MeSH descriptor: [Oxycodone] explode all trees

#30 #28 and #29

#31 #27 or #30

#32 #9 and #31

PubMed, CINAHL, and Cochrane Library searches modified from the Ford & Suares (2011) article.

PubMed (limited to past 10 years):

(Constipation OR gastrointestinal transit OR functional constipation OR idiopathic constipation OR chronic constipation OR slow transit) AND (Laxatives OR cathartics OR anthraquinones OR phenolphthaleins OR indoles OR phenols OR lactulose OR polyethylene glycol OR senna plant OR senna extract OR Bisacodyl OR phosphates OR dioctyl sulfosuccinic acid OR magnesium OR magnesium hydroxide OR sorbitol OR poloxamer OR serotonin agonists OR receptors, serotonin, 5-HT4 OR receptors, prostaglandin E OR sodium picosulphate OR docusate OR milk of magnesia OR danthron OR senna* OR poloxalkol OR prucalopride OR lubiprostone OR linaclotide) AND (cancer[sb])

("Constipation/drug therapy"[MAJR] OR "Laxatives"[MAJR]) AND (cancer[sb])

EBSCO CINAHL (limited to past 10 years):

(Constipation OR gastrointestinal transit OR functional constipation OR idiopathic constipation OR chronic constipation OR slow transit) AND (Laxatives OR cathartics OR anthraquinones OR phenolphthaleins OR indoles OR phenols OR lactulose OR polyethylene glycol OR senna plant OR senna extract OR Bisacodyl OR phosphates OR dioctyl sulfosuccinic acid OR magnesium OR magnesium hydroxide OR sorbitol OR poloxamer OR serotonin agonists OR receptors, serotonin, 5-HT4 OR receptors, prostaglandin E OR sodium picosulphate OR docusate OR milk of magnesia OR danthron OR senna* OR poloxalkol OR prucalopride OR lubiprostone OR linaclotide) AND (cancer OR oncolog* OR neoplasm* OR chemotherap*)

(MH "Constipation/DT" OR MH "Cathartics") AND (cancer OR oncolog* OR neoplasm* OR chemotherap*)

Wiley Cochrane Library (limited to past 10 years):

#1 (Constipation OR gastrointestinal transit OR functional constipation OR idiopathic constipation OR chronic constipation OR slow transit)

#2 (Laxative* OR cathartic* OR anthraquinones OR phenolphthaleins OR indoles OR phenols OR lactulose OR “polyethylene glycol” OR senna* OR Bisacodyl OR phosphates OR “dioctyl sulfosuccinic acid” OR magnesium OR magnesium OR sorbitol OR poloxamer OR “serotonin agonists” OR “sodium picosulphate” OR docusate OR “milk of magnesia” OR danthron OR poloxalkol OR prucalopride OR lubiprostone OR linaclotide)

#3 MeSH descriptor: [Receptors, Serotonin, 5-HT4] explode all trees

#4 MeSH descriptor: [Receptors, Prostaglandin E] explode all trees

#5 #2 OR #3 OR #4

#6 (cancer OR oncolog* OR chemotherap* OR neoplasm*)

#7 #1 AND #5 AND #6

PubMed, CINAHL, and Cochrane Library searches for acupuncture or electroacupuncture for cancer-related constipation.

PubMed (limited to past 10 years):

(acup* OR electroacup*) AND constipat* AND cancer[sb]

EBSCO CINAHL (limited to past 10 years):

(acup* OR electroacup*) AND constipat* AND (cancer OR oncolog* OR neoplasm* OR chemotherap*)

Wiley Cochrane Library (limited to past 10 years):

(acup* OR electroacup*) AND constipat* AND (cancer OR oncolog* OR chemotherap* OR neoplasm*)

Therapies or treatments for constipation not limited to cancer

PubMed (limited to past 10 years):

(Therapy/Broad[filter]) AND (constipation[majr] OR constipat*[ti])

EBSCO CINAHL (limited to past 10 years):

MJ constipat* OR TI constipat*

With the following Clinical Queries limits:

Therapy - High Sensitivity

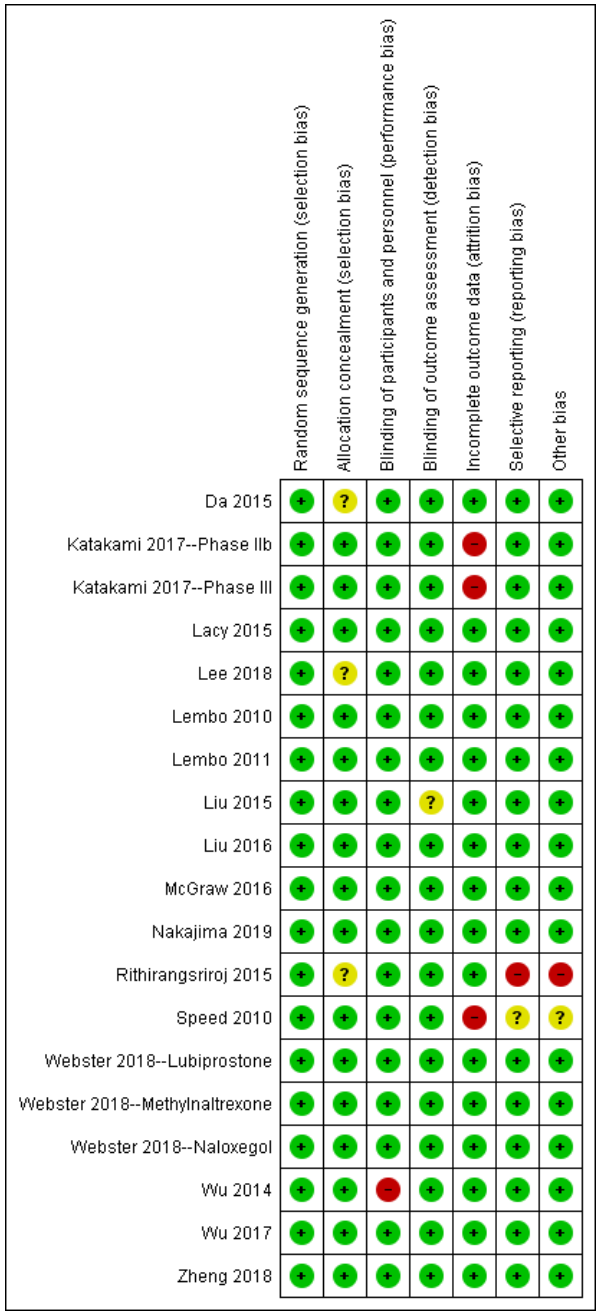
Therapy - High Specificity

Therapy - Best Balance

Wiley Cochrane Library (limited to past 10 years):

MeSH descriptor: [Constipation] explode all trees and with qualifier(s): [therapy - TH]

3. Evidence risk of bias figure (Developed using Review Manager Web (RevMan Web) [Systematic review software]. (2019). https://revman.cochrane.org).



Reviewers' assessment of risk of bias for each included study

4. Evidence Profiles (Developed using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.)

- Bowel regimen and lifestyle education vs. lifestyle education for opioid-induced constipation
- Osmotic PEG and lifestyle education vs. lifestyle education for opioid-induced constipation
- Methylnaltrexone (subcutaneous or oral) and bowel regimen vs. bowel regimen for opioid-induced constipation
- Naldemedine (0.2 mg) and bowel regimen vs. bowel regimen for opioid-induced constipation
- Naloxegol and bowel regimen vs. bowel regimen for opioid-induced constipation
- Lubiprostone and bowel regimen vs. bowel regimen for opioid-induced constipation
- Linaclotide and bowel regimen vs. bowel regimen for opioid-induced constipation
- Prucalopride and bowel regimen vs. bowel regimen for opioid-induced constipation
- Osmotic or stimulant laxatives and lifestyle education vs. lifestyle education for non-opioid-related constipation
- Acupuncture and lifestyle education vs. lifestyle education for non-opioid-related constipation
- Electroacupuncture and lifestyle education vs. lifestyle education for non-opioid-related constipation

Bowel regimen and lifestyle education vs. lifestyle education for opioid-induced constipation

Question: Should a bowel regimen and lifestyle education rather than lifestyle education alone be used in adult patients with cancer receiving opioids who are not yet constipated or who are experiencing OIC?

Setting: Clinical care

Bibliography:

Ford, A.C., & Suares, N.C. (2011). Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut, 60*, 209–218. http://doi.org/10.1136/gut.2010.227132

Ginex, P.K., Hanson, B., Lefebvre, K., Lin, Y., Maloney, C., Moriarty, K., . . . Morgan, R. (2020). Opioid-related and non-opioid related constipation in patients with cancer: A systematic review and meta-analysis. *Oncology Nursing Forum*, co-submitted with guideline.

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic or stimulant laxatives	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
SBM response (defined as ≥3 SBMs/wk. or ≥3 stools/wk.)												
7 [1,2,3,4,5,6,7]	randomized trials	not serious	not serious	serious [a]	not serious	none	525/876 (59.9%)	143/535 (26.7%)	**RR 2.24** (1.93 to 2.61)	**33 more per 100** (from 25 more to 43 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change in BM frequency												
6 [2,4,5,6,7,8]	randomized trials	not serious	serious [b]	serious [a]	not serious	none	805	464	-	MD 2.55 higher (1.53 higher to 3.57 higher)	⊕⊕◯◯ LOW	CRITICAL
Reduction in straining												
2 [2,3]	randomized trials	not serious	not serious	serious [a]	not serious	none	49/58 (84.5%)	33/60 (55.0%)	**RR 1.52** (1.18 to 1.96)	**29 more per 100** (from 10 more to 53 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Stool consistency improvement (assessed with: measured as hard/pellet stools)												
3 [2,3,4]	randomized trials	not serious	not serious	serious [a]	not serious	none	123/138 (89.1%)	76/131 (58.0%)	**RR 1.55** (1.33 to 1.82)	**32 more per 100** (from 19 more to 48 more)	⊕⊕⊕◯ MODERATE	CRITICAL
AEs leading to treatment discontinuation												
3 [9,10,11]	randomized trials	not serious	not serious	serious [c]	not serious	none	45/358 (12.6%)	6/231 (2.6%)	**RR 3.55** (1.60 to 7.89)	**66 more per 1,000** (from 16 more to 179 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic or stimulant laxatives	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Bristol Stool Scale												
1 [10]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	80	76	-	MD 1 higher (0.64 higher to 1.36 higher)	⨁⨁◯◯ LOW	CRITICAL
PAC-QoL												
1 [12]	randomized trials	serious [e]	not serious	serious [f]	serious [g]	none	PAC-QoL MD at 12 months for Personalized education (n=13) vs laxative (n=27) use: -0.09 (95% CI: -0.38, 0.21); PAC-QoL MD at 12 months for Standard education (n=42) vs laxative (n=27) use: -0.04 (95% CI: -0.32, 0.23).				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Rated down for indirectness because population consisted of non-OIC patients. We did not rate down because the population consisted of non-cancer patients.

b. Meta-analysis conducted in Ford 1998 presents an I^2 of 100%; greater heterogeneity is expected when presenting absolute values and all effects are on the same side of the line of no effect; however, we still rated down by one.

c. Rated down for indirectness because of difference in complementary treatments. McGraw prohibited use of laxatives with PEG 3350 + Senna.

d. The 95% CI includes the potential for harm, as well as benefit.

e. Concerns with reporting bias, recall bias, randomization and allocation.

f. Trial is conducted among older persons with chronic constipation, not among persons with opioid-induced constipation.

g. Small sample does not meet OIS. Additionally, the 95% CI includes the potential for both a reduction in QoL, as well as an improvement; however, it may not be clinically meaningful.

References

1. Wesselius-De Casparis, A, Braadbaart, S, Bergh-Bohlken, Gevd, Mimica, Milorad. Treatment of chronic constipation with lactulose syrup: results of a double-blind study. Gut; 1968.

2. Corazziari, E, Badiali, D, Habib, FI, Reboa, G, Pitto, G, Mazzacca, G, Sabbatini, F, Galeazzi, R, Cilluffo, Te, Vantini, I. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. Digestive Diseases and Sciences; 1996.

3. Corazziari, E, Badiali, D, Bazzocchi, G, Bassotti, G, Roselli, P, Mastropaolo, G, Lucà, MG, Galeazzi, R, Peruzzi, E. Long term efficacy, safety, and tolerability of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut; 2000.

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5. DiPalma, Jack A, Cleveland, Mark, McGowan, John, Herrera, Jorge L. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. Am J Gastroenterol; 2007.

6. Mueller-Lissner, Stefan, Kamm, Michael A, Wald, Arnold, Hinkel, Ulrika, Koehler, Ursula, Richter, Erika, Bubeck, Jürgen. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium Pico sulfate in patients with chronic constipation. Am J Gastroenterol; 2010.

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10. Nakajima, Atsushi, Shinbo, Kazuhiko, Oota, Akira, Kinoshita, Yoshikazu. Polyethylene glycol 3350 plus electrolytes for chronic constipation: a 2-week, randomized, double-blind, placebo-controlled study with a 52-week open-label extension. Journal of Gastroenterology; 2019.

11. McGraw, Thomas. Safety of polyethylene glycol 3350 solution in chronic constipation: randomized, placebo-controlled trial. Clinical and Experimental Gastroenterology; 2016.

12. Speed, Chris, Heaven, Ben, Adamson, Ashley, Bond, John, Corbett, Sally, Lake, AA, May, Carl, Vanoli, Alessandra, McMeekin, Peter, Moynihan, P. LIFELAX-diet and LIFEstyle versus LAXatives in the management of chronic constipation in older people: randomised controlled trial. Health Technology Assessment.; 2010.

Osmotic PEG and lifestyle education vs. lifestyle education for opioid-induced constipation

Question: Should osmotic PEG and lifestyle education rather than lifestyle education alone be used in adult patients with cancer with opioid-induced constipation?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic PEG	no treatment	Relative (95% CI)	Absolute (95% CI)		
Stool consistency (assessed with: Hard stool/week)												
1 [1]	randomized trials	not serious	not serious	not serious [a]	very serious [b, c]	none	57	57	-	MD 0.69 lower (1.28 lower to 0.1 lower)	⨁⨁◯◯ LOW	CRITICAL
Stool consistency (assessed with: Soft stool/week)												
1 [1]	randomized trials	not serious	not serious	not serious [a]	very serious [b, d]	none	57	57	-	MD 0.3 higher (0.95 lower to 1.55 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (assessed with: Excess gas/week)												
1 [1]	randomized trials	not serious	not serious	not serious [a]	very serious [b, d]	none	57	57	-	MD 1.1 higher (0.24 higher to 2.44 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic PEG	no treatment	Relative (95% CI)	Absolute (95% CI)		
Adverse events (assessed with: Severe cramping/week)												
1 [1]	randomized trials	not serious	not serious	not serious [a]	very serious [b, d]	none	57	57	-	MD 0.04 higher (1.15 lower to 1.07 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Conducted among persons with OIC, however, not among persons with cancer.

b. Small sample reported.

c. The 95% CI may not include a meaningful difference.

d. The 95% CI includes the potential for both possible harms, as well as possible benefit.

References

1. Freedman, Michael D, Schwartz, H Jeffrey, Roby, Robert, Fleisher, Steven. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. The Journal of Clinical Pharmacology; 1997.

Methylnaltrexone (subcutaneous or oral) and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should methylnaltrexone (subcutaneous or oral) and a bowel regimen rather than bowel regimen alone be used for adult patients with cancer with opioid-induced constipation?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	methylnaltrexone (SQ or oral)	bowel regime	Relative (95% CI)	Absolute (95% CI)		
Rescue-free bowel movement (defined as > or equal to 3 RFBM per week)												
3 [1,2,3]	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	485/963 (50.4%)	171/434 (39.4%)	**RR 1.33** (1.16 to 1.52)	**13 more per 100** (from 6 more to 20 more)	⨁◯◯◯ VERY LOW	CRITICAL
Laxation response (defined as a BM within 4 hours and no laxative in the prior 24 hours)												
5 [1,3,4,5,6]	randomized trials	not serious	not serious	very serious [a]	not serious	none	220/602 (36.5%)	48/396 (12.1%)	**RR 3.50** (2.65 to 4.62)	**30 more per 100** (from 20 more to 44 more)	⨁⨁◯◯ LOW	CRITICAL
Change in rescue-free bowel movement frequency												
3 [1,2]	randomized trials	not serious	not serious	very serious [a]	serious [c]	none	MD 1.60 more with 12 mg sq qd and 0.60 more with 12 mg sq qod (Michna 2011); MD 0.5 more 300 mg/450 mg and 0.1 more with 150mg (Rauck 2016)				⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	methylnaltrexone (SQ or oral)	bowel regime	Relative (95% CI)	Absolute (95% CI)		
Reduction in straining assessed using a straining scale 0 (none) to 4 (very severe)												
1 [2]	randomized trials	not serious	not serious	very serious [a]	serious [d]	none	Compared with placebo, methylnaltrexone led to more RFBM with none or mild straining (MD 11% to 15% more). No raw data provided.				⨁◯◯◯ VERY LOW	CRITICAL
AEs leading to treatment discontinuation												
4 [1,2,3,6]	randomised trials	not serious	not serious	very serious [a]	serious [e, f]	none	49/1080 (4.5%)	20/548 (3.6%)	**RR 1.51** (0.83 to 2.71)	**2 more per 100** (from 1 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
QOL												
1 [2]	randomised trials	not serious	not serious	very serious [a]	serious [d]	none	Methylnaltrexone group showed an improvement in the total score of 0.74 (12mg sc qd) and 0.39 (12mg sc qod).				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Some trials include terminally ill and cancer patients, but some do not. Different doses and formulations of methylnaltrexone were used. In addition, most trial participants had to quit their current bowel regimen.

b. The CI crossed our threshold of a clinically meaningful difference (defined as a number needed to treat of 10 per 100).

c. A pooled effect estimate could not be calculated. The mean change in RFBM frequency follows: (Michna) 1.60 more 12 mg SC daily dose and MD 0.60 with the 12 mg SC qod dose: (Rauck) MD 0.5 more with 300 mg and 450 mg, and MD 0.1 more with 150 mg. The Portenoy study was excluded because it was a combined one-week RCT and 3 three-week open-label study. No CIs or standard deviations were provided.

d. Data not available to determine precision of the estimate or important difference.

e. The 95% CI includes the potential for both benefit and harm.

f. Few events reported.

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Naldemedine (0.2 mg) and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should naldemedine (0.2 mg) in addition to a bowel regimen rather than bowel regimen alone be used for adult patients with cancer with OIC?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	naldemedine (0.2 mg)	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
SBM response (at least 3 SBMs/wk. and an increase from baseline of 1 SBM/wk.; follow-up 4-12 wk.)												
4 [1,2,3,4]	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	431/763 (56.5%)	264/759 (34.8%)	**OR 2.44** (1.99 to 3.01)	**501 more per 1,000** (from 344 more to 699 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	naldemedine (0.2 mg)	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
Change in SBM frequency (change from baseline in mean number of SBMs/wk.; follow-up 4-12 wk.)												
5 [1,2,3,4]	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	763	759	-	MD 2.02 SBM/wk. more (1.3 more to 2.74 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change in frequency of BMs without straining (frequency from baseline to the last 2 weeks of the treatment period)												
5 [1,2,3,4]	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	763	759	-	MD 1.43 BM w/o straining more (0.75 more to 2.11 more)	⊕⊕◯◯ LOW	CRITICAL
Change in BM frequency (change from baseline in mean number of SMBs/wk.; follow-up 52 wk.)												
1 [1]	randomized trials	not serious	not serious	serious [d]	serious [c]	none	621	620	-	MD 0.95 more (0.57 more to 1.33 more)	⊕⊕◯◯ LOW	IMPORTANT
QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk.)												
1 [1]	randomized trials	not serious	not serious	serious [d]	not serious	none	621	620	-	MD 0.3 higher (0.16 higher to 0.44 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
AEs leading to treatment discontinuation (follow-up 4-52 wk.)												
6 [1,2,3,4,5]	randomized trials	not serious	not serious	serious [b]	not serious	none	212/1378 (15.4%)	150/1378 (10.9%)	**RR 1.41** (1.17 to 1.70)	**4 more per 100** (from 2 more to 8 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	naldemedine (0.2 mg)	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
Change in frequency of SBMs rated 3 or 4 on the BSFS												
1 [1]	randomized trials	not serious	not serious	serious [d]	not serious	none	59	20	-	MD 1.51 more (0.51 more to 2.51 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The I^2 suggests some inconsistency; however, this may be due to the continuous nature of the outcome. All studies demonstrate benefit from the intervention.

b. Some trials conducted among persons with cancer.

c. The 95% CI may not include a clinically meaningful difference.

d. Trial not conducted among persons with cancer.

References

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Naloxegol and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should naloxegol and a bowel regimen rather than a bowel regimen alone be used for adult patients with cancer with opioid-induced constipation?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	naloxegol + bowel regimen	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
SBM response rate (at least 3 SBMs/wk. and an increase from baseline of 1 SBM for at least 9 of 12 wk. and for at least 3 of the final 4 wk.)												
2 [1]	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	187/446 (41.9%)	131/446 (29.4%)	RR 1.43 (1.19 to 1.71)	**13 more per 100** (from 6 more to 21 more)	⊕◯◯◯ VERY LOW	CRITICAL
Change in SBM frequency (change from baseline in mean number of SBMs/wk.)												
2 [1]	randomized trials	not serious	not serious	very serious [a]	serious [c]	none	438	442	-	MD **1.02 higher** (0.67 higher to 1.37 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining)												
2 [1]	randomized trials	not serious	not serious	very serious [a]	not serious	none	438	442	-	MD **0.24 lower** (0.35 lower to 0.14 lower)	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	naloxegol + bowel regimen	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
Stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7 denoting watery stool)												
2 [1]	randomized trials	not serious	serious [d]	very serious [a]	not serious	none	438	442	-	MD **0.33 higher** (0.2 higher to 0.46 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
AEs leading to treatment discontinuation												
4 [1,2]	randomized trials	not serious	not serious	very serious [a]	serious [e]	none	141/1500 (9.4%)	34/809 (4.2%)	RR 2.33 (1.62 to 3.35)	**6 more per 100** (from 3 more to 10 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Pain score (follow up: 12 weeks; assessed with: 11-point numerical rating scale (0=no pain; 10=worst pain) CID=2 points)												
2 [3]	randomized trials	not serious	not serious	very serious [a]	not serious [f]	none	880	443	-	MD **0 points** (0.11 lower to 0.12 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The trials were not conducted among persons with cancer because the trials would exclude patients with concomitant therapy that may also lead to constipation. Bowel regimen had to be stopped at the start of the Chey trials. Trial excluded patients on medications other than opioids that may lead to constipation. Half of patients were laxative refractory. Difficult to know in which direction the effect would change, whether less or more response to the therapy.

b. The CI crossed the threshold of a clinically meaningful difference (defined as a number needed to treat 10 per 100).

c. The CI crossed the threshold of a clinically meaningful difference (defined as an increase of at least 1 SBM).

d. I^2 was 73%

e. Data were pooled from the Chey studies as well as from a 4-week phase 2 study (Webster) and an open-label extension study (Webster). This was rated down for imprecision because the CI crossed the threshold of a clinically meaningful difference.

f. The OIS is met demonstrating no difference in mean change in pain score at follow-up between patients randomized to naloxegol or placebo.

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Lubiprostone and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should lubiprostone and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer with OIC?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lubiprostone	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
SBM response (assessed with: ≥3 SBMs/wk. for at least 9 of 12 treatment weeks and at least ≥1 SBM improvement/wk. for all weeks)												
2 [1,2]	randomized trials	not serious	not serious	serious [a]	serious [b]	publication bias strongly suspected [c]	166/437 (38.0%)	141/431 (32.7%)	**RR 1.15** (0.97 to 1.37)	**5 more per 100** (from 1 fewer to 12 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in SBM frequency (assessed with mean increase in weekly SBM from baseline)												
3 [1,2,3]	randomized trials	not serious	not serious	serious [a]	serious [d]	publication bias strongly suspected [e]	MD 0.8 more (Jamal) and 0.6 more (Cryer) MD 0.10 less (0.78 less to 0.58 more) (Spierings)				⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lubiprostone	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
Reduction in straining (assessed with 5-point scale ranging from 0 (absent) to 4 (very severe))												
1 [1]	randomized trials	not serious	not serious	serious [a]	not serious	publication bias strongly suspected [f]	223	212	-	MD 0.3 lower (0.47 lower to 0.13 lower)	⊕⊕◯◯ LOW	CRITICAL
Stool consistency (assessed with 5-point scale ranging from 0 (very loose) to 4 (very hard, little balls))												
1 [1]	randomized trials	not serious	not serious	serious [a]	not serious	publication bias strongly suspected [f]	223	212	-	MD 0.2 lower (0.37 lower to 0.03 lower)	⊕⊕◯◯ LOW	CRITICAL
Quality of life (assessed with: PAC-QoL; MID 1 point)												
1 [2]	randomized trials	not serious	not serious	serious [a]	serious [g]	publication bias strongly suspected [f]	PAC-QOL median change from baseline -0.861 in lubiprostone arm vs -0.695 in placebo arm; EQ-5D median change from baseline 0 in both arms.				⊕◯◯◯ VERY LOW	CRITICAL
AEs leading to treatment discontinuation												
3 [1,2,3]	randomized trials	not serious	not serious	serious [a]	serious [h]	none	41/643 (6.4%)	19/632 (3.0%)	**RR 2.13** (1.25 to 3.61)	**3 more per 100** (from 1 more to 8 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The trials were not conducted among persons with cancer. There was indirectness because trial participants could not be on a bowel regimen (only rescue medication/fiber supplement). Unknown laxative refractory status.

b. The CIs did not cross the threshold of a clinically meaningful difference.

c. This was rated down for selective outcome reporting bias. Cryer did not report results on the responder outcome, and Spierings (2017) did not report the responder outcome from the 12-week OPAL trial. Data to inform the SBM responder outcome were obtained from ClinicalTrails.gov (NCT00597428).

d. No CIs or SDs were reported and there was uncertainty about the range of possible effects.

e. The Jamal and Cryer studies reported a statistically significant improvement in this outcome; however, no quantitative information was provided for this outcome.

f. Rated down because of issues with how the data were analyzed and reported. The Spierings data were obtained from ClinicalTrials.gov.

g. Rated down for imprecision as no CIs or SDs were reported, and there was uncertainty about the range of possible effects.

h. Few events reported.

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Linaclotide and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should linaclotide and a bowel regimen rather than a bowel regimen alone only be used in adult patients with cancer with opioid-induced constipation?

Setting: Clinical care

Bibliography:

Nelson, A.D., Camilleri, M., Chirapongsathorn, S., Vijayvargiya, P., Valentin, N., Shin, A., ... Murad, M.H. (2017). Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: A systematic review and network meta-analysis. *Gut*, *66*, 1611–1622. http://doi.org/10.1136/gutjnl-2016-311835

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linaclotide	no treatment or OTC medications	Relative (95% CI)	Absolute (95% CI)		
SBM frequency (follow up: 8 weeks; assessed with: Change from baseline in 8-Week SBM frequency rate (SBMs/week))												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [a]	publication bias strongly suspected [b]	174	78	-	MD **1.62 more** (0.92 more to 2.31 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linaclotide	no treatment or OTC medications	Relative (95% CI)	Absolute (95% CI)		
Bristol Stool Scale (follow up: 8 weeks; assessed with: 7-point scale: 1=hard, 7=watery; Scale from: 1 to 7)												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [a, c]	publication bias strongly suspected [b]	174	78	-	MD **0.87 more** (0.54 more to 1.2 more)	⨁◯◯◯ VERY LOW	CRITICAL
Reduction in straining (assessed with 1 is "not at all" and a value of 5 is "an extreme amount."; Scale from: 1 to 5)												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [c]	publication bias strongly suspected [b]	174	78	-	MD **0.56 points lower** (0.79 lower to 0.34 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events												
1 [1]	randomized trials	not serious	not serious	not serious [d]	not serious	publication bias strongly suspected [b]	1/174 (0.6%)	5/78 (6.4%)	**RR 0.12** (0.02 to 0.73)	**56 fewer per 1,000** (from 63 fewer to 17 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Complete spontaneous bowel movements (follow up: 12 weeks; assessed with: ≥3 CSBM/week)												
1 [2]	randomized trials	not serious	not serious	very serious [e]	not serious	none	314	173	-	MD **1.96 higher** (1.12 higher to 3.44 higher)	⨁⨁◯◯ LOW	CRITICAL
Increase over baseline by >1 CSBM/week (follow up: 12 weeks)												
1 [2]	randomized trials	not serious	not serious	very serious [e]	not serious	none	314	173	-	MD **1.72 higher** (1.18 higher to 2.52 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Linaclotide	no treatment or OTC medications	Relative (95% CI)	Absolute (95% CI)		
Change in CSBM from baseline (follow up: 12 weeks)												
3 [3,4]	randomized trials	not serious	not serious	very serious [e]	not serious	none	1091	492	-	MD **1.57 higher** (1.11 higher to 2.04 higher)	⨁⨁◯◯ LOW	CRITICAL
Change in SBM from baseline (follow up: 12 weeks)												
3 [3,4]	randomized trials	not serious	not serious	very serious [e]	not serious	none	1091	492	-	MD **2.11 higher** (1.68 higher to 2.54 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. The 95% CI may not include a meaningful difference.

b. Has not been published in the peer-reviewed literature. Findings are from NCT02270983.

c. Small sample reported.

d. Unknown details of bowel regimen during study time period.

e. Trials are conducted among persons with chronic idiopathic constipation, not opioid-induced constipation and not among persons with cancer.

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Prucalopride and bowel regimen vs. bowel regimen for opioid-induced constipation

Question: Should prucalopride and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer with OIC?

Setting: Clinical care

Bibliography:

Hanson, B., Siddique, S.M., Scarlett, Y., & Sultan, S. (2019). American Gastroenterological Association Institute technical review on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 229–253. https://doi.org/10.1053/j.gastro.2018.08.018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prucalopride	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
SBM response (defined as an average of > or = to 3 SBMs/wk.) (follow-up:4 wk.)												
2 [1,2]	randomized trials	not serious	not serious	very serious [a]	serious [b, c]	publication bias strongly suspected [d]	126/216 (58.3%)	62/149 (41.6%)	**RR 1.36** (1.08 to 1.70)	**15 more per 100** (from 3 more to 29 more)	⨁◯◯◯ VERY LOW	CRITICAL
Change in SBM frequency												
1 [1]	randomized trials	not serious	not serious	very serious [a]	serious [e]	publication bias strongly suspected [d]	MD 0.7 more with 2mg; MD 1.0 more with 4mg				⨁◯◯◯ VERY LOW	CRITICAL
Reduction in painful defecation/lack of straining - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Stool consistency - not reported												
-	-	-	-	-	-	-	No quantitative data reported. Authors state prucalopride increased the percentage of stools with normal consistency and decreased the percentage of hardness of stools (data not shown).				-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prucalopride	bowel regimen	Relative (95% CI)	Absolute (95% CI)		
QoL improvement as measured by PAC-QoL (responder defined as patient achieving improvement or 1 or greater point on satisfaction subscale)												
1 [1]	randomized trials	not serious	not serious	very serious [a]	serious [c, f]	publication bias strongly suspected [d]	37/130 (28.5%)	12/66 (18.2%)	**RR 1.57** (0.88 to 2.80)	**10 more per 100** (from 2 fewer to 33 more)	⨁◯◯◯ VERY LOW	CRITICAL
AEs leading to treatment discontinuation												
1 [1]	randomized trials	not serious	not serious	very serious [a]	serious [c, f]	publication bias strongly suspected [d]	8/130 (6.2%)	7/66 (10.6%)	**RR 0.58** (0.22 to 1.53)	**4 fewer per 100** (from 8 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Trials not conducted among persons with cancer. Patients not laxative refractory, and participants in the trial had to go off bowel regimen. Excluded if constipation thought to be drug induced.

b. The 95% CI crossed the threshold of a clinically meaningful difference.

c. Few events reported.

d. Publication bias was a concern as no other studies were published since the Sloot study. On Clinical Trials.gov a study titled "Prucalopride Effects on Subjects with Chronic Non-Cancer Pain Suffering from Opioid Induced Constipation" was found (NCT0117051), but this study was terminated early (2014) by Movetis after 174 patients were recruited.

e. Publications did not provide CIs or SDs. Small sample reported.

f. The 95% CI included both possible harms, as well as potential benefit.

References

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2. ClinicalTrials.gov Id: NCT01117051. https://clinicaltrials.gov/ct2/show/NCT01117051

Osmotic or stimulant laxatives and lifestyle education vs. lifestyle education for non-opioid-related constipation

Question: Should osmotic or stimulant laxatives and lifestyle education rather than lifestyle education be used in adult patients with cancer with non-opioid-related constipation?

Setting: Clinical care

Bibliography:

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic or stimulant laxatives + lifestyle factors	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
SBM response (defined as ≥3 SBMs/wk. or ≥3 stools/wk.)												
7 [1,2,3,4,5,6,7]	randomized trials	not serious	not serious	serious [a]	not serious	none	525/876 (59.9%)	143/535 (26.7%)	**RR 2.24** (1.93 to 2.61)	**33 more per 100** (from 25 more to 43 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change in BM frequency												
6 [2,4,5,6,7,8]	randomized trials	not serious	serious [b]	serious [a]	not serious	none	805	464	-	MD 2.55 higher (1.53 higher to 3.57 higher)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic or stimulant laxatives + lifestyle factors	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Reduction in straining												
2 [2,3]	randomized trials	not serious	not serious	serious [a]	not serious	none	49/58 (84.5%)	33/60 (55.0%)	**RR 1.52** (1.18 to 1.96)	**29 more per 100** (from 10 more to 53 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Stool consistency improvement (assessed with measured as hard/pellet stools)												
3 [2,3,4]	randomized trials	not serious	not serious	serious [a]	not serious	none	123/138 (89.1%)	76/131 (58.0%)	**RR 1.55** (1.33 to 1.82)	**32 more per 100** (from 19 more to 48 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
AEs leading to treatment discontinuation												
3 [9,10,11]	randomized trials	not serious	not serious	serious [c]	not serious	none	45/358 (12.6%)	6/231 (2.6%)	**RR 3.55** (1.60 to 7.89)	**66 more per 1,000** (from 16 more to 179 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Bristol Stool Scale												
1 [10]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	80	76	-	MD 1 higher (0.64 higher to 1.36 higher)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	osmotic or stimulant laxatives + lifestyle factors	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
PAC-QoL												
1 [12]	randomized trials	serious [e]	not serious	serious [f]	serious [g]	none	PAC-QoL MD at 12 months for Personalized education (n=13) vs laxative (n=27) use: -0.09 (95% CI: -0.38, 0.21); PAC-QoL MD at 12 months for Standard education (n=42) vs laxative (n=27) use: -0.04 (95% CI: -0.32, 0.23).				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Rated down for indirectness because population consisted of persons with functional constipation, and constipation related to treatments received by patients with cancer may be different.

b. Meta-analysis conducted in Ford 1998 presents an I^2 of 100%; greater heterogeneity is expected when presenting absolute values and all effects are on the same side of the line of no effect; however, we still rated down by one.

c. Rated down for indirectness because of the difference in complementary treatments. Tarumi participants used laxatives throughout with docusate; McGraw prohibited use of laxatives with PEG 3350 + Senna.

d. The 95% CI includes the potential for harm, as well as benefit.

e. Concerns with reporting bias, recall bias, randomization and allocation.

f. Trial is conducted among older persons with chronic constipation, not among persons with cancer treatment-related constipation.

g. Small sample does not meet OIS. Additionally, the 95% CI includes the potential for both a reduction in QoL, as well as an improvement; however, may not be clinically meaningful.

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Acupuncture and lifestyle education vs. lifestyle education for non-opioid-related constipation

Question: Should acupuncture and lifestyle education rather than lifestyle education alone be used in adult patients with cancer with non-opioid related constipation?

Setting: Clinical care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acupuncture	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Spontaneous bowel movement (follow up: range 9 weeks to 16 weeks; assessed with: SBM/wk)												
6 [1,2,3]	randomized trials	serious [a]	not serious	serious [b, c]	serious [d]	none	860	300	-	MD 0.85 higher (0.59 higher to 1.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acupuncture	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Constipation Assessment Scale (follow up: 9 weeks; Scale from: 0 to 16 (higher scores = severe constipation))												
1 [2]	randomized trials	serious [e]	not serious	serious [2, f]	serious [g]	none	15	15	-	MD 0.63 lower (3.14 lower to 1.88 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Bristol Stool Scale (follow up: range 9 weeks to 12 weeks; Scale from: 1 to 7 (higher score = softer feces))												
4 [2,3]	randomized trials	not serious [a]	not serious	serious [b, c]	serious [d]	none	520	185	-	MD 0.41 higher (0.26 higher to 0.55 higher)	⊕⊕◯◯ LOW	CRITICAL
Adverse events (follow up: range 9 weeks to 16 weeks)												
3 [1,2]	randomized trials	serious [a]	not serious	serious [3,4, b,c,h]	serious [g, i]	none	15/355 (4.2%)	14/130 (10.8%)	**RR 0.53** (0.27 to 1.02)	**51 fewer per 1,000** (from 79 fewer to 2 more)	⊕◯◯◯ VERY LOW	CRITICAL
Defecation frequency (follow up: 9 weeks; assessed with: frequency/week)												
1 [2]	randomized trials	not serious [a]	not serious	serious [b]	very serious [g, i]	none	15	15	-	MD 1.74 lower (4.02 lower to 0.54 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Use of rescue medication (follow up: 9 weeks)												
1 [2]	randomized trials	not serious [a]	not serious	serious [b]	very serious [g, i]	none	1/15 (6.7%)	5/15 (33.3%)	**RR 0.20** (0.03 to 1.51)	**267 fewer per 1,000** (from 323 fewer to 170 more)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	acupuncture	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Cleveland Clinic Score (follow up: 16 weeks; Scale from: 0 to 30 (higher score = more severe constipation))												
2 [5]	randomized trials	not serious	not serious	serious [b, j]	serious [i]	none	340	115	-	MD 0.45 higher (0.64 lower to 1.53 higher)	⨁⨁◯◯ LOW	IMPORTANT
FACT-G (assessed with higher score = better QOL)												
1 [6]	randomized trials	not serious	not serious	serious [k]	serious [i]	none	70	70	-	MD 2.6 higher (1.39 lower to 6.59 higher)	⨁⨁◯◯ LOW	IMPORTANT
Development of constipation												
2 [4,6]	randomized trials	not serious	serious [l]	serious [k]	serious [m]	none	20/100 (20.0%)	43/100 (43.0%)	**RR 0.47** (0.30 to 0.73)	**228 fewer per 1,000** (from 301 fewer to 116 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. High risk of bias for blinding of participants and personnel in the Wu 2014 study - both participants and personnel knew treatment allocation.

b. Trial conducted among persons without cancer with functional constipation.

c. Lee 2018 compares acupuncture (n=15) vs. sham acupuncture (n=15). Wu 2014 compares deep needling (n=228) vs. shallow needling (n=112) vs. control (lactulose; n=115). Zheng 2018 compares He (n=172) vs. Shu-mu (n=168) vs. He-shu-mu (n=165) vs. control (mosapride; n=170).

d. The 95% CI may not include a meaningful difference.

e. Small sample size may not have allowed for equipoise of baseline characteristics; therefore, the inability to calculate a MD based on mean change from baseline may skew the effect estimate.

f. Lee 2018 was conducted among persons without cancer with functional constipation. MD calculated from mean change from baseline.

g. Small sample reported.

h. One trial, Liu 2015, conducted among persons receiving treatment for cancer who were not constipated at baseline, reported no adverse events in either intervention (n=15) or control (n=15) arms. Zheng 2017 conducted among persons without cancer with functional constipation reported 11 adverse events across 3 interventions (He, Shu-mu, He-shu-mu) arms (n=505) and 6 adverse events in the control (mosapride) arm (n=170).

i. The 95% CI includes the potential for both harm and benefit.

j. Persons in the comparison arm were randomized to lactulose.

k. Crossover trial conducted among persons with cancer but not experiencing constipation.

l. Some heterogeneity present (I2=77%); however, it may be explained by differences in treatment interventions.

m. Few events reported.

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Electroacupuncture and lifestyle education vs. lifestyle education for non-opioid-related constipation

Question: Should electroacupuncture and lifestyle education rather than lifestyle education alone be used in adult patients with cancer with non-opioid-related constipation?

Setting: Clinical care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electroacupuncture	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
≥3 CSBMs per week (follow up: 8 weeks)												
1 [1]	randomized trials	not serious	not serious	very serious [a, b]	not serious	none	168/536 (31.3%)	65/539 (12.1%)	**RR 3.33** (2.42 to 4.57)	**281 more per 1,000** (from 171 more to 431 more)	⨁⨁◯◯ LOW	CRITICAL
PAC-QoL (follow up: 8 weeks; assessed with: 5-point scale (lower score = higher QoL))												
3 [1,2]	randomized trials	not serious	not serious	very serious [a, b]	serious [c]	none	659	606	-	MD 0.31 lower (0.36 lower to 0.25 lower)	⨁◯◯◯ VERY LOW	CRITICAL
CSBM (follow up: 8 weeks; assessed with: CSBM/wk.)												
2 [1,3]	randomized trials	not serious	not serious	very serious [a, b]	serious [c]	none	571	576	-	MD 0.85 higher (0.64 higher to 1.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Bristol Stool Scale (follow up: 8 weeks; Scale from: 1 to 7 (higher score = softer feces))												
3 [1,2]	randomized trials	not serious	not serious	very serious [a, b]	serious [c]	none	659	606	-	MD 0.19 higher (0.06 higher to 0.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electroacupuncture	lifestyle factors	Relative (95% CI)	Absolute (95% CI)		
Adverse events leading to treatment discontinuation (follow up: 8 weeks)												
1 [1]	randomized trials	not serious	not serious	very serious [a, b]	serious [d, e]	none	4/536 (0.7%)	9/539 (1.7%)	**RR 0.45** (0.14 to 1.44)	**9 fewer per 1,000** (from 14 fewer to 7 more)	⨁◯◯◯ VERY LOW	CRITICAL
Use of rescue medication (follow up: 8 weeks)												
1 [1]	randomized trials	not serious	not serious	very serious [a, b]	serious [c]	none	155/536 (28.9%)	183/539 (34.0%)	**RR 0.85** (0.71 to 1.02)	**51 fewer per 1,000** (from 98 fewer to 7 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SBM (follow up: 8 weeks; assessed with: SBM/wk.)												
4 [1,2,3]	randomized trials	not serious	not serious [f]	very serious [a, b]	serious [c]	none	641	590	-	MD 0.99 higher (0.92 higher to 1.05 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Change in straining severity (follow up: 8 weeks)												
3 [1,2]	randomized trials	not serious	not serious	very serious [a, b]	serious [c]	none	659	606	-	MD 0.23 lower (0.27 lower to 0.19 lower)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Trial conducted among persons without cancer with functional constipation.

b. Liu 2016 compares 28 sessions of EA (n=536) vs. shallow EA (n=539). Wu 2017 compares 16 sessions of strong current EA (n=65) vs. weak current EA (n=58) vs. mosapride (n=67). Da 2016 compares 28 sessions of EA (n=35) vs. shallow EA (n=37).

c. The 95% CI may not include a meaningful difference.

d. The 95% CI includes the potential for both harm and benefit.

e. Few events reported.

f. I^2 of 77% suggests some heterogeneity; however, it may be due to the comparisons or other differences in the study populations accounted for within indirectness.

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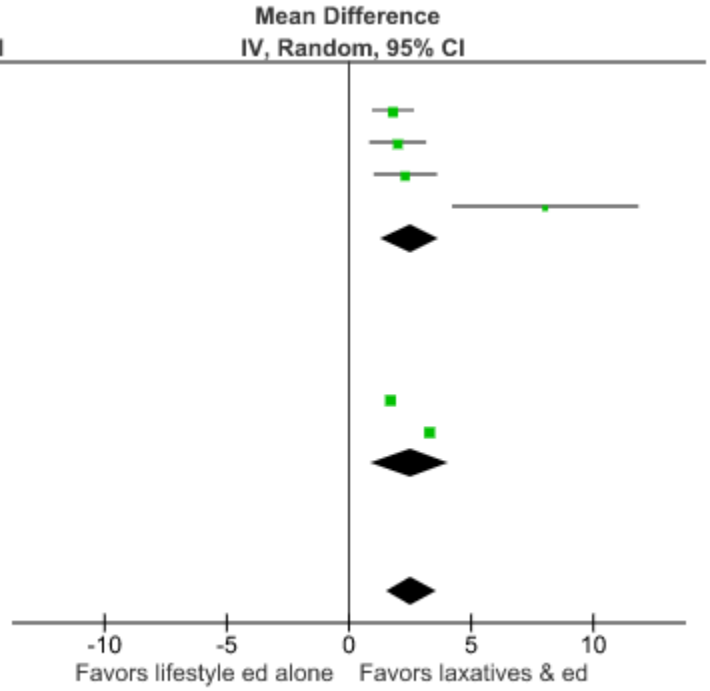
5. Forest plots (Developed using Review Manager Web (RevMan Web) [Systematic review software]. (2019). https://revman.cochrane.org)

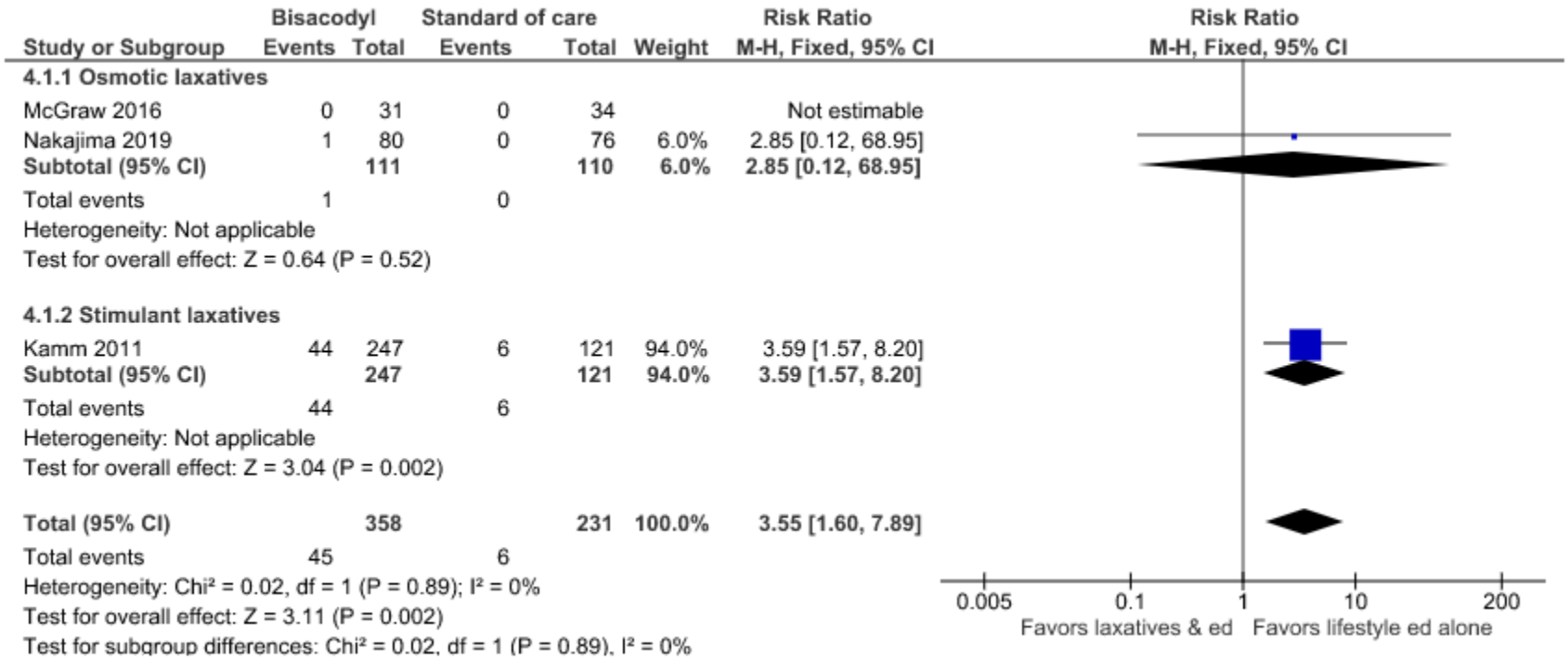
- Laxatives—Bowel movement frequency
- Laxatives—Adverse events leading to treatment discontinuation
- Naldemedine—Spontaneous Bowel Movements (SBMs)
- Naldemedine—Adverse events leading to treatment discontinuation
- Acupuncture—Bristol Stool Form Scale
- Acupuncture—Adverse events
- Acupuncture—Development of constipation

Laxatives—Bowel movement frequency

	Laxatives			Standard of care				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
4.5.1 Osmotic laxatives								
DiPalma 2000	4.5	3	80	2.7	1.8	71	18.9%	1.80 [1.02, 2.58]
Corazziari 1996	4.8	2.3	25	2.8	1.6	23	17.0%	2.00 [0.89, 3.11]
DiPalma 2007	7.9	4.5	204	5.6	5.5	100	16.2%	2.30 [1.06, 3.54]
Baldonedo 1991	13.56	6.74	16	5.53	3.58	15	5.4%	8.03 [4.26, 11.80]
Subtotal (95% CI)			**325**			**209**	**57.5%**	**2.51 [1.30, 3.71]**
Heterogeneity: Tau² = 0.95; Chi² = 10.22, df = 3 (P = 0.02); I² = 71%								
Test for overall effect: Z = 4.08 (P < 0.0001)								
4.5.2 Stimulant laxatives								
Kamm 2010	3.4	0.2	223	1.7	0.14	134	21.3%	1.70 [1.66, 1.74]
Mueller-Lissner 2010	5.2	0.27	247	1.9	0.34	121	21.3%	3.30 [3.23, 3.37]
Subtotal (95% CI)			**470**			**255**	**42.5%**	**2.50 [0.93, 4.07]**
Heterogeneity: Tau² = 1.28; Chi² = 1624.21, df = 1 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 3.12 (P = 0.002)								
Total (95% CI)			**795**			**464**	**100.0%**	**2.55 [1.53, 3.57]**
Heterogeneity: Tau² = 1.26; Chi² = 1634.47, df = 5 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 4.92 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%								

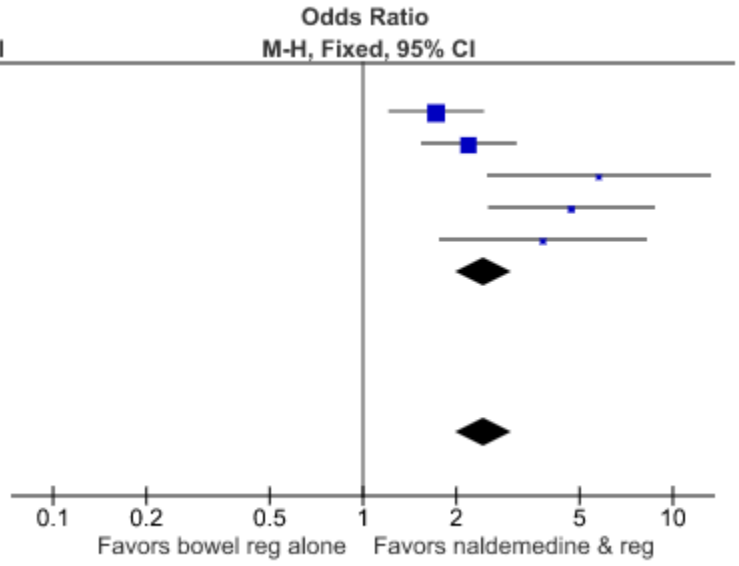


Laxatives—Adverse events leading to treatment discontinuation



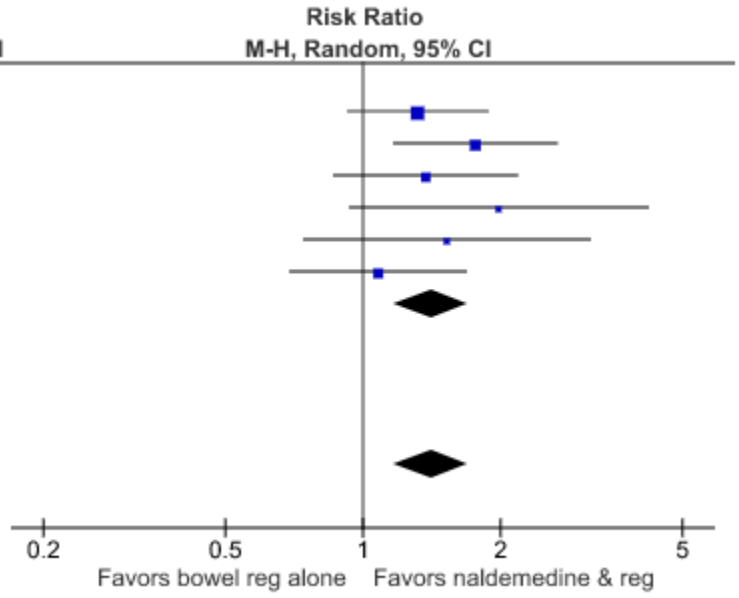
Naldemedine—Spontaneous Bowel Movements (SBMs)

Study or Subgroup	Naldemedine Events	Total	Standard of care Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.2 0.2 mg						
Hale 2017a	130	273	94	272	43.2%	1.72 [1.22, 2.43]
Hale 2017b	145	276	92	274	38.3%	2.19 [1.55, 3.09]
Katakami 2017a	45	58	21	56	4.2%	5.77 [2.54, 13.11]
Katakami 2017b	69	97	33	96	8.4%	4.70 [2.56, 8.65]
Webster 2017	42	59	24	61	5.9%	3.81 [1.78, 8.16]
Subtotal (95% CI)		**763**		**759**	**100.0%**	**2.44 [1.99, 3.01]**
Total events	431		264			
Heterogeneity: Chi² = 14.32, df = 4 (P = 0.006); I² = 72%						
Test for overall effect: Z = 8.44 (P < 0.00001)						
Total (95% CI)		**763**		**759**	**100.0%**	**2.44 [1.99, 3.01]**
Total events	431		264			
Heterogeneity: Chi² = 14.32, df = 4 (P = 0.006); I² = 72%						
Test for overall effect: Z = 8.44 (P < 0.00001)						
Test for subgroup differences: Not applicable						



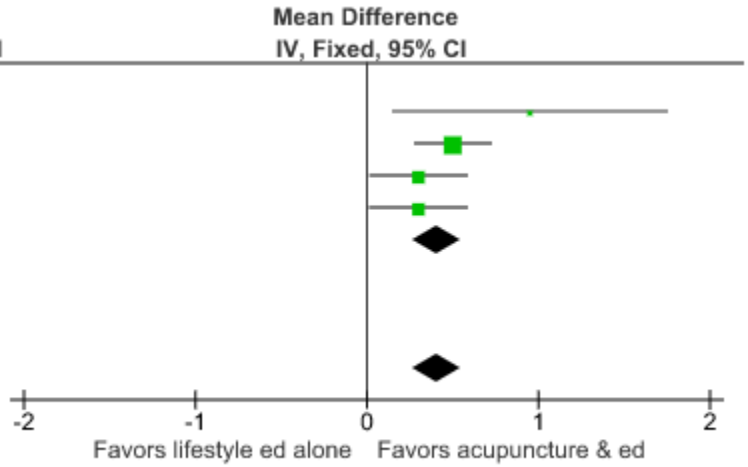
Naldemedine—Adverse events leading to treatment discontinuation

Study or Subgroup	Naldemedine Events	Naldemedine Total	Standard of care Events	Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.2 0.2 mg						
Hale 2017a	59	271	45	272	29.4%	1.32 [0.93, 1.87]
Hale 2017b	54	271	31	274	21.5%	1.76 [1.17, 2.65]
Katakami 2017a	27	58	19	56	17.1%	1.37 [0.87, 2.17]
Katakami 2017b	18	97	9	96	6.4%	1.98 [0.94, 4.19]
Webster 2017	15	60	10	61	7.0%	1.52 [0.74, 3.12]
Webster 2018	39	621	36	619	18.6%	1.08 [0.70, 1.68]
Subtotal (95% CI)		**1378**		**1378**	**100.0%**	**1.41 [1.17, 1.70]**
Total events	212		150			
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Total (95% CI)		**1378**		**1378**	**100.0%**	**1.41 [1.17, 1.70]**
Total events	212		150			
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Test for subgroup differences: Not applicable						

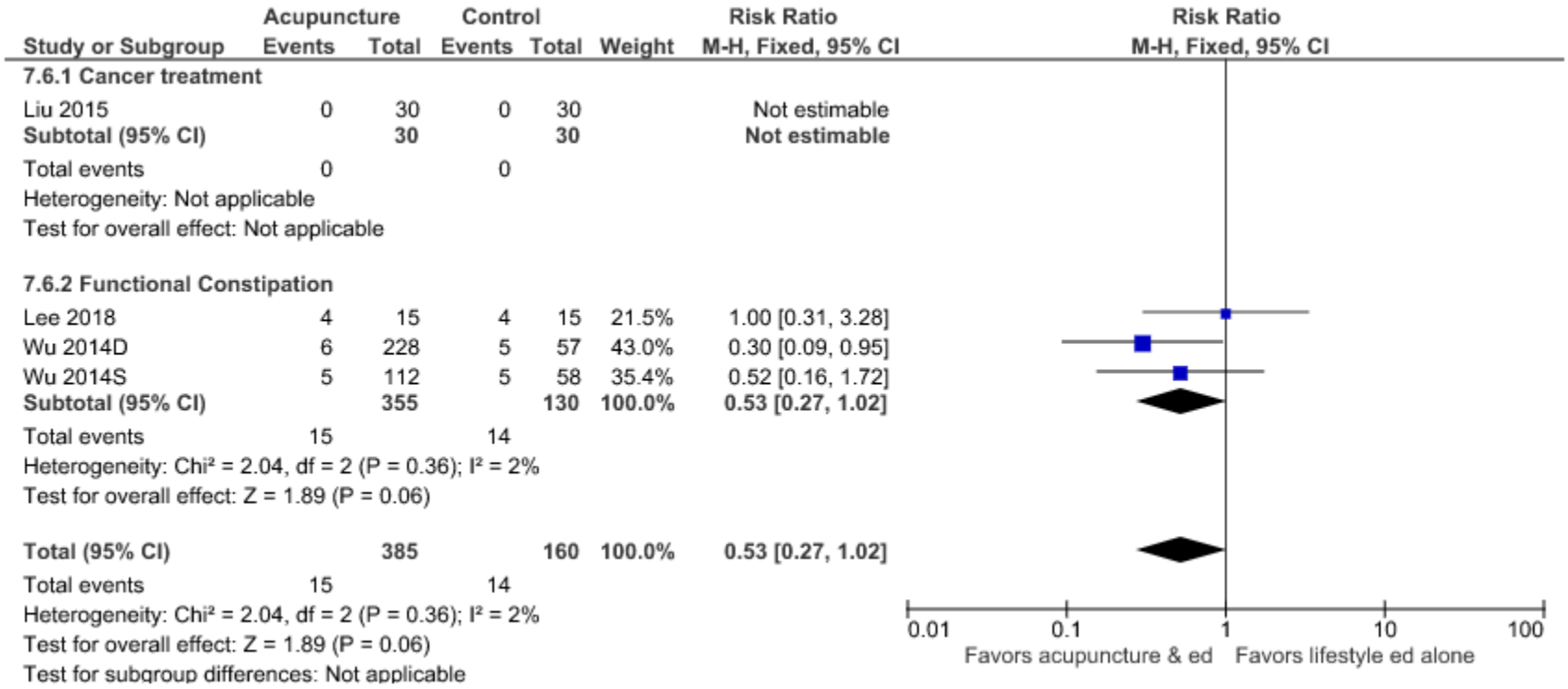


Acupuncture—Bristol Stool Form Scale

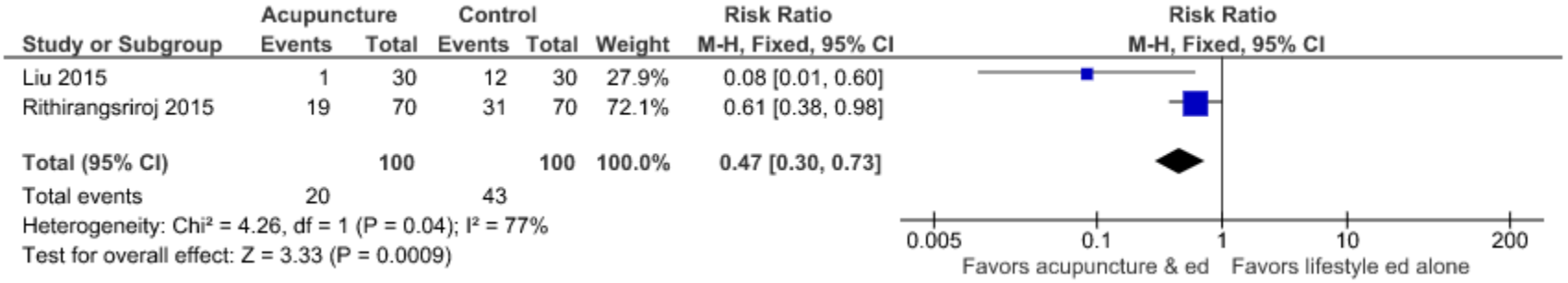
Study or Subgroup	Acupuncture Mean	Acupuncture SD	Acupuncture Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
7.2.3 MD MC 9wk								
Lee 2018	1.09	1.3	15	0.14	0.88	15	3.3%	0.95 [0.16, 1.74]
Zheng 2018H	3.6	0.6644	172	3.1	0.7538	57	43.3%	0.50 [0.28, 0.72]
Zheng 2018HS	3.4	1.3011	165	3.1	0.7538	57	26.8%	0.30 [0.02, 0.58]
Zheng 2018S	3.4	1.313	168	3.1	0.7538	56	26.6%	0.30 [0.02, 0.58]
Subtotal (95% CI)			**520**			**185**	**100.0%**	**0.41 [0.26, 0.55]**
Heterogeneity: Chi² = 3.61, df = 3 (P = 0.31); I² = 17%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
Total (95% CI)			**520**			**185**	**100.0%**	**0.41 [0.26, 0.55]**
Heterogeneity: Chi² = 3.61, df = 3 (P = 0.31); I² = 17%								
Test for overall effect: Z = 5.54 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Acupuncture—Adverse events



Acupuncture—Development of constipation



6. Characteristics of Included Studies

Study	Setting	Population	No. of patients	Intervention	Comparison	Outcomes
Da et al., 2015	Single site, China	Functional constipation	67	Deep electroacupuncture	Shallow electroacupuncture	SBM response, Bristol stool scores, quality of life, adverse events
Freedman 1997	Single site, US	Opioid-induced constipation	57	Polyethylene glycol 3350	Lactulose	Self-reported frequencies, consistency and ease of defecation
Hanai et al., 2016	Single site, Japan	Cancer, receiving chemotherapy with 5HT3 receptor antagonist	30	Non-pharmacologic self-management	Standard care	Constipation assessment scale, Short Form 36 survey, nausea, vomiting
Katakami, Harada et al., 2017 JCO Phase III	Multisite, Japan	Opioid-induced constipation, cancer pain	298	Naldemedine	Placebo	SBM, safety
Katakami, Oda et al., 2017 JCO Phase IIb	Multisite, Japan	Cancer: lung, breast, large intestine or other	193	Naldemedine	Placebo	Proportion of spontaneous bowel movement (SBM) responders (> 3 SBMs/week and an increase of > 1 SBM/week from baseline), safety
Katakami study Annals 2018	Multisite, Japan	Cancer: mixed diagnoses (none that impacted GI function)	193	Naldemedine	Placebo	Proportion of SBM responders, quality of life
Lacy et al., 2015	Multisite, US and Canada	Chronic constipation	486	Linaclotide 145mg, 290 mg	Placebo	Complete SBM, other additional bowel endpoints (bloating, straining, time to first SBM, pain, cramping, fullness)
Lee et al., 2018	Single site, South Korea	Functional constipation	30	Acupuncture	Sham acupuncture	SBM, defecation frequency, Bristol stool scale
Lembo et al., 2010	Multisite, US	Chronic constipation	310	Linaclotide (75mg, 150mg, 300mg or 600mg)	Placebo	SBM, complete SBM, stool consistency, straining, abdominal discomfort, bloating, quality of life, adverse events
Lembo et al., 2011	Multisite, US and Canada	Chronic constipation	1276	Linaclotide, 145mg, 290 mg	Placebo	Complete SBM, adverse events

Study	Setting	Population	No. of patients	Intervention	Comparison	Outcomes
Liu et al., 2015	Single site, China	Cancer	60	Acupuncture and ginger moxibustion	Usual care	Nausea, constipation, cost
Liu et al., 2016	Multisite, China	Functional constipation	1075	Electroacupuncture	Sham acupuncture	SBM response, reduction in straining, quality of life
McGraw, 2016	Multisite, US	Chronic constipation	65	Polyethylene glycol 3350	Placebo	Adverse events, laboratory evaluations, endoscopic abnormalities
Nakajima, et al., 2019	Multisite, Japan	Chronic constipation	156	Polyethylene glycol 3350	Placebo	Change in frequency of SBMs adverse events, safety and efficacy
Rauck et al., 2019	Multisite, US	Non-malignant pain	803	Methylnaltrexone 150mg, 300mg, 450mg	Placebo	Improve the percentage of dosing days resulting in a rescue-free bowel movement within 4 hours of dosing, % responders with 3 or > RFBMs/week, increase from baseline of one or more RFBMs/week during at least 3 of 4 weeks
Rithirangsriroj et al., 2015	Single site, Thailand	Cancer	70	Acupuncture	Usual care	Emetic control, adverse events, quality of life
Shen et al., 2018	Single site, China	Functional constipation	66	Routine nursing care + constipation specific education	Routine nursing care	SBM (defecation interval), evacuator difficulty, Bristol stool scale
Speed et al., 2010	Multisite, United Kingdom	Chronic constipation	154	Laxatives	Diet and lifestyle	Patient assessment of constipation symptoms, quality of life
Tarumi et al., 2013	Multisite, Canada	Cancer and non-cancer patients in palliative care	74	Docusate	Placebo	Mean bowel movements per day, Bristol Stool scale
Webster, Brewer et al., 2018	Multisite, location not reported	Opioid-induced constipation	1452	Lubiprostone	Placebo	SBM frequency, overall treatment response, opioid-induced constipation symptoms
Webster, Diva et al., 2018	Multisite, US and Europe	Non-malignant pain	1352	Naloxegol 12.5mg/d	Placebo	Average and worst pain scores

Study	Setting	Population	No. of patients	Intervention	Comparison	Outcomes
Webster & Israel, 2018	Multisite, US	Non cancer chronic pain	120	Methylnaltrexone 150mg, 300mg, 450mg	Placebo	Rescue free bowel movements, percentage of responders, change in weekly number of rescue free bowel movements, adverse events
Wu et al., 2014	Multisite, China	Functional constipation	475	Deep or shallow acupuncture	Lactulose	SBM, reduction in straining, change in SBM frequency, stool consistency, adverse events
Wu et al., 2017	Multisite, China	Functional constipation	201	Low or high current intensity electroacupuncture	Mosapride	Change in SBM frequency, stool consistency, adverse events
Zheng et al., 2018	Multisite, China	Functional constipation	675	3 groups of electroacupuncture	Mosapride	Spontaneous bowel movement response