ONS CONSTIPATION SYMPTOM MANAGEMENT GUIDELINE

Supplementary Material

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1. Guideline panel conflict of interest disclosures

Panel member	Conflict of interest disclosures
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Brian Hanson, MD Internist Division of Gastroenterology and Hepatology, University of Minnesota, and Minneapolis Veterans Affairs Healthcare System, Minneapolis, MN	No conflicts listed
Rachael Lopez, MPH, RD, CSO Clinical Research Dietitian National Institutes of Health	No conflicts listed
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Brenda Wolles, RN, MSN, CNL, OCN® Clinical Nurse Leader Medical-Oncology Sanford Health, Sioux Falls, SD	No conflicts listed

2. PICO questions

Population	Intervention(s)	Comparator	Outcomes
Opioid-induced constipation			
Adult patients with cancer receiving opioids who are not yet constipated	Prophylactic bowel regimen with laxatives 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 who have opioid-induced constipation	Osmotic or stimulant laxatives 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 polyethylene glycol and lifestyle education	Lifestyle education	Stool consistency Occurrence of constipation (y/n) Quality of life Adverse events that lead to treatment discontinuation
Opioid-induced constipation in patients with cancer; have not responded to a bowel regimen			
Adult patients with cancer who have OIC and have not responded to a bowel regimen	Methylnaltrexone (subcutaneous or oral) and a 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 who have opioid-induced constipation	Naldemedine 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 who have 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 who have 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

Adult patients with cancer who have 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 who have 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
Non-opioid-related constipation in patients with cancer			
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

3. Evidence-to-Decision Frameworks (Developed using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.)

- Prophylactic bowel regimen and lifestyle education vs. lifestyle education for opioid-induced constipation
- Osmotic or stimulant laxatives and lifestyle education vs. lifestyle education for opioid-induced constipation
- Osmotic polyethylene glycol 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
- Prucalopride 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
- 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

Prophylactic bowel regimen and lifestyle education vs. lifestyle education for opioid-induced constipation

RECOMMENDATION

Should a prophylactic bowel regimen and lifestyle education rather than lifestyle education alone be used in adult patients with cancer receiving opioids who are not yet constipated?	
POPULATION:	Adult patients with cancer receiving opioids who are not yet constipated
INTERVENTION:	Prophylactic bowel regimen and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Stool consistency; Occurrence of constipation (y/n); Quality of life; Adverse events that lead to treatment discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	The panel agreed that the risk of developing constipation from opioid treatment varied considerably.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		The panel decided that the magnitude of the effect is less because not all patients would develop constipation.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with a prophylactic bowel regimen
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁◯◯ LOW[a,b]	RR 2.24 (1.93 to 2.61)	Study population	
				27 per 100	**33 more per 100** (25 more to 43 more)
Change in BM frequency	1269 (6 RCTs)[2,4,5,6,7,8]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean change in BM frequency was **0**	MD **2.55 higher** (1.53 higher to 3.57 higher)
Reduction in straining	118 (2 RCTs)[2,3]	⨁⨁◯◯ LOW[a,b]	RR 1.52 (1.18 to 1.96)	Study population	
				55 per 100	**29 more per 100** (10 more to 53 more)
Stool consistency improvement assessed with: measured as hard/pellet stools	269 (3 RCTs)[2,3,4]	⨁⨁◯◯ LOW[a,b]	RR 1.55 (1.33 to 1.82)	Study population	
				58 per 100	**32 more per 100** (19 more to 48 more)
Quality of life - not reported	-	-	-	-	-
AEs leading to treatment discontinuation	589 (3 RCTs)[10,11,9]	⨁⨁◯◯ LOW[b,d]	RR 3.55 (1.60 to 7.89)	Study population	
				26 per 1,000	**66 more per 1,000** (16 more to 179 more)

References:

1. Wesselius-De Casparis, A., Braadbaart, S., Bergh-Bohlken, G., Mimica, M. 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
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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.

Explanations:

a. Rated down twice for indirectness because population consisted of non-OIC and non-cancer patients.
b. Indirect because participants in the trial had constipation at start.
c. Check Ford article for I squared of 100%
d. Rated down for indirectness because of difference in complementary treatments. McGraw prohibited use of laxatives with PEG 3350 + senna.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		The panel agreed that patients who aren't constipated may experience diarrhea and estimated that at minimum this would affect 20% of people. The risk with diarrhea would be electrolyte imbalance or dehydration.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with a prophylactic bowel regimen
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁◯◯ LOW[a,b]	RR 2.24 (1.93 to 2.61)	Study population	
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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.

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Explanations:

a. Rated down twice for indirectness because population consisted of non-OIC and non-cancer patients.
b. Indirect because participants in the trial had constipation at start.
c. Check Ford article for i squared of 100%
d. Rated down for indirectness because of difference in complementary treatments. McGraw prohibited use of laxatives with PEG 3350 + senna.

In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose use can result in worsening abdominal distension and flatulence. They also indicated that a large body of evidence shows that polyethylene glycol has fewer side effect than lactulose. The authors said senna and lactulose have similar adverse effects. They also said that use of stimulant laxatives like senna can result in drug dependence and that potential side effects are usually mild but can include abdominal discomfort, cramps, nausea, diarrhea, GI irritation, and fluid and electrolyte depletion.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		The certainty in the estimates for osmotic or stimulant laxatives in addition to lifestyle education was judged as low due to concerns with indirectness of the evidence because the studies were not conducted among persons experiencing OIC, and trial participants experienced constipation at start of study. The certainty of the evidence was largely driven by the outcomes: adverse events leading to treatment discontinuation and SBM response.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determined there may be greater uncertainty because patients may place higher value on avoiding constipation, but others may place higher value on undue harms.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The guideline panel considered that patients who place a higher value on avoidance of constipation may prefer to start on a prophylactic regimen; however, patients who place a higher value on avoiding undue costs/taking medications/undue harms (diarrhea) may prefer to not start on a bowel regimen prophylactically.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Over the Counter Medication** Source: Walmart.com 6-24-19	The panel agreed that the expense of a bowel regimen would be greater than providing lifestyle education alone.

Medication	Product	Price
Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	$4.74
Docusate sodium	Equate Stool Softener Docusate Sodium Softgels, 100 mg, 60 Ct	$2.84
Magnesium citrate	Equate Lemon Flavor Magnesium Citrate Saline Laxative Oral Solution, 10 fl oz	$0.98
Magnesium hydroxide (milk of magnesia)	Equate Milk of Magnesia Saline Laxative, Original Flavor, 1200 mg, 26 fl oz	$3.57
Polyethylene glycol (PEG) (Miralax)	ClearLAX Polyethylene Glycol 3350 Laxative Powder, 30 Doses	$12.92
Senna	Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	$4.78

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that while patients would most likely need to pay out of pocket, options for a bowel regimen are widely available and of limited cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose is widely available.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	•	○	○

CONCLUSIONS

Recommendation

Good practice statement: The ONS Guidelines panel recommends that, before starting an opioid regimen, patients with cancer have a clear understanding of constipation prophylaxis lifestyle education of increased fiber, water intake, and exercise.

Recommendation: Among adult patients with cancer who are receiving opioids, the ONS Guidelines panel *suggests* either prophylactic bowel regimen with laxatives and lifestyle education or lifestyle education alone for prevention of constipation (conditional recommendation, low certainty of evidence ⊕⊕◯◯).

Remarks: Patients who place a higher value on avoidance of constipation may prefer to start on a prophylactic bowel regimen; however, patients who place a higher value on avoiding undue costs, taking pills, or undue harms (diarrhea) may prefer to not start on a bowel regimen prophylactically.

Justification

Patients who are starting opioids for cancer-related pain are at high risk of developing constipation. The evidence for a prophylactic bowel regimen in addition to lifestyle education was judged to be low certainty, however, the ONS guideline panel balanced the desirable and undesirable health effects to make a conditional recommendation for a prophylactic bowel regimen in addition to lifestyle education for patients with cancer who are taking opioids.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Shared decision-making is important for patients and clinicians to discuss options so that patients will have a clear understanding of the risks of constipation and the education/clinical indications for use of a bowel regimen. Health professionals should note that patients can have laxatives on hand to start when symptoms start.

Monitoring and evaluation

No monitoring considerations.

Research priorities

No research priorities consideration.

IN-TEXT CITED REFERENCES

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

RECOMMENDATION

Should osmotic or stimulant laxatives and lifestyle education rather than lifestyle education alone be used in adult patients with cancer who have opioid-induced constipation?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Osmotic or stimulant laxatives and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Stool consistency; Occurrence of constipation (y/n); Quality of life; Adverse events that lead to treatment discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).

CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	(see table below)	The panel determined the magnitude of the desirable outcomes to be moderate.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁⨁◯ MODERATE[a]	RR 2.24 (1.93 to 2.61)	Study population	
				27 per 100	**33 more per 100** (25 more to 43 more)
Change in BM frequency	1269 (6 RCTs)[2,4,5,6,7,8]	⨁⨁◯◯ LOW[a,b]	-	The mean change in BM frequency was **0**	MD **2.55 higher** (1.53 higher to 3.57 higher)
Reduction in straining				Study population	

	118 (2 RCTs)[2,3]	⨁⨁⨁◯ MODERATE[a]	RR 1.52 (1.18 to 1.96)	55 per 100	**29 more per 100** (10 more to 53 more)
Stool consistency improvement assessed with: measured as hard/pellet stools	269 (3 RCTs)[2,3,4]	⨁⨁⨁◯ MODERATE[a]	RR 1.55 (1.33 to 1.82)	Study population	
				58 per 100	**32 more per 100** (19 more to 48 more)
Quality of life - not reported	-	-	-	-	-
AEs leading to treatment discontinuation	589 (3 RCTs)[10,11,9]	⨁⨁⨁◯ MODERATE[c]	RR 3.55 (1.60 to 7.89)	Study population	
				26 per 1,000	**66 more per 1,000** (16 more to 179 more)

References:

1. Wesselius-De Casparis, A, Braadbaart, S, Bergh-Bohlken, GE, 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.
4. DiPalma, Jack A, DeRidder, Peter H, Orlando, Roy C, Kolts, Byron E, Cleveland, Mark B. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol; 2000.
5. DiPalma, Jack A, Cleveland, Mark B, 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 picosulfate in patients with chronic constipation. Am J Gastroenterol; 2010.
7. Kamm, Michael A, Mueller-Lissner, Stefan A, Wald, Arnold, Hinkel, Ulrika, Richter, Erika, Swallow, Ros, Bubeck, Juergen. S1321 stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo-controlled trial of bisacodyl. Gastroenterology; 2010.
8. Baldonedo, YC, Lugo, E, Uzcategui, AA, Guelrud, M, Skornicki, J. Evaluation and use of polyethylene glycol in constipated patients. GEN; 1991.
9. Kamm, Michael A, Mueller-Lissner, Stefan, Wald, Arnold, Richter, Erika, Swallow, Ros, Gessner, Ulrika. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clinical Gastroenterology and Hepatology; 2011. (*This is an update of the following found in Ford & Suares, 2011*: Kamm, MA,,Mueller-Lissner, S, Wald, A, Hinkel, U, Richter, E, Swallow, R, Bubeck, J. S1321 Stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo-controlled trial of bisacodyl. Gastroenterology; 2010.)

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.

Explanations:

a. Rated down twice for indirectness because population consisted of non-OIC and non-cancer patients.
b. Check Ford article for I squared of 100%
c. Rated down for indirectness because of difference in complementary treatments. McGraw prohibited use of laxatives with PEG 3350 + senna.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ● Small
- ○ Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁⨁◯ MODERATE[a]	RR 2.24 (1.93 to 2.61)	Study population	
				27 per 100	**33 more per 100** (25 more to 43 more)
Change in BM frequency	1269 (6 RCTs)[2,4,5,6,7,8]	⨁⨁◯◯ LOW[a,b]	-	The mean change in BM frequency was **0**	MD **2.55 higher** (1.53 higher to 3.57 higher)
Reduction in straining	118 (2 RCTs)[2,3]	⨁⨁⨁◯ MODERATE[a]	RR 1.52 (1.18 to 1.96)	Study population	
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Stool consistency improvement assessed with: measured as hard/pellet stools	269 (3 RCTs)[2,3,4]	⨁⨁⨁◯ MODERATE[a]	RR 1.55 (1.33 to 1.82)	Study population	
				58 per 100	**32 more per 100** (19 more to 48 more)

ADDITIONAL CONSIDERATIONS

The panel determined the magnitude of the undesirable outcomes to be small.

Quality of life - not reported	-	-	-	-	-
AEs leading to treatment discontinuation	589 (3 RCTs)[10,11,9]	⨁⨁⨁◯ MODERATE[c]	RR 3.55 (1.60 to 7.89)	Study population	
				26 per 1,000	**66 more per 1,000** (16 more to 179 more)

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.
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4. DiPalma, Jack A, DeRidder, Peter H, Orlando, Roy C, Kolts, Byron E, Cleveland, Mark B. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol; 2000.
5. DiPalma, Jack A, Cleveland, Mark B, 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 picosulfate in patients with chronic constipation. Am J Gastroenterol; 2010.
7. Kamm, Michael A, Mueller-Lissner, Stefan A, Wald, Arnold, Hinkel, Ulrika, Richter, Erika, Swallow, Ros, Bubeck, Juergen. S1321 stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo-controlled trial of bisacodyl. Gastroenterology; 2010.
8. Baldonedo, YC, Lugo, E, Uzcategui, AA, Guelrud, M, Skornicki, J. Evaluation and use of polyethylene glycol in constipated patients. GEN; 1991.
9. Kamm, Michael A, Mueller–Lissner, Stefan, Wald, Arnold, Richter, Erika, Swallow, Ros, Gessner, Ulrika. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clinical Gastroenterology and Hepatology; 2011.
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.

Explanations:

a. Rated down twice for indirectness because population consisted of non-OIC and non-cancer patients.
b. Check Ford article for I squared of 100%
c. Rated down for indirectness because of difference in complementary treatments. Tarumi participants used laxatives throughout with docusate; McGraw prohibited use of laxatives with PEG 3350 + senna.

	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose use can result in worsening abdominal distension and flatulence. They also indicated that a large body of evidence shows that polyethylene glycol has fewer side effect than lactulose. The authors said senna and lactulose have similar adverse effects. They also said that use of stimulant laxatives like senna can result in drug dependence and that potential side effect are usually mild but can include abdominal discomfort, cramps, nausea, diarrhea, GI irritation, and fluid and electrolyte depletion.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies		The panel judged the certainty in these estimated effects as moderate due to serious indirectness because the studies were not conducted among persons experiencing OIC.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit favors the intervention based on the large treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Over the Counter Medication** Source: Walmart.com 6-24-19	The panel decided that the costs were negligible when factoring in the cost of fiber (i.e., a component of lifestyle factors).

Medication	Product	Price
Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	$4.74
Docusate sodium	Equate Stool Softener Docusate Sodium Softgels, 100 mg, 60 Ct	$2.84
Magnesium citrate	Equate Lemon Flavor Magnesium Citrate Saline Laxative Oral Solution, 10 fl oz	$0.98
Magnesium hydroxide (milk of magnesia)	Equate Milk of Magnesia Saline Laxative, Original Flavor, 1200 mg, 26 fl oz	$3.57
Polyethylene glycol (PEG) (Miralax)	ClearLAX Polyethylene Glycol 3350 Laxative Powder, 30 Doses	$12.92
Senna	Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	$4.78

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that while patients would most likely need to pay out of pocket, options for a bowel regimen are widely available and of limited cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose is widely available.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends* osmotic or stimulant laxatives and lifestyle education rather than lifestyle education alone for treatment of OIC (strong recommendation; moderate certainty of evidence ⊕⊕⊕◯).

Justification

The ONS guideline panel determined that there was moderate certainty in the evidence that the desirable effects of osmotic or stimulant laxatives outweigh the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are starting opioids for cancer-related pain and made a strong recommendation for using osmotic or stimulant laxatives in addition to lifestyle education as first line therapy in patients with cancer who have OIC.

Subgroup considerations

No subgroup considerations.

Implementation considerations

The panel noted an implementation consideration regarding dosing as the studies were mostly in patients with chronic idiopathic constipation and dosing for other conditions may be different.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Head to head comparisons of treatment options
- PEG compared to other osmotic laxatives
- Dosing of laxatives for opioid-induced constipation in patients with cancer

IN-TEXT CITED REFERENCES

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Costilla, V.C., & Foxx-Orenstein, A.E. (2014). Constipation: Understanding mechanisms and management. *Clinical Geriatric Medicine, 30*, 107–115. http://dx.doi. org/10.1016/j.cger.2013.10.001

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McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. http://dx.doi.org/10.1188/13.ONF.E92-E100

Osmotic polyethylene glycol and lifestyle education vs. lifestyle education for opioid-induced constipation

RECOMMENDATION

Should osmotic polyethylene glycol and lifestyle education rather than lifestyle education alone be used in adult patients with cancer with opioid-induced constipation?	
POPULATION:	Adult patients with cancer with opioid-induced constipation
INTERVENTION:	Osmotic polyethylene glycol and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Stool consistency; Occurrence of constipation (y/n); Quality of life; Adverse events that lead to treatment discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with osmotic PEG (MiraLAX)
Stool consistency assessed with: Hard stool/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c]	-	The mean stool consistency was 0	MD 0.69 lower (1.28 lower to 0.1 lower)
Stool consistency assessed with: Soft stool/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d]	-	The mean stool consistency was 0	MD 0.3 higher (0.95 lower to 1.55 higher)
Adverse events assessed with: Excess gas/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d]	-	The mean adverse events was 0	MD 1.1 higher (0.24 higher to 2.44 higher)
Adverse events assessed with: Severe cramping/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d]	-	The mean adverse events was 0	MD 0.04 higher (1.15 lower to 1.07 higher)

ADDITIONAL CONSIDERATIONS

The panel agreed that the benefits reported may not be good indicators of patient-important outcomes, however, decided the benefit to be small.

Reference:

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.

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 harm as well as possible benefit.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel decided that the magnitude of the harms is trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with osmotic PEG (MiraLAX)
Stool consistency assessed with: Hard stool/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,c]	-	The mean stool consistency was 0	MD 0.69 lower (1.28 lower to 0.1 lower)
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Adverse events assessed with: Severe cramping/week	114 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b,d]	-	The mean adverse events was 0	MD 0.04 higher (1.15 lower to 1.07 higher)

	Reference: 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. **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 harm as well as possible benefit. In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that a large body of evidence shows polyethylene glycol has fewer side effects than lactulose. They said side effects can include bloating, abdominal discomfort, diarrhea, dizziness and increased sweating. They also reported that an RCT found PEG to be effective related to side effects and that another study of PEG use for 12 months found no evidence of tachyphylaxis.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		The quality of evidence supporting the use of polyethylene glycol (PEG) was low based on very serious concerns of imprecision.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit favors the intervention based on large treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Over the Counter Medication** Source: Walmart.com 6-24-19	The panel decided that the costs were negligible when factoring in the cost of fiber (i.e., a component of lifestyle factors).

Medication	Product	Price
Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	$4.74
Docusate sodium	Equate Stool Softener Docusate Sodium Softgels, 100 mg, 60 Ct	$2.84
Magnesium citrate	Equate Lemon Flavor Magnesium Citrate Saline Laxative Oral Solution, 10 fl oz	$0.98
Magnesium hydroxide (milk of magnesia)	Equate Milk of Magnesia Saline Laxative, Original Flavor, 1200 mg, 26 fl oz	$3.57
Polyethylene glycol (PEG) (Miralax)	ClearLAX Polyethylene Glycol 3350 Laxative Powder, 30 Doses	$12.92
Senna	Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	$4.78

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that while patients would most likely need to pay out of pocket, options for a bowel regimen are widely available and of limited cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a comparative review of common laxatives for constipation (Fiorinii et al., 2017), the authors noted that PEG is widely available over the counter.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among adults with cancer, the ONS Guidelines panel *suggests* osmotic polyethylene glycol (PEG) and lifestyle education rather than lifestyle education alone for OIC (conditional recommendation, low certainty of evidence ⊕⊕◯◯).

Justification

The ONS guideline panel determined that there was low certainty in the evidence that the desirable effects of polyethylene glycol (PEG) outweigh the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are starting opioids for cancer-related pain and made a conditional recommendation for using polyethylene glycol (PEG) in addition to lifestyle education as first line therapy in patients with cancer who have OIC.

Subgroup considerations

No subgroup considerations.

Implementation considerations

A thorough discussion of potential side effects is important to guide a person's decision making.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Head to head comparisons of treatment options
- PEG compared to other osmotic laxatives
- Dosing of laxatives for opioid-induced constipation in patients with cancer

IN-TEXT CITED REFERENCES

Arthur, J.A., & Hui, D. (2018). Safe opioid use: Management of opioid-related adverse effects and aberrant behaviors. *Hematology/Oncology Clinics of North America, 32*, 387–403. https://doi.org/10.1016/j.hoc.2018.01.003

Bharucha, A.E., Pemberton, J.H., & Locke, G.R. (2013). American Gastroenterological Association technical review on constipation. *Gastroenterology, 144*, 218–238. http://dx.doi.org/10.1053/j.gastro.2012.10.028

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Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/10.1007/s12325-014-0169-x

Fiorini, K., Sato, S., Schlachta, C.M., & Alkhamesi, N.A. (2017). A comparative review of common laxatives in the treatment of constipation. *Minerva Chirurgica, 72*, 265–273. https://doi.org/10.23736/S0026-4733.17.07236-4

McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. http://dx.doi.org/10.1188/13.ONF.E92-E100

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

RECOMMENDATION

Once a bowel regimen has failed for adult patients with cancer who have opioid-induced constipation, should methylnaltrexone (subcutaneous or oral) and a bowel regimen rather than bowel regimen alone be used?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation and have not responded to a bowel regimen
INTERVENTION:	Methylnaltrexone (subcutaneous or oral) and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen + metoclopramide (or other active comparator)	Risk difference with methylnaltrexone (SQ or oral)
Rescue-free bowel movement (defined as > or equal to 3 RFBM per week)	1397 (3 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,b]	RR 1.33 (1.16 to 1.52)	Study population	
				39 per 100	**13 more per 100** (6 more to 20 more)
Laxation response (defined as a BM within 4 hours and no laxative in the prior 24 hours)	998 (5 RCTs)[1,3,4,5,6]	⨁⨁◯◯ LOW[a]	RR 3.50 (2.65 to 4.62)	Study population	
				12 per 100	**30 more per 100** (20 more to 44 more)
Change in rescue-free bowel movement frequency	861 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,c]	-	MD 1.60 more with 12 mg sc qd and 0.60 more with 12 mg sc qod (Michna 2011); MD 0.5 more 300 mg/450 mg and 0.1 more with 150mg (Rauck 2016)	

ADDITIONAL CONSIDERATIONS

The panel decided on small because they weighed RFBM heavier than laxation response when deciding on the magnitude of the desirable outcomes. The panel agreed that because compared to placebo, they would expect a smaller difference in the effect on RFBM/LR.

Reduction in straining assessed using a straining scale 0 (none) to 4 (very severe)	460 (1 RCT)[2]	⨁◯◯◯ VERY LOW[a,d]	-	Compared with placebo, methylnaltrexone led to more RFBM with none or mild straining (MD 11% to 15% more). No raw data provided.	
AEs leading to treatment discontinuation	1628 (4 RCTs)[1,2,3,6]	⨁◯◯◯ VERY LOW[a,e,f]	RR 1.51 (0.83 to 2.71)	Study population	
				4 per 100	**2 more per 100** (1 fewer to 6 more)
QOL	460 (1 RCT)[2]	⨁◯◯◯ VERY LOW[a,d]	-	Methylnaltrexone group showed an improvement in the total score of 0.74 (12mg sc qd) and 0.39 (12mg sc qod).	

References:

1. Rauck, Richard, Slatkin, Neal E, Stambler, Nancy, Harper, Joseph R, Israel, Robert J. Randomized, double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Practice; 2017.
2. Michna, Edward, Blonsky, E Richard, Schulman, Seth, Tzanis, Evan, Manley, Amy, Zhang, Haiying, Iyer, Shrividya, Randazzo, Bruce. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. The Journal of Pain; 2011.
3. Thomas, Jay, Karver, Sloan, Cooney, Gail Austin, Chamberlain, Bruce H, Watt, Charles Kevin, Slatkin, Neal E, Stambler, Nancy, Kremer, Alton B, Israel, Robert J. Methylnaltrexone for opioid-induced constipation in advanced illness. New England Journal of Medicine; 2008.
4. Slatkin, Neal, Thomas, Jay, Lipman, Arthur G, Wilson, George, Boatwright, Michelle L, Wellman, Charles, Zhukovsky, Donna S, Stephenson, Richard, Portenoy, Russell, Stambler, Nancy. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. The Journal of Supportive Oncology; 2009.
5. Portenoy, Russell K, Thomas, Jay, Boatwright, Michele L Moehl, Tran, Diep, Galasso, Frank L, Stambler, Nancy, Von Gunten, Charles F, Israel, Robert J. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage; 2008.
6. Bull, Janet, Wellman, Charles V, Israel, Robert J, Barrett, Andrew C, Paterson, Craig, Forbes, William P. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. Journal of Palliative Medicine; 2015.

Explanations:

a. Some trials include terminally ill and cancer patients but some do not. Different doses and formulations of methylnaltrexone used.
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 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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel agreed that alternative therapies are available if patients need to stop methylnaltrexone due to adverse events.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen + metoclopramide (or other active comparator)	Risk difference with methylnaltrexone (SQ or oral)
Rescue-free bowel movement (defined as > or equal to 3 RFBM per week)	1397 (3 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,b]	RR 1.33 (1.16 to 1.52)	Study population	
				39 per 100	**13 more per 100** (6 more to 20 more)
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AEs leading to treatment discontinuation	1628 (4 RCTs)[1,2,3,6]	⨁◯◯◯ VERY LOW[a,e,f]	RR 1.51 (0.83 to 2.71)	Study population	
				4 per 100	**2 more per 100** (1 fewer to 6 more)

QOL	460 (1 RCT)[2]	⨁◯◯◯ VERY LOW[a,d]	-	Methylnaltrexone group showed an improvement in the total score of 0.74 (12mg sc qd) and 0.39 (12mg sc qod).

References:

1. Rauck, Richard, Slatkin, Neal E, Stambler, Nancy, Harper, Joseph R, Israel, Robert J. Randomized, double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Practice; 2017.
2. Michna, Edward, Blonsky, E Richard, Schulman, Seth, Tzanis, Evan, Manley, Amy, Zhang, Haiying, Iyer, Shrividya, Randazzo, Bruce. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. The Journal of Pain; 2011.
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6. Bull, Janet, Wellman, Charles V, Israel, Robert J, Barrett, Andrew C, Paterson, Craig, Forbes, William P. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. Journal of Palliative Medicine; 2015.

Explanations:

a. Some trials include terminally ill and cancer patients but some do not. Different doses and formulations of methylnaltrexone used.
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 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.

The AGA guideline (Crockett et al., 2019) noted that PAMORAS should be avoided in patients with conditions that compromise the blood-brain barrier because there is a potential for serious withdrawal or reversal of anesthesia.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty in the evidence reflected additional uncertainty due to the generalization of the evidence to the PICO question, i.e., trial participants had to quit current bowel regimen and were compared to placebo, not standard of care/bowel regimen, which would more likely reflect real life.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation. A Canadian study of cancer patients experiencing opioid-induced constipation receiving palliative care (Iskedjian et al., 2011) reported a willingness to pay additional monthly insurance premiums of $8.65 Canadian dollars.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit probably favors the intervention based on the size of the treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The AGA guideline for opioid-induced constipation (Crockett et al., 2019) says that methylnaltrexone may be costly compared to other agents, but the subcutaneous administration may have an advantage in some clinical situations. In a National Institute for Health and Care Excellence (NICE) costing statement for treating opioid-induced constipation (2015), estimated annual drug costs for three regimens were naloxegol, £ 671.60; subcutaneous methylnaltrexone, £1,284.05; and bisacodyl, £12.52.	The panel agreed that compared with a bowel regimen the cost was large based on the price of the therapy, as well as the duration of therapy needed (i.e. the treatment would be required for the duration of the opioid therapy.

Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards. 6-24-19 & 6-25-19

Drug	Product	Lowest Pittsburgh-area Price	Average Retail Price
Lactulose	473 ml 10g/15ml of lactulose oral solution	Walmart (with GoodRx discount card): $12.14	$33.72
Linaclotide	30 capsules of Linzess 145mcg	Giant Eagle (with GoodRx discount card): $427.99	$518.24
Lubiprostone	60 capsules of Amitiza 24mcg	Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29	Not available
Methylnaltrexone	90 tablets of Relistor 150mg	Giant Pharmacy (with GoodRx coupon): $1686.16	$2,084.62
Naldemedine	30 tablets of Symproic 0.2mg	Giant Eagle (with GoodRx coupon): $319.21	Not available
Naloxegol (Movantik)	30 tablets of Movantik 25mg	Giant Eagle (with GoodRx coupon): $360.23	$459.39
Prucalopride	30 tablets of Motegrity 2mg	Giant Eagle (with GoodRx coupon): $428.06	Not available

Methylnaltrexone, subcutaneous solution:

- Source: https://www.drugs.com/price-guide/relistor Retrieved 7-1-19

8 mg/0.4 mL Relistor subcutaneous solution: From $738.78 for 2.8 milliliters		
Quantity	*Per unit*	*Price*
2.8 (7 x 0.4 milliliters)	$263.85	$738.78
12 mg/0.6 mL Relistor subcutaneous solution: From $129.13 for 0.6 milliliters		
Quantity	*Per unit*	*Price*
0.6 milliliters	$215.22	$129.13
4.2 (7 x 0.6 milliliters)	$203.06	$852.84

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	In the MTF [Military Treatment Facility] Formulary Management for Gastrointestinal-2 Miscellaneous (GI-2) Drug Class - Opioid-Induced Constipation (OIC) Subclass document (Defense Health Agency Pharmacy Operations Division, May 2018), Methylnaltrexone (Relistor) tablets and injection are not permitted to be on MTF formularies. Methylnaltrexone is considered “least cost-effective,” meaning having the highest cost with similar clinical efficacy.	The panel agreed that methylnaltrexone is more expensive than the alternatives and while there would be some benefit, it would come at a great cost. When making their judgment, the panel decided that the Monte Carlo simulation conducted (Iskedjian et al., 2011) to inform Canadian decisions was not relevant to US.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	In the National Health and Nutrition Examination Survey (NHANES) in 2005–2006 and 2007–2008 (Alayne et al., 2013), women had higher rates of constipation than men. Women and men ≥60 did not have higher rates of constipation than those under age 60. However, the authors noted that several other cross-sectional and longitudinal studies named age as a significant risk factor and named one other study that supported the NHANES findings. People with lower education levels and fair/poor self-rated health had higher constipation rates. Non-Hispanic Black Americans had significantly higher constipation rates than all other racial/ethnic groups. No differences were found related to BMI, vigorous physical activity, or number of chronic diseases. In a systematic review of constipation management in people with intellectual disability (Robertson et al.,2018), the authors reported that several factors put people with intellectual disability at increased risk of constipation.	The panel decided that because of the high cost of the therapy, some patients may be disadvantaged.

Acceptability

Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that this therapy would probably be acceptable when considering the providers and payers.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among adult patients with cancer who have OIC and have not responded to a bowel regimen, the ONS Guidelines panel *suggests* methylnaltrexone and a bowel regimen rather than a bowel regimen alone for treatment (conditional recommendation; very low certainty of evidence ⊕◯◯◯).

Remarks: Subcutaneous methylnaltrexone may present an additional option for people who are unable to take other forms of peripherally acting mu-opioid receptor antagonists (PAMORAs).

Justification

The ONS guideline panel determined that there was very low certainty in the evidence that the desirable effects of methylnaltrexone outweighs the undesirable effect in patients with cancer who have OIC. The ONS guideline panel issued a conditional recommendation for methylnaltrexone for the management of OIC in patients with cancer.

Subgroup considerations

Methylnaltrexone provides the option of subcutaneous delivery, which some patients may require.

Implementation considerations

Providers should have the following discussion with patients considering methylnaltrexone:

- Discussion about cost/coverage
- Extensiveness of the bowel regimen to determine need of this drug
- Assessment of the effectiveness of the bowel regimen

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Trial among patients with cancer and OIC who are laxative refractory
- Head to head trials with other PAMORAs or bowel regimens
- Validated tools to evaluate outcomes
- Quality of life

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

RECOMMENDATION

Should naldemedine (0.2 mg) in addition to a bowel regimen rather than bowel regimen alone be used for adult patients with cancer who have opioid-induced constipation?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Naldemedine (0.2 mg) and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with naldemedine (0.2 mg)
SBM response (at least 3 SBMs/wk and an increase from baseline of 1 SBM/wk; follow-up 4-12 wk)	1522 (4 RCTs)[1,2,3,4]	⨁⨁⨁◯ MODERATE[a,b]	OR 2.44 (1.99 to 3.01)	Study population	
				348 per 1,000	**501 more per 1,000** (344 more to 699 more)
Change in SBM frequency (change from baseline in mean number of SBMs/wk; follow-up 4-12 wk)	1522 (5 RCTs)[1,2,3,4]	⨁⨁⨁◯ MODERATE[a,b]	-	The mean change in SBM frequency (change from baseline in mean number of SBMs/wk; follow-up 4-12 wk) was **0** SBM/wk	MD **2.02 SBM/wk more** (1.3 more to 2.74 more)
Change in frequency of BMs without straining (frequency from baseline to the last 2 weeks of the treatment period)	1522 (5 RCTs)[1,2,3,4]	⨁⨁◯◯ LOW[a,b,c]	-	The mean change in frequency of BMs without straining (frequency from baseline to the last 2 weeks	MD **1.43 BM w/o straining more** (0.75 more to 2.11 more)

ADDITIONAL CONSIDERATIONS

The panel decided that the magnitude of the benefits was large, however, agreed that the comparison may overestimate the benefit of naldemedine.

				of the treatment period) was **0** BM w/o straining	
Change in BM frequency (change from baseline in mean number of SMBs/wk; follow-up 52 wk)	1241 (1 RCT)[1]	⨁⨁◯◯ LOW[c,d]	-	The mean change in BM frequency (change from baseline in mean number of SMBs/wk; follow-up 52 wk) was **0**	MD **0.95 more** (0.57 more to 1.33 more)
QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk)	1241 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[d]	-	The mean QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk) was **0**	MD **0.3 higher** (0.16 higher to 0.44 higher)
AEs leading to treatment discontinuation (follow-up 4-52 wk)	2756 (6 RCTs)[1,2,3,4,5]	⨁⨁⨁◯ MODERATE[b]	RR 1.41 (1.17 to 1.70)	Study population	
				11 per 100	**4 more per 100** (2 more to 8 more)
Change in frequency of SBMs rated 3 or 4 on the BSFS	79 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[d]	-	The mean change in frequency of SBMs rated 3 or 4 on the BSFS was **0**	MD **1.51 more** (0.51 more to 2.51 more)

References:

1. Webster, Lynn R, Yamada, Tadaaki, Arjona Ferreira, Juan Camilo. A phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Medicine; 2017.
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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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with naldemedine (0.2 mg)
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				348 per 1,000	**501 more per 1,000** (344 more to 699 more)
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Change in frequency of BMs without straining (frequency from baseline to the last 2 weeks of the treatment period)	1522 (5 RCTs)[1,2,3,4]	⨁⨁◯◯ LOW[a,b,c]	-	The mean change in frequency of BMs without straining (frequency from baseline to the last 2 weeks of the treatment period) was **0** BM w/o straining	MD **1.43 BM w/o straining more** (0.75 more to 2.11 more)
Change in BM frequency (change from baseline in mean number of SMBs/wk; follow-up 52 wk)	1241 (1 RCT)[1]	⨁⨁◯◯ LOW[c,d]	-	The mean change in BM frequency (change from baseline in mean	MD **0.95 more** (0.57 more to 1.33 more)

ADDITIONAL CONSIDERATIONS

The panel determined the magnitude of the undesirable outcomes to be small.

				number of SMBs/wk; follow-up 52 wk) was **0**	
QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk)	1241 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[d]	-	The mean QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk) was **0**	MD **0.3 higher** (0.16 higher to 0.44 higher)
AEs leading to treatment discontinuation (follow-up 4-52 wk)	2756 (6 RCTs)[1,2,3,4,5]	⨁⨁⨁◯ MODERATE[b]	RR 1.41 (1.17 to 1.70)	Study population	
				11 per 100	**4 more per 100** (2 more to 8 more)
Change in frequency of SBMs rated 3 or 4 on the BSFS	79 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[d]	-	The mean change in frequency of SBMs rated 3 or 4 on the BSFS was **0**	MD **1.51 more** (0.51 more to 2.51 more)

References:

1. Webster, Lynn R, Yamada, Tadaaki, Arjona Ferreira, Juan Camilo. A phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Medicine; 2017.
2. Katakami, Nobuyuki, Oda, Koji, Tauchi, Katsunori, Nakata, Ken, Shinozaki, Katsunori, Yokota, Takaaki, Suzuki, Yura, Narabayashi, Masaru, Boku, Narikazu. Phase IIb, randomized, double-blind, placebo-controlled study of naldemedine for the treatment of opioid-induced constipation in patients with cancer. Journal of Clinical Oncology; 2017.
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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.

	The AGA guideline (Crockett et al., 2019) noted that PAMORAS should be avoided in patients with conditions that compromise the blood-brain barrier because there is a potential for serious withdrawal or reversal of anesthesia.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The Katakami trials and Webster use a bowel regimen (more direct to the PICO question); no additional rating down for indirectness.	The ONS guideline panel judged the certainty of the evidence of effects to be moderate for naldemedine. The panel rated down for indirectness as some studies were in patients with non-malignant pain although the panel noted that the populations in this body of evidence was less indirect and reflected a more realistic population similar to patients with cancer with OIC.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit favors the intervention based on large treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards.** 6-24-19 & 6-25-19	The panel agreed that compared with a bowel regimen, the cost was large based on the price of the therapy, as well as the duration of therapy needed (i.e., the treatment would be required for the duration of the opioid therapy).

Drug	Product	Lowest Pittsburgh-area Price	Average Retail Price
Lactulose	473 ml 10g/15ml of lactulose oral solution	Walmart (with GoodRx discount card): $12.14	$33.72
Linaclotide	30 capsules of Linzess 145mcg	Giant Eagle (with GoodRx discount card): $427.99	$518.24
Lubiprostone	60 capsules of Amitiza 24mcg	Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29	Not available
Methylnaltrexone	90 tablets of Relistor 150mg	Giant Pharmacy (with GoodRx coupon): $1686.16	$2,084.62
Naldemedine	30 tablets of Symproic 0.2mg	Giant Eagle (with GoodRx coupon): $319.21	Not available
Naloxegol (Movantik)	30 tablets of Movantik 25mg	Giant Eagle (with GoodRx coupon): $360.23	$459.39
Prucalopride	30 tablets of Motegrity 2mg	Giant Eagle (with GoodRx coupon): $428.06	Not available

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	Costly and effective when compared to bowel regimen. Cost-effectiveness probably favors the intervention, but there are no included studies.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	In the National Health and Nutrition Examination Survey (NHANES) in 2005–2006 and 2007–2008 (Markland et al., 2013), women had higher rates of constipation than men. Women and men ≥60 did not have higher rates of constipation than those under age 60. However, the authors noted several other cross-sectional and longitudinal studies named age as a significant risk factor and named one other study that supported the NHANES findings. People with lower education levels and fair/poor self-rated health had higher constipation rates. Non-Hispanic Black Americans had significantly higher constipation rates than all other racial/ethnic groups. No differences were found related to BMI, vigorous physical activity, or number of chronic diseases. In a systematic review of constipation management in people with intellectual disability (Robertson et al., 2018), the authors reported that several factors put people with intellectual disability at increased risk of constipation.	The panel determined that because of the cost to the patient and limited opportunity for coverage of the therapy, this option may be inaccessible, therefore, leading to increase health inequities.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that this therapy would probably be acceptable when considering the providers and payers. This includes the extensive process needed to determine appropriateness of treatment and resources needed to obtain it.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	●

CONCLUSIONS

Recommendation

Among adult patients with cancer who have OIC, the ONS Guidelines panel *recommends* naldemedine and a bowel regimen rather than a bowel regimen alone for treatment (strong recommendation; moderate certainty of evidence ⊕⊕⊕◯).

Justification

The ONS guideline panel determined that there was moderate certainty in the evidence that the desirable effects of naldemedine outweighs the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are taking opioids for cancer-related pain and made a strong recommendation for using naldemedine in addition to a bowel regimen for treatment of OIC in patients with cancer.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Trial among patients with cancer and OIC who are laxative refractory
- Head to head trials with other PAMORAs or bowel regimens
- Validated tools to evaluate outcomes
- Quality of life

IN-TEXT CITED REFERENCES

Arthur, J.A., & Hui, D. (2018). Safe opioid use: Management of opioid-related adverse effects and aberrant behaviors. *Hematology/Oncology Clinics of North America, 32*, 387-403. https://doi.org/10.1016/j.hoc.2018.01.003

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Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/10.1007/s12325-014-0169-x

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

RECOMMENDATION

Should naloxegol and a bowel regimen rather than a bowel regimen alone be used for adult patients with cancer who have opioid-induced constipation?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Naloxegol and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	See table below	The panel determined the magnitude of the desirable outcomes to be small.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with naloxegol + bowel regimen
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)	892 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,b]	RR 1.43 (1.19 to 1.71)	Study population	
				29 per 100	**13 more per 100** (6 more to 21 more)
Change in SBM frequency (change from baseline in mean number of SBMs/wk)	880 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,c]	-	The mean change in SBM frequency (change from baseline in mean number of SBMs/wk) was **0**	MD **1.02 higher** (0.67 higher to 1.37 higher)
Reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining)	880 (2 RCTs)[1]	⨁⨁◯◯ LOW[a]	-	The mean reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining) was **0**	MD **0.24 lower** (0.35 lower to 0.14 lower)
Stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7 denoting watery stool)	880 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,d]	-	The mean stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7	MD **0.33 higher** (0.2 higher to 0.46 higher)

				denoting watery stool) was **0**	
AEs leading to treatment discontinuation	2309 (4 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,e]	RR 2.33 (1.62 to 3.35)	Study population	
				4 per 100	**6 more per 100** (3 more to 10 more)
Pain score assessed with: 11-point numerical rating scale (0=no pain; 10=worst pain) CID=2 points follow up: 12 weeks	1323 (2 RCTs)[3]	⨁⨁◯◯ LOW[a,f]	-	The mean pain score was **0** points	MD **0 points** (0.11 lower to 0.12 higher)

References:

1. Chey, William D, Webster, Lynn, Sostek, Mark, Lappalainen, Jaakko, Barker, Peter N, Tack, Jan. Naloxegol for opioid-induced constipation in patients with noncancer pain. New England Journal of Medicine; 2014.
2. Webster, L, Chey, WD, Tack, J, Lappalainen, J, Diva, U, Sostek, M. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Alimentary Pharmacology & Therapeutics; 2014.
3. Webster, Lynn, Diva, Ulysses, Tummala, Raj, Sostek, Mark. Treatment with naloxegol versus placebo: Pain assessment in patients with noncancer pain and opioid-induced constipation. Pain Practice; 2018.

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 start of 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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Outcomes**	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**		The panel determined the magnitude of the undesirable outcomes to be small.
					Risk with bowel regimen	**Risk difference with naloxegol + bowel regimen**	
	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)	892 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,b]	RR 1.43 (1.19 to 1.71)	Study population		
					29 per 100	**13 more per 100** (6 more to 21 more)	
	Change in SBM frequency (change from baseline in mean number of SBMs/wk)	880 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,c]	-	The mean change in SBM frequency (change from baseline in mean number of SBMs/wk) was **0**	MD **1.02 higher** (0.67 higher to 1.37 higher)	
	Reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining)	880 (2 RCTs)[1]	⨁⨁◯◯ LOW[a]	-	The mean reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining) was **0**	MD **0.24 lower** (0.35 lower to 0.14 lower)	
	Stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7 denoting watery stool)	880 (2 RCTs)[1]	⨁◯◯◯ VERY LOW[a,d]	-	The mean stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7 denoting watery stool) was **0**	MD **0.33 higher** (0.2 higher to 0.46 higher)	
	AEs leading to treatment discontinuation	2309 (4 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,e]	RR 2.33 (1.62 to 3.35)	Study population		
					4 per 100	**6 more per 100** (3 more to 10 more)	
	Pain score assessed with: 11-point numerical rating scale (0=no pain; 10=worst pain) CID=2 points follow up: 12 weeks	1323 (2 RCTs)[3]	⨁⨁◯◯ LOW[a,f]	-	The mean pain score was **0** points	MD **0 points** (0.11 lower to 0.12 higher)	

References:

1. Chey, William D, Webster, Lynn, Sostek, Mark, Lappalainen, Jaakko, Barker, Peter N, Tack, Jan. Naloxegol for opioid-induced constipation in patients with noncancer pain. New England Journal of Medicine; 2014.
2. Webster, L, Chey, WD, Tack, J, Lappalainen, J, Diva, U, Sostek, M. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Alimentary Pharmacology & Therapeutics; 2014.
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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 start of 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.

The AGA guideline (Crockett et al., 2019) noted that PAMORAS should be avoided in patients with conditions that compromise the blood-brain barrier because there is a potential for serious withdrawal or reversal of anesthesia.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Indirectness led to serious uncertainty across all outcomes because the population likely did not reflect those on cancer treatments with concomitant therapy that may have also led to constipation.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel agreed that there was some uncertainty about the net benefit because of previously noted concerns with indirectness.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards.** 6-24-19 & 6-25-19	The panel agreed that compared with a bowel regimen the cost was large based on the price of the therapy.

Drug	Product	Lowest Pittsburgh-area Price	Average Retail Price
Lactulose	473 ml 10g/15ml of lactulose oral solution	Walmart (with GoodRx discount card): $12.14	$33.72
Linaclotide	30 capsules of Linzess 145mcg	Giant Eagle (with GoodRx discount card): $427.99	$518.24
Lubiprostone	60 capsules of Amitiza 24mcg	Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29	Not available
Methylnaltrexone	90 tablets of Relistor 150mg	Giant Pharmacy (with GoodRx coupon): $1686.16	$2,084.62
Naldemedine	30 tablets of Symproic 0.2mg	Giant Eagle (with GoodRx coupon): $319.21	Not available
Naloxegol (Movantik)	30 tablets of Movantik 25mg	Giant Eagle (with GoodRx coupon): $360.23	$459.39
Prucalopride	30 tablets of Motegrity 2mg	Giant Eagle (with GoodRx coupon): $428.06	Not available

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	Costly and effective when compared to bowel regimen based on indirect evidence from a UK-based cost-effectiveness study (Lawson et al., 2017). Cost-effectiveness probably favors the intervention, but there are no included studies.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel decided that some proportion of the population lacks coverage and therefore would be disadvantaged. While naloxegol may have a better insurance profile (more coverage available), it may still not be affordable for people without coverage.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	No research evidence identified.	

○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention

○	○	○	●	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *suggests* naloxegol and a bowel regimen rather than a bowel regimen alone for OIC (conditional recommendation; very low certainty of evidence ⊕◯◯◯).

Justification

The ONS guideline panel determined that there was very low certainty in the evidence that the desirable effects of naloxegol outweighs the undesirable effect in patients with cancer who have OIC. The panel acknowledged the high risk of developing constipation in patients who are taking opioids for cancer-related pain and made a conditional recommendation for the use of naloxegol for treatment of OIC in patients with cancer.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Trial among patients with cancer and OIC who are laxative refractory
- Head to head trials with other PAMORAs or bowel regimens
- Validated tools to evaluate outcomes
- Quality of life

IN-TEXT CITED REFERENCES

Arthur, J.A., & Hui, D. (2018). Safe opioid use: Management of opioid-related adverse effects and aberrant behaviors. *Hematology/Oncology Clinics of North America, 32*, 387-403. https://doi.org/10.1016/j.hoc.2018.01.003

Bharucha, A.E., Pemberton, J.H., & Locke, G.R. (2013). American Gastroenterological Association technical review on constipation. *Gastroenterology, 144*, 218–238. http://dx.doi.org/10.1053/j.gastro.2012.10.028

Clemens, K.E., Faust, M., Jaspers, B., & Mikus, G. (2013). Pharmacological treatment of constipation in palliative care. *Current Opinion in Supportive and Palliative Care, 7*, 183–191. http://dx.doi.org/10.1097/SPC.0b013e32835f1e17

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Crockett, S.D., Greer, K.B., Heidelbaugh, J.J., Falck-Ytter, Y., Hanson, B.J., & Sultan, S. (2019). American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 218–226. https://doi.org/10.1053/j.gastro.2018.07.016

Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/ 10.1007/s12325-014-0169-x

Lawson, R., Ryan, J., King, F., Goh, J.W., Tichy, E., & Marsh, K. (2017). Cost effectiveness of naloxegol for opioid-induced constipation in the UK. *Pharmacoeconomics, 35*, 225–235. 10.1007/s40273-016-0454-4

McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. http://dx.doi.org/10.1188/13.ONF.E92-E100

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

RECOMMENDATION

Should prucalopride and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced constipation?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Prucalopride and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		The panel determined the magnitude of the desirable outcomes to be small.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with prucalopride
SBM response (defined as an average of > or = to 3 SBMs/wk) (follow-up:4 wk)	365 (2 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c,d]	RR 1.36 (1.08 to 1.70)	Study population	
				42 per 100	**15 more per 100** (3 more to 29 more)
Change in SBM frequency	196 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,d,e]	-	MD 0.7 more with 2mg; MD 1.0 more with 4mg	
Reduction in painful defecation/lack of straining - not reported	-	-	-	-	-
Stool consistency - not reported	-[1]	-	-	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).	
QoL improvement as measured by PAC-QoL (responder defined as patient achieving improvement or 1 or greater point on satisfaction subscale)	196 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,c,d,f]	RR 1.57 (0.88 to 2.80)	Study population	
				18 per 100	**10 more per 100** (2 fewer to 33 more)
AEs leading to treatment discontinuation	196 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,c,d,f]	RR 0.58 (0.22 to 1.53)	Study population	
				11 per 100	**4 fewer per 100** (8 fewer to 6 more)

References:

1. Sloots, Cornelius EJ, Rykx, An, Cools, Marina, Kerstens, Rene, De Pauw, Martine. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Digestive Diseases and Sciences; 2010.
2. ClinicalTrials.gov ID: NCT01117051. https://clinicaltrials.gov/ct2/show/NCT01117051

Explanations:

a. Trials not conducted among persons with cancer.
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 Sloots 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 harm as well as potential benefit.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		The panel determined the magnitude of the harms outcomes to be small based on the adverse events of abdominal pain and headache reported in Sloots (2010).

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with prucalopride
SBM response (defined as an average of > or = to 3 SBMs/wk) (follow-up:4 wk)	365 (2 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c,d]	RR 1.36 (1.08 to 1.70)	Study population	
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Reduction in painful defecation/lack of straining - not reported	-	-	-	-	-
Stool consistency - not reported	-[1]	-	-	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).	
QoL improvement as measured by PAC-QoL (responder defined as patient achieving improvement or 1 or greater point on satisfaction subscale)	196 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,c,d,f]	RR 1.57 (0.88 to 2.80)	Study population	
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				11 per 100	**4 fewer per 100** (8 fewer to 6 more)

References:

1. Sloots, Cornelius EJ, Rykx, An, Cools, Marina, Kerstens, Rene, De Pauw, Martine. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Digestive Diseases and Sciences; 2010.
2. ClinicalTrials.gov Id: NCT01117051. https:// clinicaltrials.gov/ct2/show/NCT01117051

Explanations:

a. Trials not conducted among persons with cancer.
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 harm as well as potential benefit.

The AGA guideline (Crockett et al., 2019) noted that PAMORAS should be avoided in patients with conditions that compromise the blood-brain barrier because there is a potential for serious withdrawal or reversal of anesthesia.

A technology appraisal (NICE, 2010) said the most common adverse effects include headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhea) but that most adverse effects subside within a few days.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Overall, the certainty in the evidence of effects was very low due to the indirectness to patients with cancer and possible publication bias. The panel also noted imprecision due to uncertainty of a clinically meaningful difference in outcomes and the low number of events reported. Publication bias was a concern because an RCT (ClinicalTrials.gov ID: NCT01117051) was terminated by the manufacturer prior to completion and study results were never published.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less "stomach" pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention		The panel agreed that the net benefit is negligible based on the very low certainty in the evidence.

○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards.** 6-24-19 & 6-25-19	The panel agreed that compared with a bowel regimen, the cost was large based on the price of the therapy.

Drug	Product	Lowest Pittsburgh-area Price	Average Retail Price
Lactulose	473 ml 10g/15ml of lactulose oral solution	Walmart (with GoodRx discount card): $12.14	$33.72
Linaclotide	30 capsules of Linzess 145mcg	Giant Eagle (with GoodRx discount card): $427.99	$518.24
Lubiprostone	60 capsules of Amitiza 24mcg	Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29	Not available
Methylnaltrexone	90 tablets of Relistor 150mg	Giant Pharmacy (with GoodRx coupon): $1686.16	$2,084.62
Naldemedine	30 tablets of Symproic 0.2mg	Giant Eagle (with GoodRx coupon): $319.21	Not available
Naloxegol (Movantik)	30 tablets of Movantik 25mg	Giant Eagle (with GoodRx coupon): $360.23	$459.39
Prucalopride	30 tablets of Motegrity 2mg	Giant Eagle (with GoodRx coupon): $428.06	Not available

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel decided that a National Institute for Health and Care Excellence UK technical appraisal (2010) was not direct enough to inform this recommendation for the U.S. environment.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel decided that because of the high cost of the therapy, some patients may be disadvantaged.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that this therapy would probably be acceptable when considering the providers and payers, however, noted that this therapy was not widely known or used.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No research evidence identified.	The panel determined that this therapy may not have been available in the U.S. until recently, thus, impacting the potential feasibility of implementation.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends prucalopride for treatment of OIC only in the context of a clinical trial* (no recommendation; knowledge gap).

Justification

Limited consistent evidence exists to support a recommendation for prucalopride for the treatment of OIC in patients with cancer. Based on the very low quality and limitations of evidence the guideline panel made no recommendation for prucalopride and identified this intervention as an evidence gap that warrants further research.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Trials compared to a bowel regimen
- Safety studies

IN-TEXT CITED REFERENCES

Bharucha, A.E., Pemberton, J.H., & Locke, G.R. (2013). American Gastroenterological Association technical review on constipation. *Gastroenterology, 144*, 218–238. http://dx.doi.org/10.1053/j.gastro.2012.10.028

Clemens, K.E., Faust, M., Jaspers, B., & Mikus, G. (2013). Pharmacological treatment of constipation in palliative care. *Current Opinion in Supportive and Palliative Care, 7*, 183–191. http://dx.doi.org/10.1097/SPC.0b013e32835f1e17

Costilla, V.C., & Foxx-Orenstein, A.E. (2014). Constipation: Understanding mechanisms and management. *Clinical Geriatric Medicine, 30*, 107–115. http://dx.doi. org/10.1016/j.cger.2013.10.001

Crockett, S.D., Greer, K.B., Heidelbaugh, J.J., Falck-Ytter, Y., Hanson, B.J., & Sultan, S. (2019). American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology, 156*, 218–226. https://doi.org/10.1053/j.gastro.2018.07.016

Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–1271. https://doi.org/10.1007/s12325-014-0169-x

McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. http://dx.doi.org/10.1188/13.ONF.E92-E100

National Institute for Health and Care Excellence. (15 December 2010). NICE: Prucalopride for the treatment of chronic constipation in women. Technology appraisal guidance [TA211]. Retrieved from https://www.nice.org.uk/guidance/TA211

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

RECOMMENDATION

Should lubiprostone and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced constipation?

POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Lubiprostone and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		The panel decided that the magnitude of the benefits was trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	**Risk difference with Lubiprostone**
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	868 (2 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	RR 1.15 (0.97 to 1.37)	Study population	
				33 per 100	**5 more per 100** (1 fewer to 12 more)
Change in SBM frequency assessed with: mean increase in weekly SBM from baseline	1275 (3 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,d,e]	-	MD 0.8 more (Jamal) and 0.6 more (Cryer) MD 0.10 less (0.78 less to 0.58 more) (Spierings)	
Reduction in straining assessed with: 5-point scale ranging from 0 (absent) to 4 (very severe)	435 (1 RCT)[1]	⨁⨁◯◯ LOW[a,f]	-	The mean reduction in straining was **0**	MD **0.3 lower** (0.47 lower to 0.13 lower)
Stool consistency assessed with: 5-point scale ranging from 0 (very loose) to 4 (very hard, little balls)	435 (1 RCT)[1]	⨁⨁◯◯ LOW[a,f]	-	The mean stool consistency was **0**	MD **0.2 lower** (0.37 lower to 0.03 lower)
Quality of life assessed with: PAC-QoL; MID 1 point	433 (1 RCT)[2]	⨁◯◯◯ VERY LOW[a,f,g]	-	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.	
AEs leading to treatment discontinuation	1275 (3 RCTs)[1,2,3]	⨁⨁◯◯ LOW[a,h]	RR 2.13 (1.25 to 3.61)	Study population	
				3 per 100	**3 more per 100** (1 more to 8 more)

References:

1. Spierings, Egilius LH, Rauck, Richard, Brewer, Randall, Marcuard, Stefano, Vallejo, Ricardo. Long-term safety and efficacy of lubiprostone in opioid-induced constipation in patients with chronic noncancer pain. Pain Practice; 2016.
2. Jamal, M Mazen, Adams, Atoya B, Jansen, Jan-Peter, Webster, Lynn R. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol; 2015.
3. Cryer, Byron, Katz, Seymour, Vallejo, Ricardo, Popescu, Anca, Ueno, Ryuji. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Medicine; 2014.

Explanations:

a. The trials were not conducted among persons with cancer.
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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	See table below	The panel determined the magnitude of the undesirable outcomes to be small.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with bowel regimen	Risk difference with Lubiprostone
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	868 (2 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	RR 1.15 (0.97 to 1.37)	Study population	
				33 per 100	**5 more per 100** (1 fewer to 12 more)
Change in SBM frequency assessed with: mean increase in weekly SBM from baseline	1275 (3 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,d,e]	-	MD 0.8 more (Jamal) and 0.6 more (Cryer) MD 0.10 less (0.78 less to 0.58 more) (Spierings)	

Reduction in straining assessed with: 5-point scale ranging from 0 (absent) to 4 (very severe)	435 (1 RCT)[1]	⨁⨁◯◯ LOW[a,f]	-	The mean reduction in straining was **0**	MD **0.3 lower** (0.47 lower to 0.13 lower)
Stool consistency assessed with: 5-point scale ranging from 0 (very loose) to 4 (very hard, little balls)	435 (1 RCT)[1]	⨁⨁◯◯ LOW[a,f]	-	The mean stool consistency was **0**	MD **0.2 lower** (0.37 lower to 0.03 lower)
Quality of life assessed with: PAC-QoL; MID 1 point	433 (1 RCT)[2]	⨁◯◯◯ VERY LOW[a,f,g]	-	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.	
AEs leading to treatment discontinuation	1275 (3 RCTs)[1,2,3]	⨁⨁◯◯ LOW[a,h]	RR 2.13 (1.25 to 3.61)	Study population	
				3 per 100	**3 more per 100** (1 more to 8 more)

References:

1. Spierings, Egilius LH, Rauck, Richard, Brewer, Randall, Marcuard, Stefano, Vallejo, Ricardo. Long-term safety and efficacy of lubiprostone in opioid-induced constipation in patients with chronic noncancer pain. Pain Practice; 2016.
2. Jamal, M Mazen, Adams, Atoya B, Jansen, Jan-Peter, Webster, Lynn R. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol; 2015.
3. Cryer, Byron, Katz, Seymour, Vallejo, Ricardo, Popescu, Anca, Ueno, Ryuji. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Medicine; 2014.

Explanations:

a. The trials were not conducted among persons with cancer.
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.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Overall, the certainty in the evidence of effects for lubiprostone for the treatment of OIC was very low due to the indirectness to patients with cancer. In addition, persons in the control arms were unable to receive a bowel regimen. The panel also noted imprecision due to uncertainty of a clinically meaningful difference in outcomes and the low number of events reported.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel agreed that the net benefits probably favor no lubiprostone; however, they were unable to determine the response to laxatives prior to trials.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards.** 6-24-19 & 6-25-19 **Drug** / **Product** / **Lowest Pittsburgh-area Price** / **Average Retail Price** Lactulose / 473 ml 10g/15ml of lactulose oral solution / Walmart (with GoodRx discount card): $12.14 / $33.72 Linaclotide / 30 capsules of Linzess 145mcg / Giant Eagle (with GoodRx discount card): $427.99 / $518.24 Lubiprostone / 60 capsules of Amitiza 24mcg / Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29 / Not available Methylnaltrexone / 90 tablets of Relistor 150mg / Giant Pharmacy (with GoodRx coupon): $1686.16 / $2,084.62 Naldemedine / 30 tablets of Symproic 0.2mg / Giant Eagle (with GoodRx coupon): $319.21 / Not available Naloxegol (Movantik) / 30 tablets of Movantik 25mg / Giant Eagle (with GoodRx coupon): $360.23 / $459.39 Prucalopride / 30 tablets of Motegrity 2mg / Giant Eagle (with GoodRx coupon): $428.06 / Not available In an economic evaluation of linaclotide for chronic idiopathic constipation (Huang et al., 2016), when the response was based on global treatment satisfaction, linaclotide-treated patients had an estimated direct cost of $946 versus $1,015 for lubiprostone. When the response was based on SBM frequency, estimated direct costs were $727 for linaclotide-treated and $737 for lubiprostone-treated.	The panel agreed that compared with a bowel regimen, the cost was large based on the price of the therapy.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that because of the cost to the patient and limited opportunity for coverage of the therapy, this option may be inaccessible, therefore, leading to increase health inequities.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel noted that while lubiprostone is widely available, it is not widely used for this indication.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends lubiprostone for OIC only in the context of a clinical trial* (no recommendation, knowledge gap).

Justification

Limited consistent evidence exists to support a recommendation for lubiprostone for the treatment of OIC in patients with cancer. Based on the low quality and limitations of evidence the guideline panel made no recommendation for lubiprostone and identified this intervention as an evidence gap that warrants further research.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No implementation considerations.

Research priorities

- Trials compared to a bowel regimen
- Safety studies

IN-TEXT CITED REFERENCES

Arthur, J.A., & Hui, D. (2018). Safe opioid use: management of opioid-related adverse effects and aberrant behaviors. *Hematology/Oncology Clinics of North America, 32*, 387–403. https://doi.org/10.1016/j.hoc.2018.01.003

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

RECOMMENDATION

Should linaclotide and a bowel regimen rather than a bowel regimen alone only be used in adult patients with cancer who have opioid-induced constipation?	
POPULATION:	Adult patients with cancer who have opioid-induced constipation
INTERVENTION:	Linaclotide and bowel regimen
COMPARISON:	Bowel regimen
MAIN OUTCOMES:	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
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Opioid induced constipation (OIC) is the most common side effect of opioids and affects 40%–80% of patients who are taking opioids; it is believed to be dose dependent (Arthur & Hui, 2018).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment or OTC medications	Risk difference with Linaclotide
SBM frequency assessed with: Change from baseline in 8-Week SBM frequency rate (SBMs/week) follow up: 8 weeks	252 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b]	-	The mean SBM frequency was 0	MD 1.62 more (0.92 more to 2.31 more)
Bristol Stool Scale assessed with: 7-point scale: 1=hard, 7=watery Scale from: 1 to 7 follow up: 8 weeks	252 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean Bristol Stool Scale was 0	MD 0.87 more (0.54 more to 1.2 more)
Reduction in straining assessed with: 1 is “not at all” and a value of 5 is “an extreme amount.” Scale from: 1 to 5	252 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a]	-	The mean reduction in straining was 0 points	MD 0.56 points lower (0.79 lower to 0.34 lower)
Serious adverse events	252 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[a,d]	**RR 0.12** (0.02 to 0.73)	Study population	
				64 per 1,000	56 fewer per 1,000 (63 fewer to 17 fewer)
Complete spontaneous bowel movements assessed with: ≥3 CSBM/week follow up: 12 weeks	487 (1 RCT)[2]	⨁⨁◯◯ LOW[e]	-	The mean complete spontaneous bowel movements was 0	MD 1.96 higher (1.12 higher to 3.44 higher)
Increase over baseline by >1 CSBM/week follow up: 12 weeks	487 (1 RCT)[2]	⨁⨁◯◯ LOW[e]	-	The mean increase over baseline by >1 CSBM/week was 0	MD 1.72 higher (1.18 higher to 2.52 higher)

ADDITIONAL CONSIDERATIONS

The panel decided that the magnitude of the benefits was small.

Change in CSBM from baseline follow up: 12 weeks	1583 (3 RCTs)[3,4]	⨁⨁◯◯ LOW[e]	-	The mean change in CSBM from baseline was 0	MD 1.57 higher (1.11 higher to 2.04 higher)
Change in SBM from baseline follow up: 12 weeks	1583 (3 RCTs)[3,4]	⨁⨁◯◯ LOW[e]	-	The mean change in SBM from baseline was 0	MD 2.11 higher (1.68 higher to 2.54 higher)

References:

1. ClinicalTrials.gov Id: NCT02270983. https://clinicaltrials.gov/ct2/show/results/NCT02270983
2. Lacy, Brian E, Schey, Ron, Shiff, Steven J, Lavins, Bernard J, Fox, Susan M, Jia, Xinwei D, Blakesley, Rick E, Hao, Xinming, Cronin, Jacquelyn A, Currie, Mark G. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. PLoS One; 2015.
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Explanations:

a. Has not been published in the peer-reviewed literature. Findings are from NCT02270983.
b. The 95% CI may not include a meaningful difference.
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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Outcomes**	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**		The panel determined the magnitude of the undesirable outcomes to be trivial.
					Risk with no treatment or OTC medications	**Risk difference with Linaclotide**	
	SBM frequency assessed with: Change from baseline in 8-Week SBM frequency rate (SBMs/week) follow up: 8 weeks	252 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b]	-	The mean SBM frequency was 0	MD 1.62 more (0.92 more to 2.31 more)	
	Bristol Stool Scale assessed with: 7-point scale: 1=hard, 7=watery Scale from: 1 to 7 follow up: 8 weeks	252 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean Bristol Stool Scale was 0	MD 0.87 more (0.54 more to 1.2 more)	
	Reduction in straining assessed with: 1 is “not at all” and a value of 5 is “an extreme amount.” Scale from: 1 to 5	252 (1 RCT)[1]	⨁⨁◯◯ LOW[a]	-	The mean reduction in straining was 0 points	MD 0.56 points lower (0.79 lower to 0.34 lower)	
	Serious adverse events	252 (1 RCT)[1]	⨁⨁⨁◯ MODERATE[a,d]	**RR 0.12** (0.02 to 0.73)	Study population		
					64 per 1,000	56 fewer per 1,000 (63 fewer to 17 fewer)	
	Complete spontaneous bowel movements assessed with: ≥3 CSBM/week follow up: 12 weeks	487 (1 RCT)[2]	⨁⨁◯◯ LOW[e]	-	The mean complete spontaneous bowel movements was 0	MD 1.96 higher (1.12 higher to 3.44 higher)	
	Increase over baseline by >1 CSBM/week follow up: 12 weeks	487 (1 RCT)[2]	⨁⨁◯◯ LOW[e]	-	The mean increase over baseline by >1 CSBM/week was 0	MD 1.72 higher (1.18 higher to 2.52 higher)	

Change in CSBM from baseline follow up: 12 weeks	1583 (3 RCTs)[3,4]	⨁⨁◯◯ LOW[e]	-	The mean change in CSBM from baseline was 0	MD 1.57 higher (1.11 higher to 2.04 higher)
Change in SBM from baseline follow up: 12 weeks	1583 (3 RCTs)[3,4]	⨁⨁◯◯ LOW[e]	-	The mean change in SBM from baseline was 0	MD 2.11 higher (1.68 higher to 2.54 higher)

References:

1. ClinicalTrials.gov Id: NCT02270983. https://clinicaltrials.gov/ct2/show/results/NCT02270983
2. Lacy, Brian E, Schey, Ron, Shiff, Steven J, Lavins, Bernard J, Fox, Susan M, Jia, Xinwei D, Blakesley, Rick E, Hao, Xinming, Cronin, Jacquelyn A, Currie, Mark G. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. PLoS One; 2015.
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Explanations:

a. Has not been published in the peer-reviewed literature. Findings are from NCT02270983.
b. The 95% CI may not include a meaningful difference.
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.

Preliminary results published on clinicaltrials.gov for NCT02270983, include the following incidence of adverse events diarrhea and nausea for the groups: Placebo (n=78), Linaclotide 145 micrograms (n=78), and Linaclotide 290 micrograms (n=87)

Diarrhea: 13/78 (16.67%), 24/87 (27.59%), 32/87 (36.78%)

Nausea: 4/78 (5.13%), 0/87 (0.00%), 1/87 (1.15%)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel agreed that with the inclusion of the unpublished and not peer-reviewed results from trial NCT02270983 that they had very low certainty in the evidence.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation.	The panel determine that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Source: GoodRx: www.goodrx.com (Drug price comparison among local pharmacies). Offers coupons and discount cards.** 6-24-19 & 6-25-19 **Drug** / **Product** / **Lowest Pittsburgh-area Price** / **Average Retail Price** Lactulose / 473 ml 10g/15ml of lactulose oral solution / Walmart (with GoodRx discount card): $12.14 / $33.72 Linaclotide / 30 capsules of Linzess 145mcg / Giant Eagle (with GoodRx discount card): $427.99 / $518.24 Lubiprostone / 60 capsules of Amitiza 24mcg / Giant Eagle (with GoodRx discount card. Restrictions apply): $288.29 / Not available Methylnaltrexone / 90 tablets of Relistor 150mg / Giant Pharmacy (with GoodRx coupon): $1686.16 / $2,084.62 Naldemedine / 30 tablets of Symproic 0.2mg / Giant Eagle (with GoodRx coupon): $319.21 / Not available Naloxegol (Movantik) / 30 tablets of Movantik 25mg / Giant Eagle (with GoodRx coupon): $360.23 / $459.39 Prucalopride / 30 tablets of Motegrity 2mg / Giant Eagle (with GoodRx coupon): $428.06 / Not available In an economic evaluation of linaclotide for chronic idiopathic constipation (Huang et al., 2016), when the response was based on global treatment satisfaction, linaclotide-treated patients had an estimated direct cost of $946 versus $1,015 for lubiprostone. When the response was based on SBM frequency, estimated direct costs were $727 for linaclotide-treated and $737 for lubiprostone-treated.	The panel agreed that compared with a bowel regimen the cost was large based on the price of the therapy.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that because of the cost to the patient and limited opportunity for coverage of the therapy, that this option may be inaccessible; therefore, leading to increase health inequities.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends linaclotide for OIC only in the context of a clinical trial* (no recommendation, knowledge gap).

Justification

Limited consistent evidence exists to support a recommendation for linaclotide in patients with cancer. Based on the low quality and limitations of evidence the guideline panel made no recommendation for linaclotide and identified this intervention as an evidence gap that warrants further research.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Additional comparative trials are needed.

IN-TEXT CITED REFERENCES

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

RECOMMENDATION

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

POPULATION:	Adult patients with cancer with non-opioid-related constipation
INTERVENTION:	Osmotic or stimulant laxatives and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Duration of constipation; Frequency of constipation; Severity of constipation; Resolution of constipation (y/n); Quality of life; Adverse events (diarrhea, dehydration)
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al. 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Constipation occurs in almost 60% of patients with cancer (McMillan et al., 2013).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives + lifestyle factors
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁⨁◯ MODERATE[a]	RR 2.24 (1.93 to 2.61)	Study population	
				27 per 100	**33 more per 100** (25 more to 43 more)
Change in BM frequency	1269 (6 RCTs)[2,4,5,6,7,8]	⨁⨁◯◯ LOW[a,b]	-	The mean change in BM frequency was **0**	MD **2.55 higher** (1.53 higher to 3.57 higher)
Reduction in straining	118 (2 RCTs)[2,3]	⨁⨁⨁◯ MODERATE[a]	RR 1.52 (1.18 to 1.96)	Study population	
				55 per 100	**29 more per 100** (10 more to 53 more)
Stool consistency improvement assessed with: measured as hard/pellet stools	269 (3 RCTs)[2,3,4]	⨁⨁⨁◯ MODERATE[a]	RR 1.55 (1.33 to 1.82)	Study population	
				58 per 100	**32 more per 100** (19 more to 48 more)
Quality of life - not reported	-	-	-	-	-
AEs leading to treatment discontinuation	589 (3 RCTs)[10,11,9]	⨁⨁⨁◯ MODERATE[c]	RR 3.55 (1.60 to 7.89)	Study population	
				26 per 1,000	**66 more per 1,000** (16 more to 179 more)

The panel decided that the magnitude of the benefits was moderate.

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

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. Check Ford article for I^2 of 100%
c. Rated down for indirectness because of difference in complementary treatments. Tarumi participants used laxatives throughout with docusate; McGraw prohibited use of laxatives with PEG 3350 + senna.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives + lifestyle factors
SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7 RCTs)[1,2,3,4,5,6,7]	⨁⨁⨁◯ MODERATE[a]	RR 2.24 (1.93 to 2.61)	Study population	
				27 per 100	**33 more per 100** (25 more to 43 more)
Change in BM frequency	1269 (6 RCTs)[2,4,5,6,7,8]	⨁⨁◯◯ LOW[a,b]	-	The mean change in BM frequency was **0**	MD **2.55 higher** (1.53 higher to 3.57 higher)
Reduction in straining	118 (2 RCTs)[2,3]	⨁⨁⨁◯ MODERATE[a]	RR 1.52 (1.18 to 1.96)	Study population	
				55 per 100	**29 more per 100** (10 more to 53 more)
Stool consistency improvement assessed with: measured as hard/pellet stools	269 (3 RCTs)[2,3,4]	⨁⨁⨁◯ MODERATE[a]	RR 1.55 (1.33 to 1.82)	Study population	
				58 per 100	**32 more per 100** (19 more to 48 more)
Quality of life - not reported	-	-	-	-	-
AEs leading to treatment discontinuation	589 (3 RCTs)[10,11,9]	⨁⨁⨁◯ MODERATE[c]	RR 3.55 (1.60 to 7.89)	Study population	
				26 per 1,000	**66 more per 1,000** (16 more to 179 more)

The panel determined the magnitude of the undesirable outcomes to be small.

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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 B, 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.
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7. Kamm, Michael A, Mueller-Lissner, Stefan A, Wald, Arnold, Hinkel, Ulrika, Richter, Erika, Swallow, Ros, Bubeck, Juergen. S1321 stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo-controlled trial of bisacodyl. Gastroenterology; 2010.
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9. Kamm, Michael A, Mueller–Lissner, Stefan, Wald, Arnold, Richter, Erika, Swallow, Ros, Gessner, Ulrika. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clinical Gastroenterology and Hepatology; 2011.
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.

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. Check Ford article for I^2 of 100%
c. Rated down for indirectness because of difference in complementary treatments. Tarumi participants used laxatives throughout with docusate; McGraw prohibited use of laxatives with PEG 3350 + senna.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ● Moderate ○ High ○ No included studies		Overall, the certainty in the estimated effects was moderate owing to indirectness. The panel decided that constipation related to treatments received by patients with cancer may differ from the persons included in the trial with functional constipation.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following to be important: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit probably favors the intervention based on the moderate treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Over the Counter Medication** Source: Walmart.com 6-24-19	The panel decided that the costs were negligible when factoring in the cost of fiber (i.e., a component of lifestyle factors).

Medication	Product	Price
Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	$4.74
Docusate sodium	Equate Stool Softener Docusate Sodium Softgels, 100 mg, 60 Ct	$2.84
Magnesium citrate	Equate Lemon Flavor Magnesium Citrate Saline Laxative Oral Solution, 10 fl oz	$0.98
Magnesium hydroxide (milk of magnesia)	Equate Milk of Magnesia Saline Laxative, Original Flavor, 1200 mg, 26 fl oz	$3.57
Polyethylene glycol (PEG) (Miralax)	ClearLAX Polyethylene Glycol 3350 Laxative Powder, 30 Doses	$12.92
Senna	Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	$4.78

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that while patients would most likely need to pay out of pocket, options for a bowel regimen are widely available and of limited cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose use can result in worsening abdominal distension and flatulence. They also indicated that a large body of evidence shows that polyethylene glycol has fewer side effect than lactulose. The authors said senna and lactulose have similar adverse effects. They also said that use of stimulant laxatives like senna can result in drug dependence and that potential side effects are usually mild but can include abdominal discomfort, cramps, nausea, diarrhea, GI irritation, and fluid and electrolyte depletion.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose is widely available.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *suggests* osmotic or stimulant laxatives in addition to lifestyle education over lifestyle education alone for constipation (conditional recommendation; moderate certainty of evidence ⊕⊕⊕◯).

Remark: Patients with a higher tolerance of constipation symptoms or duration and/or placing a greater value on avoiding laxatives may wish to not use osmotic or stimulant laxatives.

Justification

The guideline panel determined that there is moderate certainty in the evidence and made a conditional recommendation because, due to the spectrum of reasons for constipation in this population, clinicians and patients should carefully evaluate treatment options and risk factors and develop a personalized treatment plan. Patients' preferences and values as well as their individual tolerance of constipation and tolerance of the duration of symptoms will inform how they weigh laxatives and other options.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Trials of laxatives for treating different causes in different groups

IN-TEXT CITED REFERENCES

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Costilla, V.C., & Foxx-Orenstein, A.E. (2014). Constipation: Understanding mechanisms and management. *Clinical Geriatric Medicine, 30*, 107–115. http://dx.doi. org/10.1016/j.cger.2013.10.001

Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/10.1007/s12325-014-0169-x

Fiorini, K., Sato, S., Schlachta, C.M., & Alkhamesi, N.A. (2017). A comparative review of common laxatives in the treatment of constipation. *Minerva Chirurgica, 72*, 265–273. https://doi.org/10.23736/S0026-4733.17.07236-4

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

RECOMMENDATION

Should acupuncture and lifestyle education rather than lifestyle education alone be used in adult patients with cancer with non-opioid-related constipation?	
POPULATION:	Adult patients with cancer with non-opioid-related constipation
INTERVENTION:	Acupuncture and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Duration of constipation; Frequency of constipation; Severity of constipation; Resolution of constipation (y/n); Quality of life
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Constipation occurs in almost 60% of patients (McMillan et al., 2013) with cancer.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with acupuncture
Spontaneous bowel movement assessed with: SBM/wk follow up: range 9 weeks to 16 weeks	1160 (6 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,b,c,d]	-	The mean spontaneous bowel movement was 0	MD 0.85 higher (0.59 higher to 1.1 higher)
Bristol Stool Scale Scale from: 1 to 7 (higher score = softer feces) follow up: range 9 weeks to 12 weeks	705 (4 RCTs)[2,3]	⨁⨁◯◯ LOW[a,b,c,d,e]	-	The mean Bristol Stool Scale was 0	MD 0.41 higher (0.26 higher to 0.55 higher)
Adverse events follow up: range 9 weeks to 16 weeks	485 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[3,4,a,b,c,f,g,h]	**RR 0.53** (0.27 to 1.02)	Study population	
				108 per 1,000	51 fewer per 1,000 (79 fewer to 2 more)

References:

1. Wu, Jiani, Liu, Baoyan, Li, Ning, Sun, Jianhua, Wang, Lingling, Wang, Liping, Cai, Yuying, Ye, Yongming, Liu, Jun, Wang, Yang. Effect and safety of deep needling and shallow needling for functional constipation: a multicenter, randomized controlled trial. Medicine; 2014.
2. Lee, Hye-Yoon, Kwon, Oh-Jin, Kim, Jung-Eun, Kim, Mikyeong, Kim, Ae-Ran, Park, Hyo-Ju, Cho, Jung-Hyo, Kim, Joo-Hee, Choi, Sun-Mi. Efficacy and safety of acupuncture for functional constipation: a randomised, sham-controlled pilot trial. BMC complementary and alternative medicine; 2018.

ADDITIONAL CONSIDERATIONS

The panel decided that the magnitude of the benefits was trivial.

3. Zheng, H, Liu, Z-S, Zhang, W, Chen, M, Zhong, F, Jing, X-H, Rong, P-J, Zhu, W-Z, Wang, F-C, Liu, Z-B. Acupuncture for patients with chronic functional constipation: A randomized controlled trial. Neurogastroenterology & Motility; 2018.
4. Liu, Yi-qun, Sun, Shuai, Dong, Hui-juan, Zhai, Dong-xia, Zhang, Dan-ying, Shen, Wei, Bai, Ling-ling, Yu, Jin, Zhou, Li-hong, Yu, Chao-qin. Wrist-ankle acupuncture and ginger moxibustion for preventing gastrointestinal reactions to chemotherapy: A randomized controlled trial. Chinese Journal of Integrative Medicine; 2015.

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. One trial, Shin 2018, conducted among persons receiving treatment for cancer and experiencing constipation reported MD = 1.16 (95% CI: 0.67, 1.65) at 6 weeks between intervention (n=26) and control (n=26) arms. MD from mean change from baseline could not be calculated.
f. 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 intervention (He, Shu-mu, He-shu-mu) arms (n=505) and 6 adverse events in the control (mosapride) arm (n=170).
g. Small sample reported.
h. The 95% CI includes the potential for both harm and benefit.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel decided that the magnitude of the harms was trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with acupuncture
Spontaneous bowel movement assessed with: SBM/wk follow up: range 9 weeks to 16 weeks	1160 (6 RCTs)[1,2,3]	⨁◯◯◯ VERY LOW[a,b,c,d]	-	The mean spontaneous bowel movement was 0	MD 0.85 higher (0.59 higher to 1.1 higher)
Bristol Stool Scale Scale from: 1 to 7 (higher score = softer feces)	705 (4 RCTs)[2,3]	⨁⨁◯◯ LOW[a,b,c,d,e]	-	The mean Bristol Stool Scale was 0	MD 0.41 higher (0.26 higher to 0.55 higher)

follow up: range 9 weeks to 12 weeks					
Adverse events follow up: range 9 weeks to 16 weeks	485 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[3,4,a,b,c,f,g,h]	**RR 0.53** (0.27 to 1.02)	Study population	
				108 per 1,000	51 fewer per 1,000 (79 fewer to 2 more)

References:

1. Wu, Jiani, Liu, Baoyan, Li, Ning, Sun, Jianhua, Wang, Lingling, Wang, Liping, Cai, Yuying, Ye, Yongming, Liu, Jun, Wang, Yang. Effect and safety of deep needling and shallow needling for functional constipation: a multicenter, randomized controlled trial. Medicine; 2014.
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3. Zheng, H, Liu, Z-S, Zhang, W, Chen, M, Zhong, F, Jing, X-H, Rong, P-J, Zhu, W-Z, Wang, F-C, Liu, Z-B. Acupuncture for patients with chronic functional constipation: A randomized controlled trial. Neurogastroenterology & Motility; 2018.
4. Liu, Yi-qun, Sun, Shuai, Dong, Hui-juan, Zhai, Dong-xia, Zhang, Dan-ying, Shen, Wei, Bai, Ling-ling, Yu, Jin, Zhou, Li-hong, Yu, Chao-qin. Wrist-ankle acupuncture and ginger moxibustion for preventing gastrointestinal reactions to chemotherapy: A randomized controlled trial. Chinese Journal of Integrative Medicine; 2015.

Explanations:

a. High risk of bias for blinding of participants and personnel in the Wu 2014 study - both participants and personnel knew treatment allocation.
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d. The 95% CI may not include a meaningful difference.
e. One trial, Shin 2018, conducted among persons receiving treatment for cancer and experiencing constipation reported MD = 1.16 (95% CI: 0.67, 1.65) at 6 weeks between intervention (n=26) and control (n=26) arms. MD from mean change from baseline could not be calculated.
f. 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 intervention (He, Shu-mu, He-shu-mu) arms (n=505) and 6 adverse events in the control (mosapride) arm (n=170).
g. Small sample reported.
h. The 95% CI includes the potential for both harm and benefit.

In a qualitative study (Lee & Warden, 2011) of ten Korean women with constipation living in the U.S., one woman reported cold chills and another reported pain from receiving acupuncture.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		Overall, the certainty in the evidence of effects for acupuncture for the treatment of constipation was very low due to concerns with study limitations and the indirectness to patients with cancer. The panel also noted imprecision due to uncertainty of a clinically meaningful difference in outcomes and risk of bias in the lack of blinding in some studies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In an international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following improvements to be preferred: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. More than 80% of the patients preferred bowel movements without pain, soft but not loose or watery stools, less rectal straining, and relief from the sensation of feeling bloated. Over 80% of the patients preferred the following: less fear about developing OIC when taking the opioids, less worry about having bowel movements, and less “stomach” pain. Over 79% of patients preferred to leave laxatives or suppositories out of their interventions for constipation. A review (Peng et al., 2016) noted that studies showed a significant proportion of people reporting constipation use complementary and alternative interventions in addition to medications.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A review of complementary and alternative medicine use for constipation (Peng, Liang, Sibbritt, & Adams, 2016) noted a U.S. study that estimated the median annual cost of acupuncture to be $400. **Acupuncture/Electroacupuncture/Moxibustion:** (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+). Retrieved 7-1-19 The cost of acupuncture treatment varies among practitioners. The cost ranges between $60 and $120 per session, with the first session generally costing more. Sometimes package prices are offered for multiple appointments. If the treatments are covered by insurance, the charges for individual techniques could be listed, potentially including massage therapy, cupping, electro-stimulation, and moxibustion.	The panel decided on large costs based on the assumption that multiple sessions would be needed, informed by the number of sessions used in the trials.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that because of the cost to the patient, necessary specialist, and limited opportunity for coverage of the therapy, this option may be inaccessible, therefore, leading to increase health inequities.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel decided that acceptability of this intervention would vary across stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends the use of acupuncture for constipation only in the context of a clinical trial* (no recommendation; knowledge gap).

Justification

Limited consistent evidence exists to support a recommendation for acupuncture for the treatment of constipation in patients with cancer. Based on the low quality and limitations of evidence the guideline panel made no recommendation for acupuncture and identified this intervention as an evidence gap that warrants further research.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Testing of a standard acupuncture protocol
- Head to head comparisons with laxatives

IN-TEXT CITED REFERENCES

Bharucha, A.E., Pemberton, J.H., & Locke, G.R. (2013). American Gastroenterological Association technical review on constipation. *Gastroenterology, 144*, 218–238. https://doi.org/10.1053/j.gastro.2012.10.028

Clemens, K.E., Faust, M., Jaspers, B., & Mikus, G. (2013). Pharmacological treatment of constipation in palliative care. *Current Opinion in Supportive and Palliative Care, 7*, 183–191. https://doi.org/10.1097/SPC.0b013e32835f1e17

Costilla, V.C., & Foxx-Orenstein, A.E. (2014). Constipation: Understanding mechanisms and management. *Clinical Geriatric Medicine, 30*, 107–115. https://doi. org/10.1016/j.cger.2013.10.001

Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M. B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/10.1007/s12325-014-0169-x

Lee, E.J., & Warden, S. (2011). A qualitative study of quality of life and the experience of complementary and alternative medicine in Korean women with constipation. *Gastroenterology Nursing, 34*, 118-127. https://doi.org/10.1097/SGA.0b013e3182109405

McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. https://doi.org/10.1188/13.ONF.E92-E100

Peng, W., Liang, H., Sibbritt, D., & Adams, J. (2016). Complementary and alternative medicine use for constipation: a critical review focusing upon prevalence, type, cost, and users' profile, perception and motivations. *International Journal of Clinical Practice, 70*, 712-722. https://doi.org/10.1111/ijcp.12829

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

RECOMMENDATION

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

POPULATION:	Adult patients with cancer with non-opioid-related constipation
INTERVENTION:	Electroacupuncture and lifestyle education
COMPARISON:	Lifestyle education
MAIN OUTCOMES:	Duration of constipation; Frequency of constipation; Severity of constipation; Resolution of constipation (y/n); Quality of life
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Constipation can occur in patients with cancer (McMillan et al., 2013) and can be distressing to them during treatment, in survivorship and in palliative care. Constipation is often multicausal – a result of organic, functional, or medication-related factors (Bharucha et al., 2013; Clemens et al., 2013; Costilla & Foxx-Orenstein, 2014), and it often goes unrecognized and untreated (McMillan et al., 2013).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Barbara Rogers, CRNP, MN, AOCN®, ANP-BC, Allison Anbari, PhD, RN, Brian Hanson, MD, Rachael Lopez, MPH, RD, CSO, Deborah M. Thorpe, PhD, APRN, Brenda Wolles, RN, MSN, CNL, OCN® Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Constipation occurs in almost 60% of patients (McMillan et al., 2013) with cancer.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with electroacupuncture
≥3 CSBMs per week follow up: 8 weeks	1075 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b]	RR 3.33 (2.42 to 4.57)	Study population	
				121 per 1,000	**281 more per 1,000** (171 more to 431 more)
PAC-QoL assessed with: 5-point scale (lower score = higher QoL) follow up: 8 weeks	1265 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean PAC-QoL was **0**	MD **0.31 lower** (0.36 lower to 0.25 lower)
CSBM assessed with: CSBM/wk follow up: 8 weeks	1147 (2 RCTs)[1,3]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean CSBM was **0**	MD **0.85 higher** (0.64 higher to 1.06 higher)
Bristol Stool Scale Scale from: 1 to 7 (higher score = softer feces) follow up: 8 weeks	1265 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean Bristol Stool Scale was **0**	MD **0.19 higher** (0.06 higher to 0.32 higher)
Adverse events leading to treatment discontinuation follow up: 8 weeks	1075 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,d,e]	RR 0.45 (0.14 to 1.44)	Study population	
				17 per 1,000	**9 fewer per 1,000** (14 fewer to 7 more)
Use of rescue medication follow up: 8 weeks	1075 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,c]	RR 0.85 (0.71 to 1.02)	Study population	
				340 per 1,000	**51 fewer per 1,000** (98 fewer to 7 more)

The panel determined the magnitude of the desirable outcomes to be moderate.

References:

1. Liu, Zhishun, Yan, Shiyan, Wu, Jiani, He, Liyun, Li, Ning, Dong, Guirong, Fang, Jianqiao, Fu, Wenbin, Fu, Lixin, Sun, Jianhua. Acupuncture for chronic severe functional constipation: a randomized trial. Annals of Internal Medicine; 2016.

2. Wu, Xiao, Zheng, Cuihong, Xu, Xiaohu, Ding, Pei, Xiong, Fan, Tian, Man, Wang, Ying, Dong, Haoxu, Zhang, Mingmin, Wang, Wei. Electroacupuncture for functional constipation: a multicenter, randomized, control trial. Evidence-Based Complementary and Alternative Medicine; 2017.
3. Da, Nili, Wang, Xinjun, Liu, Hairong, Xu, Xiuzhu, Jin, Xun, Chen, Chaoming, Zhu, Dan, Bai, Jiejing, Zhang, Xiaoqing, Zou, Yangyang. The effectiveness of electroacupuncture for functional constipation: a randomized, controlled, clinical trial. Evidence-Based Complementary and Alternative Medicine; 2015.

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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel determined the magnitude of the undesirable outcomes to be trivial.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with lifestyle factors	Risk difference with electroacupuncture
≥3 CSBMs per week follow up: 8 weeks	1075 (1 RCT)[1]	⨁⨁◯◯ LOW[a,b]	RR 3.33 (2.42 to 4.57)	Study population	
				121 per 1,000	**281 more per 1,000** (171 more to 431 more)
PAC-QoL assessed with: 5-point scale (lower score = higher QoL) follow up: 8 weeks	1265 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean PAC-QoL was **0**	MD **0.31 lower** (0.36 lower to 0.25 lower)
CSBM assessed with: CSBM/wk follow up: 8 weeks	1147 (2 RCTs)[1,3]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean CSBM was **0**	MD **0.85 higher** (0.64 higher to 1.06 higher)

Bristol Stool Scale Scale from: 1 to 7 (higher score = softer feces) follow up: 8 weeks	1265 (3 RCTs)[1,2]	⨁◯◯◯ VERY LOW[a,b,c]	-	The mean Bristol Stool Scale was **0**	MD **0.19 higher** (0.06 higher to 0.32 higher)
Adverse events leading to treatment discontinuation follow up: 8 weeks	1075 (1 RCT)[1]	⨁◯◯◯ VERY LOW[a,b,d,e]	RR 0.45 (0.14 to 1.44)	Study population	
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				340 per 1,000	**51 fewer per 1,000** (98 fewer to 7 more)

References:

1. Liu, Zhishun, Yan, Shiyan, Wu, Jiani, He, Liyun, Li, Ning, Dong, Guirong, Fang, Jianqiao, Fu, Wenbin, Fu, Lixin, Sun, Jianhua. Acupuncture for chronic severe functional constipation: a randomized trial. Annals of Internal Medicine; 2016.
2. Wu, Xiao, Zheng, Cuihong, Xu, Xiaohu, Ding, Pei, Xiong, Fan, Tian, Man, Wang, Ying, Dong, Haoxu, Zhang, Mingmin, Wang, Wei. Electroacupuncture for functional constipation: a multicenter, randomized, control trial. Evidence-Based Complementary and Alternative Medicine; 2017.
3. Da, Nili, Wang, Xinjun, Liu, Hairong, Xu, Xiuzhu, Jin, Xun, Chen, Chaoming, Zhu, Dan, Bai, Jiejing, Zhang, Xiaoqing, Zou, Yangyang. The effectiveness of electroacupuncture for functional constipation: a randomized, controlled, clinical trial. Evidence-Based Complementary and Alternative Medicine; 2015.

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.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies		Overall, the certainty in the evidence of effects for electroacupuncture for the treatment of constipation was very low due to the indirectness to patients with cancer and the variety of methods studied. The panel also noted imprecision due to uncertainty of a clinically meaningful difference in outcomes and the low number of events reported.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	An international survey of patients with opioid-induced constipation (Epstein et al., 2014), the majority found the following to be important: having a bowel movement on a regular basis and having one more bowel movement per week. More than half of patients took less of their pain medication when constipated. A review (Peng et al., 2016) noted that studies showed a significant proportion of people reporting constipation use complementary and alternative interventions in addition to medications.	The panel determined that there is probably no important uncertainty in how patients value the main outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel decided that the net benefit probably favors the intervention based on the moderate treatment effect.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	A review of complementary and alternative medicine use for constipation (Peng et al., 2016) noted a U.S. study that estimated the median annual cost of acupuncture to be $400. **Acupuncture/Electroacupuncture/Moxibustion:** (https://www.acufinder.com/Acupuncture+Information/Detail/How+much+does+an+acupuncture+treatment+cost+). Retrieved 7-1-19 The cost of acupuncture treatment varies among practitioners. The cost ranges between $60 and $120 per session, with the first session generally costing more. Sometimes package prices are offered for multiple appointments. If the treatments are covered by insurance, the charges for individual techniques could be listed, potentially including massage therapy, cupping, electro-stimulation, and moxibustion.	The panel decided on large costs based on the assumption that multiple sessions would be needed, informed by the number of sessions used in the trials.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel determined that because of the cost to the patient, necessary specialist, and limited opportunity for coverage of the therapy, this option may be inaccessible, therefore, leading to increase health inequities.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel decided that acceptability of this intervention would vary across stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Among adult patients with cancer, the ONS Guidelines panel *recommends the use of electroacupuncture for constipation only in the context of a clinical trial* (no recommendation; knowledge gap).

Justification

Electroacupuncture has shown emerging benefits for the treatment of functional constipation, but there is limited evidence to support a recommendation for electroacupuncture for the treatment of constipation in patients with cancer. Based on the very low quality and limitations of the evidence the guideline panel made no recommendation for electroacupuncture and identified this intervention as an evidence gap that warrants further research.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Testing of a standard acupuncture protocol
- Head-to-head comparisons with laxatives

IN-TEXT CITED REFERENCES

Bharucha, A.E., Pemberton, J.H., & Locke, G.R. (2013). American Gastroenterological Association technical review on constipation. *Gastroenterology, 144*, 218–238. https://doi.org/10.1053/j.gastro.2012.10.028

Clemens, K.E., Faust, M., Jaspers, B., & Mikus, G. (2013). Pharmacological treatment of constipation in palliative care. *Current Opinion in Supportive and Palliative Care, 7*, 183–191. https://doi.org/10.1097/SPC.0b013e32835f1e17

Costilla, V.C., & Foxx-Orenstein, A.E. (2014). Constipation: Understanding mechanisms and management. *Clinical Geriatric Medicine, 30*, 107–115. https://doi. org/10.1016/j.cger.2013.10.001

Epstein, R.S., Cimen, A., Benenson, H., Aubert, R.E., Khalid, M., Sostek, M.B., & Salimi, T. (2014). Patient preferences for change in symptoms associated with opioid-induced constipation. *Advances in Therapy, 31*, 1263–71. https://doi.org/10.1007/s12325-014-0169-x

McMillan, S.C., Tofthagen, C., Small, B., Karver, S., & Craig, D. (2013). Trajectory of medication-induced constipation in patients with cancer. *Oncology Nursing Forum, 40*, E92–E100. https://doi.org/10.1188/13.ONF.E92-E100

Peng, W., Liang, H., Sibbritt, D., & Adams, J. (2016). Complementary and alternative medicine use for constipation: A critical review focusing upon prevalence, type, cost, and users' profile, perception and motivations. *International Journal of Clinical Practice, 70*, 712–722. https://doi.org/10.1111/ijcp.12829