ONS CONSTIPATION SYMPTOM MANAGEMENT GUIDELINE

Supplementary Material

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1. Guideline panel conflict of interest disclosures

Panel member	Conflict of interest disclosures
Barbara Rogers, CRNP, MN, AOCN[®], ANP-BC Adult Hematology-Oncology Nurse Practitioner Fox Chase Cancer Center, Philadelphia, PA	Consultant or advisory: SelfCardinal Health (compensated); Genentech (compensated); Celgene (compensated); Mylan (compensated); Janssen (compensated) Honoraria: SelfAbbvie Speakers Bureau; Genentech Speakers Bureau; Coherus Speakers Bureau
Allison Anbari, PhD, RN Assistant Research Professor Sinclair School of Nursing University of Missouri Columbia	No conflicts listed
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
Deborah M. Thorpe, PhD, APRN Palliative Care Consultant and Founder INN Between, Salt Lake City, UT	No conflicts listed
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 w	ith cancer; have not responded to					
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				

Adult patients with cancer who have opioid-induced constipation	Naldemedine and bowel regimen	Bowel regimen	Adverse events that lead to treatment discontinuation Change in pain control/score 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 con	stipation in patients with cance	er
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
			Duration of constipation
Adult patients with cancer			Frequency of constipation
with non-opioid-related	Electroacupuncture and lifestyle education	Lifestyle education	Severity of constipation
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?

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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
o No o Probably no o Probably yes • Yes o Varies o 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.

ENT	RESEARCH EVIDENCE	RESEARCH EVIDENCE						
to	Outcomes	№ of participants	Certainty of the evidence	idence effect	Anticipated absolute	effects [*] (95% CI)	The panel decided that the magnitude of effect is less because not all patients we develop constipation.	
Moderate Large Varies Don't know		(studies) Follow up	(GRADE)		Risk with no treatment	Risk difference with a prophylactic bowel regimen		
	SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7	⊕⊕⊖⊖ LOWª,b	RR 2.24 Study popular (1.93 to	Study population			
		RCTs) ^{1,2,3,4,5,6,7}	LOW	2.61)	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}	UERY 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}			Study population			
		(2 RCTS) ^{2,3} LOW ^{a,b}	LOW ^{a,b}		55 per 100	29 more per 100 (10 more to 53 more)		
	Stool consistency improvement	269 (3 RCTs) ^{2,3,4}	€ LOW ^{a,b}	RR 1.55 (1.33 to	Study population	ion		
	assessed with: measured as hard/pellet stools		LOW	1.82)	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}		RR 3.55 (1.60 to 7.89)	Study population	1	-	
					26 per 1,000	66 more per 1,000 (16 more to 179 more)		

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	randomized, placebo-controlled trial of bisacodyl. Gastroenterology; 2010. (<i>This is an update of the following found in Ford & Suares, 2011</i> : 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,	
8.	placebo-controlled trial of bisacodyl. Gastroenterology; 2010.) Baldonedo, YC, Lugo, E, Uzcategui, AA, Guelrud, M, Skornicki, J. Evaluation and use of polyethylene glycol in	
9.	constipated patients. GEN; 1991. Kamm, Michael A, Mueller–Lissner, Stefan, Wald, Arnold, Richter, Erika, Swallow, Ros, Gessner, Ulrika. Oral bisacodyl	
10.	is effective and well-tolerated in patients with chronic constipation. Clinical Gastroenterology and Hepatology; 2011. 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.	
Explanati	ons:	
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.	
с.	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.	

JUDGEMENT	RESEARCH EVIDENCE	RESEARCH EVIDENCE							
 o Large Moderate o Small o Trivial o Varies o Don't know 	Outcomes	№ of participants	cipants the evidence ies) (GRADE)		Anticipated absolute effects* (95% CI)		The panel agreed that patients who aren't constipated may experience diarrhea and		
		(studies) Follow up			Risk with no treatment	Risk difference with a prophylactic bowel regimen	estimated that at minimum this would affect 209 of people. The risk with diarrhea would be electrolyte imbalance or dehydration.		
	SBM response (defined as ≥3 SBMs/wk or ≥3 stools/wk)	1411 (7		Study population	1				
		RCTs) ^{1,2,3,4,5,6,7}		2.61)	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}	OCO 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	Reduction in straining 118 (2 RCTs) ^{2,3}		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	269 (3 RCTs) ^{2,3,4}	€€ LOW ^{a,b}	RR 1.55 (1.33 to 1.82)	Study population				
	assessed with: measured as hard/pellet stools				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}		RR 3.55 (1.60 to	Study population	'			
				7.89)	26 per 1,000	66 more per 1,000 (16 more to 179 more)			
	References:								

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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6.	
7.	
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.
Explanat	ions:
a. b. c.	Rated down twice for indirectness because population consisted of non-OIC and non-cancer patients. Indirect because participants in the trial had constipation at start. 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.
	parative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose use can result ning abdominal distension and flatulence. They also indicated that a large body of evidence shows that polyethylene
glycol ha use of sti	s fewer side effect than lactulose. The authors said senna and lactulose have similar adverse effects. They also said that mulant laxatives like senna can result in drug dependence and that potential side effects are usually mild but can include al discomfort, cramps, nausea, diarrhea, GI irritation, and fluid and electrolyte depletion.

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low ● Low o Moderate o High o 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 s there important uncertainty abo	out or variability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Definition of the second state of	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 desiral	le 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 ntervention or the comparison Probably favors the interventior 		The guideline panel considered that patients wh place a higher value on avoidance of constipatio may prefer to start on a prophylactic regimen; however, patients who place a higher value on avoiding undue costs/taking medications/undue

• Favors the intervention

○ Varies ○ Don't know harms (diarrhea) may prefer to not start on a

bowel regimen prophylactically.

How large are the resource require	ements (costs)?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
 Large costs Moderate costs Negligible costs and savings 		Over the Counter Medication Source: Walmart.com 6-24-19						
o Moderate savings o Large savings o Varies o Don't know	Bisacodyl (Docusate s	sodium	Product Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct Equate Stool Softener Docusate Sodium Softgels, 100 mg, 60 Ct	Price \$4.74 \$2.84				
	Magnesiun Magnesiun	n citrate n hydroxide (milk of	Equate Lemon Flavor Magnesium Citrate Saline Laxative Oral Solution, 10 fl oz Equate Milk of Magnesia Saline Laxative,	\$0.98 \$3.57				
	(Miralax)	ne glycol (PEG)	Original Flavor, 1200 mg, 26 fl oz <u>ClearLAX</u> Polyethylene Glycol 3350 Laxative Powder, 30 Doses	\$12.92				
	Senna		Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	\$4.78				
JUDGEMENT	nce of resource requirements (cost	5)?			ADDITIONAL CONSIDERATIONS			
o Very low o Low	No research evidence identified							
o Moderateo HighNo included studies								
 High No included studies Cost effectiveness 	e intervention favor the interventio	n or the comparison?						
 o High No included studies Cost effectiveness 	e intervention favor the interventio	n or the comparison?			ADDITIONAL CONSIDERATIONS			

Equity What would be the impact on health equity? JUDGEMENT RESEARCH EVIDENCE O Reduced 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

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 imple	s the intervention feasible to implement?							
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS						
o No o Probably no o Probably yes • Yes o Varies o 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

limited cost.

	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
0	0	•	0	0

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 $\oplus \oplus \bigcirc \bigcirc$).

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).

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

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 o No 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). o Probably no O Probably yes • Yes Varies o Don't know **Desirable Effects** How substantial are the desirable anticipated effects? JUDGEMENT **RESEARCH EVIDENCE** ADDITIONAL CONSIDERATIONS o Trivial The panel determined the magnitude of the Relative Outcomes Nº of Certainty of the Anticipated absolute effects^{*} (95% CI) o Small desirable outcomes to be moderate. participants evidence effect Moderate (studies) (GRADE) (95% CI) **Risk with lifestyle Risk difference with** O Large Follow up o Varies factors osmotic or stimulant O Don't know laxatives SBM response (defined as 1411 $\oplus \oplus \oplus \bigcirc$ RR 2.24 Study population ≥3 SBMs/wk or ≥3 (7 (1.93 to **MODERATE**^a RCTs)1,2,3,4,5,6,7 stools/wk) 2.61) 27 per 100 33 more per 100 (25 more to 43 more) Change in BM frequency 1269 The mean change in MD 2.55 higher $\oplus \oplus \bigcirc \bigcirc$ (6 RCTs)^{2,4,5,6,7,8} (1.53 higher to 3.57 BM frequency was LOW^{a,b} 0 higher) Reduction in straining Study population

	118 (2 RCTs) ^{2,3}	⊕⊕⊕ ⊖ MODERATEª	RR 1.52 (1.18 to 1.96)	55 per 100	29 more per 100 (10 more to 53 more)		
Stool consistency improvement	269 (3 RCTs) ^{2,3,4}		RR 1.55 (1.33 to	Study population			
assessed with: measured as hard/pellet stools			1.82)	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}		RR 3.55 (1.60 to	Study population	ly population		
		MODERATE	7.89)	26 per 1,000	66 more per 1,000 (16 more to 179 more)		
eferences:	1				1		

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 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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	 Nakajima, Atsushi, 1 chronic constipatio extension. Journal of 11. McGraw, Thomas. S trial. Clinical and Ex Explanations: a. Rated down twice f b. Check Ford article f c. Rated down for ind with PEG 3350 + se 						
Undesirable Effects How substantial are the undesirable	e anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Large o Moderate	(studies)	Nº of participants	oarticipants evidence studies) (GRADE)	e Relative effect (95% CI)	Anticipated absolute effects [*] (95% CI)		The panel determined the magnitude of the undesirable outcomes to be small.
• Small o Trivial o Varies o Don't know		(studies) Follow up			Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives	
	SBM response (defined as ≥3 SBMs/wk or ≥3	/wk or ≥3 (7	⊕⊕⊕⊖ MODERATEª	RR 2.24 (1.93 to 2.61)	Study population		
	stools/wk)				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	Study population		
			WODERATE	1.96)	55 per 100	29 more per 100 (10 more to 53 more)	
	Stool consistency improvement	269 (3 RCTs) ^{2,3,4}	⊕⊕⊕ ⊖ MODERATE ^a	RR 1.55 (1.33 to	Study population		
	assessed with: measured as hard/pellet stools			1.82)	58 per 100	32 more per 100 (19 more to 48 more)	

AEs leading to discontinuation						
		589 (3 RCTs) ^{10,11,9}	(1.60 to Study population		n	
				7.89)	26 per 1,000	66 more per 1,000 (16 more to 179 more)
eferences:						
			t, S, Bergh-Bohlke Ible-blind study. G		ica, Milorad. Treat	ment of chronic constipation
2. Cora volu	azziari, E, Badiali ume isosmotic po	, D, Habib, FI, Re plyethylene glyco	boa, G, Pitto, G, N ol electrolyte bala	/lazzacca, G, S		zi, R, Cilluffo, Te, Vantini, I. Smal ment of chronic nonorganic
3. Cora tern	azziari, E, Badiali n efficacy, safety	, and tolerability	, Bassotti, G, Rose of low daily dose	s of isosmotic	polyethylene glyco	Galeazzi, R, Peruzzi, E. Long ol electrolyte balanced solution
4. DiPa	alma, Jack A, Del trolled, multicer	Ridder, Peter H, (olts, Byron E, C	Cleveland, Mark B.	A randomized, placebo- xative. Am J Gastroenterol;
5. DiPa	alma, Jack A, Cle					nulticenter, placebo-controlled Gastroenterol; 2007.
6. Mue Jürg	eller-Lissner, Ste gen. Multicenter	fan, Kamm, Mich , 4-week, double	nael A, Wald, Arno -blind, randomize	old, Hinkel, Ulr	ika, Koehler, Ursul	a, Richter, Erika, Bubeck, lium picosulfate in patients with
7. Kam Juer	nm, Michael A, N rgen. S1321 stim	ulant laxatives a	tefan A, Wald, Ar re effective in chr	onic constipat	ion: multi-center, 4	a, Swallow, Ros, Bubeck, 1-week, double-blind,
8. Balo	donedo, YC, Lugo	o, E, Uzcategui, A	l of bisacodyl. Gas A, Guelrud, M, Sk			polyethylene glycol in
9. Kam		Aueller–Lissner, S				Gessner, Ulrika. Oral bisacodyl
10. Nak chro	ajima, Atsushi, S onic constipatior	hinbo, Kazuhiko 1: a 2-week, rand	, Oota, Akira, Kinc omized, double-b	shita, Yoshika	zu. Polyethylene g	erology and Hepatology; 2011. lycol 3350 plus electrolytes for ith a 52-week open-label
11. McC	Graw, Thomas. S		011		onic constipation:	randomized, placebo-controllec
xplanations:						
b. Che	ck Ford article fo	or I squared of 10	00%		non-OIC and non-c	ancer patients. Imi participants used laxatives

	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 e	vidence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low Moderate o High o 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 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 requirem	ents (costs)?			
JUDGEMENT	RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS
 O Large costs O Moderate costs Negligible costs and savings 	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).		
 Moderate savings 	Medication	Product	Price	
o Large savings o Varies	Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	\$4.74	
○ Don't know	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) (<u>Miralax</u>)	ClearLAX Polyethylene Glycol 3350 Laxative Powder, 30 Doses	\$12.92	
	Senna	Equate Natural Laxative Sennosides USP Tablets, 8.6 mg, 100 Ct	\$4.78	
What is the certainty of the evidence 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 int	tervention favor the intervention or the comparison?			
JUDGEMENT	RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies No included studies 	No research evidence identified.			

Equity What would be the impact on health	equity?				
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o Reduced o Probably reduced • Probably no impact o Probably increased o Increased o Varies o 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			
o No o Probably no o Probably yes • Yes o Varies o Don't know	No research evidence identified.				
Feasibility Is the intervention feasible to implement?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
o No o Probably no o Probably yes • Yes o Varies	In a comparative review of common laxatives for constipation (Fiorini et al., 2017), the authors noted that lactulose is widely available.				

0 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

	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
0	0	0	0	•

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 $\oplus \oplus \odot$).

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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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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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

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

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

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

ASSESSMENT

Problem							
Is the problem a priority? JUDGEMENT	RESEARCH EVIDENCE	RESEARCH EVIDENCE					
o No o Probably no o Probably yes • Yes o Varies o 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 desiral	ole anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Trivial ● Small o Moderate	Outcomes	Outcomes No of Certainty o participants (studies) Follow up		evidence effect	Anticipated absolute effects* (95% CI)		The panel agreed that the benefits reported may not be good indicators of patient- important outcomes, however, decided the
o Moderate o Large o Varies o Don't know			(GRADE)		Risk with no treatment	Risk difference with osmotic PEG (MiraLAX)	benefit to be small.
	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)	

	 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% Cl may not include a meaningful difference. d. The 95% Cl includes the potential for both possible harm as well as possible benefit. 						
Undesirable Effects How substantial are the undesirable	ble anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Large o Moderate	Outcomes № of participants		Relative effect	Anticipated absolute effects* (95% CI)		The panel decided that the magnitude of the harms is trivial.	
o Small • Trivial o Varies • Don't know		(studies) Follow up	(GRADE)	(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)	

	 Reference: 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% Cl may not include a meaningful difference. d. The 95% Cl includes the potential for both possible harm as well as possible benefit. 	
	 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. 	
Certainty 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.	
What is the overall certainty of the		
JUDGEMENT • Very low • Low • Moderate • High • No included studies	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS 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 abo	ut 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 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?

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

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE			ADDITIONAL CONSIDERATIONS
O Large costs	Over the Counter Medication			The panel decided that the costs were
 Moderate costs Negligible costs and savings 	Source: Walmart.com 6-24-19			negligible when factoring in the cost of fiber (i.e., a component of lifestyle factors).
Moderate savings	Medication	Product	Price	
Large savings Varies	Bisacodyl (Dulcolax)	Equate Gentle Laxative Bisacodyl Coated Tablets, 5 mg, 100 Ct	\$4.74	
Don't know	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	

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CEItanit			IEUUIEU	I ESUUI LES

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

what is the certainty of the eviden		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low o Moderate o High No included studies 	No research evidence identified.	
Cost offortivoposs		

Cost effectiveness

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

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

Equity

What would be the impact on health equity?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
 o Reduced o Probably reduced Probably no impact o Probably increased o Increased o Varies o 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.				

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	No research evidence identified.	
Feasibility Is the intervention feasible to impl	ement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o 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
0	0	0	•	0

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 $\oplus \oplus \bigcirc \bigcirc$).

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

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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

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

Problen	า

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o No o Probably no o Probably yes • Yes o Varies o 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 desirab	e anticipated effects?	

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
o Trivial ● Small ○ Moderate	Outcomes	Nº of participants (studies) Follow up		Relative effect (95% Cl)	Anticipated absolute effects [*] (95% CI)		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.
o Large o Varies o Don't know				Risk with bowel regimen + metoclopramide (or other active comparator)	Risk difference with methylnaltrexone (SQ or oral)		
		1397 (3 RCTs) ^{1,2,3}		RR 1.33 (1.16 to 1.52)	Study population		
					39 per 100	13 more per 100 (6 more to 20 more)	
	as a BM within 4 hours and	998 (5		RR 3.50 (2.65 to 4.62)	Study population		
	no laxative in the prior 24 hours)	RCTs) ^{1,3,4,5,6}			12 per 100	30 more per 100 (20 more to 44 more)	
	Change in rescue-free bowel movement frequency	861 (3 RCTs) ^{1,2}	UERY LOW ^{a,c}	-		2 mg sc qd and 0.60 more lichna 2011); MD 0.5 more 0.1 more with 150mg	

assessed	on in straining d using a straining none) to 4 (very	460 (1 RCT) ²	UERY 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 leac disconti	ling to treatment nuation	1628 (4 RCTs) ^{1,2,3,6}	D OOO 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	UERY LOW ^{a,d}	-	Methylnaltrexone group showed an improvement in the total score of 0.74 (12mg s qd) and 0.39 (12mg sc qod).		
Reference 1. 2. 3. 4.	 methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Practice 2017. Michna, Edward, Blonsky, E Richard, Schulman, Seth, Tzanis, Evan, Manley, Amy, Zhang, Haiying, Iyer, Shrividya, Randazz 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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 2008. 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. 							
Explanati	ons:						
 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 openlabel study. No CIs or standard deviations were provided. 							

	e. The 95% Cl includes	e. The 95% CI includes the potential for both benefit and harm.							
Undesirable Effe	ects desirable anticipated effects?								
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS		
o Large o Moderate o Small	Outcomes Nº of participants Certainty of the evidence Relative effect (95% CI) Anticipated absolute effects* (95% CI)					effects [*] (95% CI)	The panel agreed that alternative therapies are available if patients need to stop methylnaltrexone due to adverse events.		
o Small • Trivial • Varies • Don't know		(studies) (GRA Follow up	(GRADE)		Risk with bowel regimen + metoclopramide (or other active comparator)	Risk difference with methylnaltrexone (SQ or oral)	ineurymanie.one due to adverse events.		
	Rescue-free bowel movement (defined as > or	rement (defined as > or $(3 \text{ RCTs})^{1,2,3}$ VERY LOW ^{a,b}	RR 1.33 (1.16 to 1.52)	Study population					
	equal to 3 RFBM per week)				39 per 100	13 more per 100 (6 more to 20 more)			
	Laxation response (defined as a BM within 4 hours and	998 (5		⊕⊕⊖⊖ RR 3.50 LOW ^a (2.65 to 4.62)	Study population				
	no laxative in the prior 24 hours)	RCTs) ^{1,3,4,5,6}		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}	-		.2 mg sc qd and 0.60 more lichna 2011); MD 0.5 more 0.1 more with 150mg			
	Reduction in straining assessed using a straining scale 0 (none) to 4 (very severe)	460 (1 RCT) ²	€ VERY LOW ^{a,d}	-		bo, methylnaltrexone led none or mild straining (MD o 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	y population			
					4 per 100	2 more per 100 (1 fewer to 6 more)			

		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).
ferenc	es:			
1.				per, Joseph R, Israel, Robert J. Randomized, double-blind trial of oral d constipation in patients with chronic noncancer pain. Pain Practice;
2.	Michna, Edward, B Bruce. Subcutaned	us methylnaltr	exone for treatment	Tzanis, Evan, Manley, Amy, Zhang, Haiying, Iyer, Shrividya, Randazzo, t of opioid-induced constipation in patients with chronic, he Journal of Pain; 2011.
3.	Thomas, Jay, Karve Nancy, Kremer, Alt	er, Sloan, Coone on B, Israel, Ro	ey, Gail Austin, Chan bert J. Methylnaltre	nberlain, Bruce H, Watt, Charles Kevin, Slatkin, Neal E, Stambler, exone for opioid-induced constipation in advanced illness. New
4.	Donna S, Stephens	nas, Jay, Lipma on, Richard, Po	n, Arthur G, Wilson, ortenoy, Russell, Star	George, Boatwright, Michelle L, Wellman, Charles, Zhukovsky, mbler, Nancy. Methylnaltrexone for treatment of opioid-induced
5.	Portenoy, Russell H Gunten, Charles F,	K, Thomas, Jay, Israel, Robert J	Boatwright, Michele J. Subcutaneous met	l of Supportive Oncology; 2009. e L Moehl, Tran, Diep, Galasso, Frank L, Stambler, Nancy, Von thylnaltrexone for the treatment of opioid-induced constipation in mized, parallel group, dose-ranging study. J Pain Symptom Manage;
6.	Bull, Janet, Wellma subcutaneous met	hylnaltrexone i	in patients with adva	ett, Andrew C, Paterson, Craig, Forbes, William P. Fixed-dose anced illness and opioid-induced constipation: results of a el extension. Journal of Palliative Medicine; 2015.
planati	ons:			
a.	Some trials include methylnaltrexone		and cancer patients l	but some do not. Different doses and formulations of
b. c.	A pooled effect est mg SC daily dose a more with 150 mg	timate could no nd MD 0.60 wi . The Portenoy	ot be calculated. The th the 12 mg SC qod	Il difference (defined as a number needed to treat of 10 per 100). e mean change in RFBM frequency follows: (Michna) 1.60 more 12 I dose: (Rauck) MD 0.5 more with 300 mg and 450 mg, and MD 0.1 I because it was a combined one-week RCT and three-week open- ded.
d.	•			nate or important difference.
e.		•	for both benefit an	d harm.
f.	Few events report	ed.		
		et al., 2019) not	ted that PAMORAS s	should be avoided in patients with conditions that compromise the
e AGA	guideline (Crockett e			
			tial for serious witho	drawal or reversal of anesthesia.
			tial for serious witho	drawal or reversal of anesthesia.

Certainty of evidence What is the overall certainty of the		
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 abo	ut 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 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	e and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 require	ements (costs)?						
JUDGEMENT	RESEARCH EVIDENCE AD						
 Large costs Moderate costs Negligible costs and savings Moderate savings Large savings Varies Don't know 	The AGA guideline for opioid-induced consolution other agents, but the subcutaneous admined in a National Institute for Health and Care estimated annual drug costs for three regist £12.52. Source: GoodRx: www.goodand discount cards. 6-24-1	istration may have an a Excellence (NICE) costir mens were naloxegol, £ odrx.com (Drug price co	dvantage in some clinical situat	ions. -induced constipat altrexone, £1,284.	tion (2015), 05; and bisacodyl,	The par bowel r the prio duratio treatmo of the c	
	Drug	Product	Lowest Pittsburgh-area Price	Average Retail			
				Price			
	Lactulose	473 ml 10g/15ml of	Walmart (with GoodRx	\$33.72			

DITIONAL CONSIDERATIONS banel agreed that compared with a el regimen the cost was large based on rice of the therapy, as well as the ion of therapy needed (i.e. the ment would be required for the duration e opioid therapy.

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

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 s	ubcutaneous solution: Fror	n \$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 eviden	ce of resource requirements (costs)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very low o Low o Moderate o High • No included studies	No research evidence identified.	
Cost effectiveness Does the cost-effectiveness of the i	ntervention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 healt	th 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				
o No o Probably no • Probably yes o Yes o Varies o 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 imple	ement?					
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS				
o No o Probably no o Probably yes • Yes o Varies o 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
0	0	0	•	0

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 $\bigcirc \bigcirc \bigcirc \bigcirc$).

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

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

IN-TEXT CITED REFERENCES

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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

ASSESSIVIEINI							
Problem Is the problem a priority?							
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o 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 a	anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Trivial o Small o Moderate	Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolute effects	(95% CI)	The panel decided that the magnitude of the benefits was large, however, agreed that the comparison may overestimate the benefit of
 Large Varies Don't know 		(studies) Follow up	(GRADE)	ADE) (95% CI)	Risk with bowel regimen	Risk difference with naldemedine (0.2 mg)	naldemedine.
	SBM response (at least 3 SBMs/wk and an increase	1522 (4 RCTs) ^{1,2,3,4}	MODERATE ^{a,b}	ATE ^{a,b} (1.99 to	Study popula	tion	
	from baseline of 1 SBM/wk; follow-up 4-12 wk)			3.01)	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)	

	 a. The l² suggests some incordemonstrate benefit from b. Some trials conducted among c. The 95% CI may not included. Trial not conducted among 	the interventio ong persons wil le a clinically me	n. th cancer. eaningful differe		continuous nature of the c	outcome. All studies	
	ndesirable anticipated effects?						
JUDGEMENT O Large O Moderate	RESEARCH EVIDENCE Outcomes	Nº of participants		Relative effect	Anticipated absolute effects [*] (95% CI)		ADDITIONAL CONSIDERATIONS The panel determined the magnitude of the undesirable outcomes to be small.
• Small o Trivial o Varies o Don't know		(studies) Follow up	(GRADE)	(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	1522 (4 RCTs) ^{1,2,3,4}	⊕⊕⊕⊖ MODERATEª,♭	RR 2.44 (1.99 to 3.01)	Study po	pulation	
	SBM/wk; follow-up 4-12 wk)				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}	⊕⊕⊕⊖ MODERATEª,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 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		-	The mean change in BM frequency (change from baseline in mean	MD 0.95 more (0.57 more to 1.33 more)	

				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	2756 (6		RR 1.41 (1.17 to	Study po	pulation
wk)	RCTs) ^{1,2,3,4,5}		1.70)	11 per 100	4 more per 100 (2 more to 8 more)

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Explanations:

- a. The I² 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		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Very low Low Moderate High No included studies Values	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.
	out or variability in how much people value the main outcomes?	ADDITIONAL CONSIDERATIONS
Is there important uncertainty abo		ADDITIONAL CONSIDERATIONS The panel determined that there is probably no important uncertainty in how patients value the main outcomes.
Is there important uncertainty about JUDGEMENT O Important uncertainty or variability O Possibly important uncertainty or variability Probably no important uncertainty or variability O No important uncertainty or variability Balance of effects	RESEARCH EVIDENCE 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	The panel determined that there is probably no important uncertainty in how patients

 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention e Favors the intervention o Varies o Don't know 	n				The panel decided that the net benefit favors the intervention based on large treatment effect.
Resources requir					
How large are the resource re					
JUDGEMENT	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
 Large costs Moderate costs Negligible costs and savings 	and discount cards.		omparison among local pharmac	ies). Offers coupons	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
 Moderate savings Large savings 	Drug	Product	Lowest Pittsburgh-area Price	Average Retail Price	therapy needed (i.e., the treatment would be required for the duration of the opioid
o Varies o Don't know	Lactulose	473 ml 10g/15ml of lactulose oral solution	Walmart (with GoodRx discount card): \$12.14	\$33.72	therapy).
	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 (Movan	tik) 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 evide	nce of required resource				
	vidence of resource requirements (costs)	·			

o Very low o Low o Moderate o 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o 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 hea		
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.
Accontability		
Acceptability Is the intervention acceptable to k	key stakeholders?	

o No o Probably no ● Probably yes o Yes o Varies o 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				
o No o Probably no o Probably yes ● Yes o Varies o 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
0	0	0	0	•

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 $\oplus \oplus \oplus \bigcirc$).

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

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

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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 t believed to be dose dependent (Arthu			opioids and	d affects 40%–80% of patien	ts who are taking opioids; it is	
Desirable Effect How substantial are the de	Sirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Trivial • Small • Moderate	Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolute effe	cts* (95% CI)	The panel determined the magnitude of the desirable outcomes to be small.
o Large o Varies o Don't know		(studies) Follow up	(GRADE)	(95% CI)	Risk with bowel regimen	Risk difference with naloxegol + bowel regimen	
	SBM response rate (at least 3 SBMs/wk and an increase from	892 (2 RCTs) ¹	DOOO VERY LOW ^{a,b}	RR 1.43 (1.19 to	Study po	opulation	
	baseline of 1 SBM for at least 9 of 12 wk and for at least 3 of the final 4 wk)			1.71)	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	⊕⊕⊖⊖ LOWª	-	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	UERY 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}	UERY LOW ^{a,e}	RR 2.33 (1.62 to	Study po	opulation	
			VERTLOW	3.35)	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	DOW ^{a,f}	-	The mean pain score was 0 points	MD 0 points (0.11 lower to 0.12 higher)	
	constipation in patients w 2. Webster, L, Chey, WD, Tac naloxegol in patients with	ith noncancer k, J, Lappalain pain and opioi ses, Tummala,	pain. New Englar en, J, Diva, U, Sos id-induced consti Raj, Sostek, Marl	nd Journal o stek, M. Rar pation. Alin k. Treatmen	ndomised clinical trial: the lo nentary Pharmacology & The t with naloxegol versus place	ng-term safety and tolerability of	
	 that may also lead to consolute than opioids that may effect would change, where b. The CI crossed the threshold. c. The CI crossed the threshold. l² was 73% e. Data were pooled from the (Webster). This was rated 	tipation. Bowe ay lead to cons ther less or mo old of a clinical old of a clinical old of a clinical e Chey studies down for impr	el regimen had to stipation. Half of pre response to ti ly meaningful dif ly meaningful dif : as well as from a recision because	be stopped patients we ne therapy. ference (de ference (de a 4-week ph the CI cross	d at start of Chey trials. Trial ere laxative refractory. Difficu fined as a number needed to fined as an increase of at lea nase 2 study (Webster) and a ed the threshold of a clinical	ast 1 SBM). In open-label extension study	
Undesirable Effec							

0 Large 0 Moderate	Outcomes	Nº of participants	Certainty of the evidence	Relative effect	Anticipated absolute effects* (9	5% CI)	The panel determined the magnitude of the undesirable outcomes to be small.
• Small o Trivial o Varies o Don't know		(studies) Follow up	(GRADE)	(95% CI)	Risk with bowel regimen	Risk difference with naloxegol + bowel regimen	
	SBM response rate (at least 3 SBMs/wk and an increase from	892 (2 RCTs) ¹	⊕⊖⊖⊖ VERY LOWª,b	RR 1.43 (1.19 to	Study popula	tion	
	baseline of 1 SBM for at least 9 of 12 wk and for at least 3 of the final 4 wk)		VERTLOW	1.71)	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	OCO 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	DOM _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	UERY 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}	O OO VERY LOW ^{a,e}	RR 2.33 (1.62 to	Study popula	tion	
			VERT LOW-	3.35)	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: 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. 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. 	
	 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. I² 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. 	
Certainty of ev	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.	
	nty of the evidence of effects?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Very low Low Moderate High No included studies 		Indirectness led to serious uncertaint across all outcomes because the population likely did not reflect those cancer treatments with concomitant therapy that may have also led to constipation.
		·
Values		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Important uncertainty or variability o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability Balance of effects	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.
	rable and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		The panel agreed that there was some uncertainty about the net benefit because of previously noted concerns with indirectness.

	RESEARCH EVIDENCE				ADDITIONAL CONSIDERATIONS
 Large costs Moderate costs Negligible costs and savings 		IRx: www.goodrx.com (Drug price cards. 6-24-19 & 6-25-19	comparison among local pharma	cies). Offers coupons	The panel agreed that compared with a bowel regimen the cost was large based on the price of the therapy.
 Moderate savings Large savings 	Dr	ug Product	Lowest Pittsburgh-area Price	Average Retail Price	
o Carge Savings o Varies o Don't know	Lactulose	473 ml 10g/15ml o 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	
	Lubiproston		Giant Eagle (with GoodRx discount card. Restrictions apply): \$288.29	Not available	
	Methylnaltr	exone 90 tablets of Relist 150mg		\$2,084.62	
	Naldemedin	Symproic 0.2mg	Giant Eagle (with GoodRx coupon): \$319.21	Not available	
	Naloxegol (N	Movantik 25mg	Giant Eagle (with GoodRx coupon): \$360.23	\$459.39	
	Prucalopride	e 30 tablets of Motegrity 2mg	Giant Eagle (with GoodRx coupon): \$428.06	Not available	
	nce of required resour	rces	- Coupony: 3428.00		
		rces	Coupon): 3428.00		ADDITIONAL CONSIDERATIONS
What is the certainty of the evi	dence of resource requirements (co	rces			ADDITIONAL CONSIDERATIONS
What is the certainty of the ev JUDGEMENT • Very low • Moderate • High • No included studies Cost effectiveness	dence of resource requirements (co RESEARCH EVIDENCE No research evidence identified.	rces osts)?			ADDITIONAL CONSIDERATIONS

comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies • No included studies		Costly and effective when compared to bowel regimen based on indirect evidence from a UK-based cost- effectiveness study (Lawson et al., 20 Cost-effectiveness probably favors th intervention, but there are no include studies.
Equity What would be the impact o	n health equity?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Reduced Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know 	No research evidence identified.	The panel decided that some proport of the population lacks coverage and therefore would be disadvantaged. W naloxegol may have a better insuranc profile (more coverage available), it n still not be affordable for people with coverage.
Acceptability Is the intervention acceptabl	e to key stakeholders?	
	e to key stakeholders? RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Is the intervention acceptabl		ADDITIONAL CONSIDERATIONS
Is the intervention acceptabl JUDGEMENT o No o Probably no • Probably yes o Yes o Varies	RESEARCH EVIDENCE No research evidence identified.	ADDITIONAL CONSIDERATIONS
Is the intervention acceptabl JUDGEMENT o No o Probably no • Probably yes o Yes o Varies o Don't know Feasibility	RESEARCH EVIDENCE No research evidence identified.	ADDITIONAL CONSIDERATIONS ADDITIONAL CONSIDERATIONS ADDITIONAL CONSIDERATIONS

bly yes	
• Yes	
o Varies	
o Probably yes • Yes o Varies o 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

intervention

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

Conditional recommendation for the intervention

Strong recommendation for the intervention

0	0	0	•	0

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 $\oplus \bigcirc \bigcirc \bigcirc$).

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.

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

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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 prucalop constipation?	ride and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced
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
o No o Probably no o Probably yes • Yes o Varies o 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		

JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
 o Trivial Small o Moderate o Large o Varies o Don't know 	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% Cl)	Anticipated absolute effects* (95% CI)		The panel determined the magnitude of the desirable outcomes to be small.
					Risk with bowel regimen	Risk difference with prucalopride	
	SBM response (defined as an average of > or = to 3 SBMs/wk)	365 (2 RCTs) ^{1,2}	⊕○○○ VERY LOW ^{a,b,c,d}	RR 1.36 (1.08 to 1.70)	Study population		
	(follow-up:4 wk)				42 per 100	15 more per 100 (3 more to 29 more)	
	Change in SBM frequency	196 (1 RCT) ¹	UERY LOW ^{a,d,e}	-	MD 0.7 more with 4mg	2mg; MD 1.0 more with	
	Reduction in painful defecation/lack of straining - not reported	-	-	-	-	-	
	Stool consistency - not reported	_1	-	-	state prucalopride percentage of stoc consistency and de		
	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	OCO 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)	
	5	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:						

How substantial are the undesi
Undesirable Effect

на

JUDGEMENT	RESEARCH EVIDENCE	RESEARCH EVIDENCE					ADDITIONAL CONSIDERATIONS	
o Large o Moderate • Small o Trivial o Varies o Don't know	Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% Cl)	Anticipated absolute effects [*] (95% CI)		The panel determined the magnitude of the harms outcomes to be small based on the	
					Risk with bowel regimen	Risk difference with prucalopride	adverse events of abdominal pain and headache reported in Sloots (2010).	
	SBM response (defined as an average of > or = to 3 SBMs/wk) (follow-up:4	365 (2 RCTs) ^{1,2} ⊕⊖⊖ VERY LOW ^{a,b,c,d}		(1.08 to	Study population			
	wk)				42 per 100	15 more per 100 (3 more to 29 more)		
	Change in SBM frequency	196 (1 RCT) ¹	UERY LOW ^{a,d,e}	-	MD 0.7 more with 2m	g; MD 1.0 more with 4mg		
	Reduction in painful defecation/lack of straining - not reported	-	-	-	-	-		
	Stool consistency - not reported	_1				reported. Authors state d the percentage of stools ncy and decreased the		

				percentage of ha shown).	rdness of stools (data not
QoL improvement as measured by PAC-QoL (responder defined as	196 (1 RCT) ¹		RR 1.57 (0.88 to 2.80)	Study population	
patient achieving improvement or 1 or greater point on satisfaction subscale)		LOW ^{a,c,d,f}		18 per 100	10 more per 100 (2 fewer to 33 more)
AEs leading to treatment discontinuation	196 (1 RCT) ¹		RR 0.58 (0.22 to	Study population	
		LOW ^{a,c,d,f}	1.53)	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.
- 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 bloodbrain 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 evider		
What is the overall certainty of t	he evidence of effects?	ADDITIONAL CONSIDERATIONS
Very low O Low O Moderate O High O 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 a	bout or variability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Important uncertainty or variability o Possibly important uncertainty or variability Probably no important uncertainty or variability o 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 desir	able and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention 		The panel agreed that the net benefit is negligible based on the very low certainty in the evidence.

o Varies

o Don't know

Moderate costs

o Moderate savings
o Large savings
o Varies
o Don't know

O Negligible costs and savings

Resources required How large are the resource requirements (costs)? JUDGEMENT RESEARCH EVIDENCE • Large costs Source: GoodBx: www.set

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	Walmart (with GoodRx	\$33.72
	lactulose oral solution	discount card): \$12.14	
Linaclotide	30 capsules of	Giant Eagle (with GoodRx	\$518.24
	Linzess 145mcg	discount card): \$427.99	
Lubiprostone	60 capsules of	Giant Eagle (with GoodRx	Not available
	Amitiza 24mcg	discount card. Restrictions	
		apply): \$288.29	
Methylnaltrexone	90 tablets of Relistor	Giant Pharmacy (with	\$2,084.62
	150mg	GoodRx coupon): \$1686.16	
Naldemedine	30 tablets of	Giant Eagle (with GoodRx	Not available
	Symproic 0.2mg	coupon): \$319.21	
Naloxegol (Movantik)	30 tablets of	Giant Eagle (with GoodRx	\$459.39
	Movantik 25mg	coupon): \$360.23	
Prucalopride	30 tablets of	Giant Eagle (with GoodRx	Not available
	Motegrity 2mg	coupon): \$428.06	

ADDITIONAL CONSIDERATIONS

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

Door the cost offectiveness	of the intervention favor	the intervention or the comparison?
DOES THE COSPERIECTIVENESS	01 THE ITTELVENTION TAVOL	

JUDGEMENTRESEARCH EVIDENCEADDITIONAL CONSIDERATIONSO Favors the comparison o Probably favors the intervention o No research evidence identified.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.O Favors the intervention o Varies • No included studiesNo research evidence identified.No research evidence identified.			
o Probably favors the comparisonfor Health and Care Excellence UK technical appraisal (2010) was not direct enough to inform this recommendation for the U.S. environment.o Does not favor either the intervention or the comparisoninform this recommendation for the U.S. environment.o Probably favors the interventiono Probably favors the interventiono Favors the intervention o Varieso Favors the intervention	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	 o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies 	No research evidence identified.	for Health and Care Excellence UK technical appraisal (2010) was not direct enough to inform this recommendation for the U.S.

Equity

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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 		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
o No o Probably no • Probably yes o Yes o Varies o Don't know		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.

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
0	0	0	0	0

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.

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

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- 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 lubipros constipation?	tone and a bowel regimen rather than a bowel regimen alone be used in adult patients with cancer who have opioid-induced
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 NTERESTS:	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				
o No o Probably no o Probably yes • Yes o Varies o 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						

JUDGEMENT	RESEARCH EVIDENCE	RESEARCH EVIDENCE							
● Trivial o Small o Moderate	Outcomes	participants evid	Certainty of the evidence	e Relative effect (95% Cl)	Anticipated absolute effects* (95% CI)		The panel decided that the magnitude of the benefits was trivial.		
o Large o Varies o Don't know		(studies) Follow up	(GRADE)		Risk with bowel regimen	Risk difference with Lubiprostone			
	SBM response assessed with: ≥3 SBMs/wk for at least	868 (2 RCTs) ^{1,2}	⊕⊖⊖⊖ VERY LOW ^{a,b,c}	RR 1.15 (0.97 to	Study p	opulation			
	9 of 12 treatment weeks and at least ≥1 SBM improvement/wk for all weeks			1.37)	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) MD 0.10 less (0.78 les (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 char 0.861 in lubiprostone placebo arm; EQ-5D n baseline 0 in both arm	arm vs -0.695 in nedian change from			
	AEs leading to treatment discontinuation	1275 (3 RCTs) ^{1,2,3}	⊕⊕ ⊖⊖ LOW ^{a,h}	RR 2.13 (1.25 to	Study population				
				3.61)	3 per 100	3 more per 100 (1 more to 8 more)			
	References		1	1					
	References:								

	 Spierings, Egilius LH, Rauck, Ric lubiprostone in opioid-induced Jamal, M Mazen, Adams, Atoya for opioid-induced constipation Cryer, Byron, Katz, Seymour, V induced constipation in patient 	e							
	Explanations:	Explanations:							
Undesirable Effe	 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. 								
How substantial are the unde	esirable anticipated effects? RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS		
○ Large ○ Moderate	Outcomes	Nº of participants	Certainty of the evidence	Relative effect	Anticipated absolute	effects [*] (95% CI)	The panel determined the magnitude of the undesirable outcomes to be small.		
 Small Trivial Varies Don't know 		(studies) Follow up	(GRADE)		Risk with bowel regimen	Risk difference with Lubiprostone			
	SBM response assessed with: ≥3 SBMs/wk for at least	868 (2 RCTs) ^{1,2}		RR 1.15 (0.97 to	Study p	opulation			
	9 of 12 treatment weeks and at least ≥1 SBM improvement/wk for all weeks			1.37)	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) MD 0.10 less (0.78 les (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}		RR 2.13 (1.25 to		
			3.61)	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 opioidinduced 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 evident What is the overall certainty of the		
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 at	oout 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		
	ble and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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)?

RESEARCH EVIDENCE

JUDGEMENT

Large costs

Moderate costs

- o Negligible costs and savings
- Moderate savings
- Large savings
- o 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	Walmart (with GoodRx	\$33.72	
	lactulose oral	discount card): \$12.14		
	solution			
Linaclotide	30 capsules of	Giant Eagle (with GoodRx	\$518.24	
	Linzess 145mcg	discount card): \$427.99		
Lubiprostone	60 capsules of	Giant Eagle (with GoodRx	Not available	
	Amitiza 24mcg	discount card. Restrictions apply): \$288.29		
Methylnaltrexone	90 tablets of Relistor	Giant Pharmacy (with	\$2,084.62	
	150mg	GoodRx coupon): \$1686.16		
Naldemedine	30 tablets of	Giant Eagle (with GoodRx	Not available	
	Symproic 0.2mg	coupon): \$319.21		
Naloxegol (Movantik)	30 tablets of	Giant Eagle (with GoodRx	\$459.39	
	Movantik 25mg	coupon): \$360.23		
Prucalopride	30 tablets of	Giant Eagle (with GoodRx	Not available	
	Motegrity 2mg	coupon): \$428.06		

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.

Certainty of evidence of required resources

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

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

ADDITIONAL CONSIDERATIONS

The panel agreed that compared with a bowel regimen, the cost was large based on the price of the therapy.

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparisor

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

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.
		1

Acceptability Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o No o Probably no Probably yes o Yes o Varies o 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 im	Feasibility s the intervention feasible to implement?						
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS					
o No o Probably no o Probably yes • Yes o Varies o 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
0	0	0	0	Ο

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

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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
o No o Probably no o Probably yes ● Yes o Varies o 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		

JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Trivial ● Small o Moderate	Outcomes	Nº of participants	Certainty of the evidence	Relative effect	Anticipated absolute effe	ects* (95% CI)	The panel decided that the magnitude of the benefits was small.
o Large o Varies o Don't know	w (studies) Follow up w						
	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	UERY 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	Study population		
			MODERATE	0.73)	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		-	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		-	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}		-	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}		-	The mean change in SBM from baseline was 0	MD 2.11 higher (1.68 higher to 2.54 higher)	
	Cronin, Jacquelyn A, Cur abdominal bloating: a ra 3. Lembo, Anthony J, Kurtz Johnston, Jeffrey M. Effi 4. Lembo, Anthony J, Schn Lavins, Bernard J, Currie England Journal of Medi Explanations: a. Has not been published b. The 95% CI may not incl c. Small sample reported. d. Unknown details of bow	n, Shiff, Steven rrie, Mark G. Lir andomized, con t, Caroline B, M cacy of linaclot eier, Harvey A, , Mark G, Fitch, icine; 2011. in the peer-rev ude a meaning rel regimen dur	J, Lavins, Bernard haclotide in chroni trolled trial. PLoS acDougall, James ide for patients w Shiff, Steven J, Ku , Donald A. Two ra iewed literature. I ful difference.	J, Fox, Susan M ic idiopathic co One; 2015. E, Lavins, BJ, C ith chronic cor rtz, Caroline B, indomized tria Findings are fro riod.	 Λ, Jia, Xinwei D, Blakesley, R nstipation patients with mo urrie, Mark G, Fitch, Donald nstipation. Gastroenterology MacDougall, James E, Jia, λ Is of linaclotide for chronic o 	oderate to severe I A, Jeglinski, Brenda I, y; 2010. Kinwei D, Shao, James Z, constipation. New	
Undesirable Effects How substantial are the undesirabl	le anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERAT

0 Large 0 Moderate	Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolute eff	ects [*] (95% CI)	The panel determined the magnitude of the undesirable outcomes to be trivial.
o Small • Trivial o Varies o Don't know		(studies) Follow up	(GRADE)	(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	⊕⊕ ⊖⊖ LOWª	-	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		RR 0.12 (0.02 to	Study popu	llation	
			MODERATE ^{a,d}	0.73)	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		-	The mean increase over baseline by >1 CSBM/week was 0	MD 1.72 higher (1.18 higher to 2.52 higher)	

	 Lacy, Brian E, Sc Cronin, Jacquely abdominal bloat Lembo, Anthony Johnston, Jeffree Lembo, Anthony Lavins, Bernard England Journal Explanations: Has not been pub b. The 95% CI may c. Small sample rej d. Unknown detail e. Trials are condu persons with car Preliminary results published nausea for the groups: Place Diarrhea: 13/78 (16.67%), 2 	ney, Ron, Shiff, Stev n A, Currie, Mark G ing: a randomized, J, Kurtz, Caroline E M. Efficacy of lina J, Schneier, Harvey , Currie, Mark G, Fi of Medicine; 2011. blished in the peer- not include a mean ported. of bowel regimen cted among person ncer. ed on clinicaltrials.g ebo (n=78), Linaclo 4/87 (27.59%), 32/	ven J, Lavins, Bernard . . Linaclotide in chronic controlled trial. PLOS 0 . MacDougall, James I clotide for patients wi / A, Shiff, Steven J, Kur tch, Donald A. Two ra -reviewed literature. F ingful difference. during study time per s with chronic idiopat ov for NCT02270983, tide 145 micrograms (87 (36.78%)	, Fox, Susan M c idiopathic cc Dne; 2015. Lavins, BJ, C th chronic cor tz, Caroline B ndomized tria indings are fr iod. nic constipatio	The mean change in CSBM from baseline was 0 The mean change in SBM from baseline was 0 results/NCT02270983 A, Jia, Xinwei D, Blakesley, Rick E urrie, Mark G, Fitch, Donald A, J hstipation patients with moderation. urrie, Mark G, Fitch, Donald A, J nstipation. Gastroenterology; 20 MacDougall, James E, Jia, Xinw Is of linaclotide for chronic cons om NCT02270983. on, not opioid-induced constipat Illowing incidence of adverse even haclotide 290 micrograms (n=87)	ate to severe eglinski, Brenda I, 10. ei D, Shao, James Z, tipation. New ion and not among	
			. ,				
	Nausea: 4/78 (5.13%), 0/87	(0.00%), 1/87 (1.15	5%)				
Certainty of evi What is the overall certain	idence nty of the evidence of effects?						

 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 abo	ut 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 desirab	le and undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 		
Resources required How large are the resource require	ements (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 Retai 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

The panel agreed that compared with a bowel regimen the cost was large based on the price of the therapy.

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.

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low o Moderate o 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

 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies No included studies 	No research evidence identified.	
Equity What would be the impact on heal	Ith 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 k	ey stakeholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes • Yes o Varies o Don't know	No research evidence identified.	
Feasibility Is the intervention feasible to impl	ement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

O NO	No research evidence identified.	
o Probably no		
o Probably yes		
• Yes		
o 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
0	0	0	0	0

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.

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 JUDGEMENT RESEARCH EVIDENCE ADDITIONAL CONSIDERATIONS o No Constipation occurs in almost 60% of patients with cancer (McMillan et al., 2013). o Probably no o Probably yes • Yes o Varies o Don't know **Desirable Effects** How substantial are the desirable anticipated effects? JUDGEMENT RESEARCH EVIDENCE ADDITIONAL CONSIDERATIONS

Frivial Small Moderate	Outcomes	№ of participants	Certainty of the evidence	effect	Anticipated absolu	ute effects [*] (95% CI)	The panel decided that the magnitude o benefits was moderate.		
o Large o Varies o Don't know		(studies) Follow up	(GRADE)	(95% CI)	Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives + lifestyle factors			
	SBM response (defined as ≥3 SBMs/wk or ≥3	1411 (7	⊕⊕⊕ ⊖ MODERATEª	RR 2.24 (1.93 to	St	udy population			
	stools/wk)	RCTs) ^{1,2,3,4,5,6,7}	MODENATE	2.61)	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)	St	udy population			
					55 per 100	29 more per 100 (10 more to 53 more)			
	Stool consistency improvement	269 (3 RCTs) ^{2,3,4}	3 RCTs) ^{2,3,4}	RR 1.55 (1.33 to 1.82)	Study population				
	assessed with: measured as hard/pellet stools	as			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	St	udy population	-		
				7.89)	26 per 1,000	66 more per 1,000 (16 more to 179 more)			
	References:	<u>.</u>							
	 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. Corazziari, E, Badiali, D, Habib, FI, Reboa, G, Pitto, G, Mazzacca, G, Sabbatini, F, Galeazzi, R, Cilluffo, T, 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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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. Check Ford article for I ² of 100% 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.	
	Check Ford article for I ² of 100% Rated down for indirectness because of difference in complementary treatments. Tarumi participants used laxatives

o Large o Moderate • Small o Trivial o Varies o Don't know	Outcomes	№ of participants	Certainty of the evidence	Relative effect	Anticipated absolu	ute effects [*] (95% CI)	The panel determined the magnitude of t undesirable outcomes to be small.
		(studies) Follow up	(GRADE)	(95% CI)	Risk with lifestyle factors	Risk difference with osmotic or stimulant laxatives + lifestyle factors	
	SBM response (defined as ≥3 SBMs/wk or ≥3	1411 (7	⊕⊕⊕ ⊖ MODERATEª	RR 2.24 (1.93 to	St	tudy population	
	stools/wk)	RCTs) ^{1,2,3,4,5,6,7}		2.61)	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}	DOW ^{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}	⊕⊕⊕⊖ MODERATEª	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	269 (3 RCTs) ^{2,3,4}	⊕⊕⊕⊖ moderateª	RR 1.55 (1.33 to 1.82)	Study population		
	assessed with: measured as hard/pellet stools				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}	-s) ^{10,11,9} MODERATE ^c	RR 3.55 (1.60 to	Study population		
			WODEIXIE		26 per 1,000	66 more per 1,000 (16 more to 179 more)	
	References: 1. Wesselius-De Caspa lactulose syrup: res 2. Corazziari, E, Badial volume isosmotic p						

	 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. 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. 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. Mueller-Lissner, Stefan, Kamm, Michael A, Wald, Arnold, Hinkel, Ulrika, Koehler, Ursual, Richter, Erika, Bubeck, Jürgen. Multicenter, A-week, double-bind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. Am J Gastroenterol; 2010. Kamm, Michael A, Mueller-Lissner, Stefan A, Wald, Arnold, Hinkel, Ulrika, Koehler, Ursual, Richter, Erika, Bubeck, Juergen. S1321 stimulant laxatives are effective in chronic constipation: multi-center, 4-week, double-blind, randomized, placebo- controlled trial of bisacodyl. Gastroenterology; 2010. Baldonedo, YC, Lugo, E, Urcategui, AA, Guelrud, M, Skornicki, J. Evaluation and use of polyethylene glycol in constipated patients. GEN; 1991. 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; 2011. Nakajima, Atsushi, Shinbo, Kazuhiko, Oota, Akira, Kinoshita, Yoshikazu. Polyethylene glycol 3350 plus electrolytes for chronic constipation: a 2-week, randomized, placebo-controlled study with a 52-week open-label extensi	
Certainty of evidence What is the overall certainty of the ev	vidence 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 o	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 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 a	ind undesirable effects favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 requirement	ents (costs)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

 o Large costs o Moderate costs Negligible costs and savings 		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).		
o Moderate savings		Medication	Product	Price	
o Large savings o Varies		Bisacodyl (Dulcolax)			
o Don't know		Docusate sodium	Tablets, 5 mg, 100 Ct 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	
JUDGEMENT o Very low	RESEARCH EVIDE	-	ADDITIONAL CONSIDERATIONS		
o Low o Moderate					
HighNo included studies					
No included studies Cost effectiveness	intervention favor the	intervention or the comparison?			
No included studies	intervention favor the RESEARCH EVIDE				ADDITIONAL CONSIDERATIONS
• No included studies Cost effectiveness Does the cost-effectiveness of the	RESEARCH EVIDE	NCE			ADDITIONAL CONSIDERATIONS
No included studies Cost effectiveness Does the cost-effectiveness of the JUDGEMENT Favors the comparison O Probably favors the comparison O Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies	RESEARCH EVIDE	NCE			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 O 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 implem	nent?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o No o Probably no o Probably yes • Yes o Varies o 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
0	0	0	•	0

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 $\oplus \oplus \oplus \bigcirc$).

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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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

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-

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

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

RECOMMENDATION

4

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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 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 **INTERESTS:** 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

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						
Desirable Effe How substantial are the	Cts desirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
• Trivial • Small • Moderate	(studies)	№ of participants	Certainty of the s evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	[*] (95% CI)	The panel decided that the magnitude of the benefits was trivial.
o Large o Varies o Don't know		(studies) Follow up			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}	UERY 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	485 (3 RCTs) ^{1,2}	UERY LOW ^{3,4,a,b,c,f,g,h}	RR 0.53 (0.27 to 1.02)	Study population		
	weeks				108 per 1,000	51 fewer per 1,000 (79 fewer to 2 more)	
	safety of deep needling an 2. Lee, Hye-Yoon, Kwon, Oh-	d shallow needl lin, Kim, Jung-Eu uncture for fun	ing for functional cons In, Kim, Mikyeong, Kim	tipation: a m n, Ae-Ran, Pai	i, Yuying, Ye, Yongming, Liu, Jun, ulticenter, randomized controlle k, Hyo-Ju, Cho, Jung-Hyo, Kim, J sham-controlled pilot trial. BMC	d trial. Medicine; 2014. oo-Hee, Choi, Sun-Mi.	

	 Zheng, H, Liu, Z-S, Zhang chronic functional consi 4. Liu, Yi-qun, Sun, Shuai, J Wrist-ankle acupunctur trial. Chinese Journal of 						
	Explanations:						
	 a. High risk of bias for blin allocation. b. Trial conducted among c. Lee 2018 compares acu (n=112) vs. control (lact (mosapride; n=170). d. The 95% CI may not incide. One trial, Shin 2018, con (95% CI: 0.67, 1.65) at 6 be calculated. f. One trial, Liu 2015, control adverse events in either functional constipation in the control (mosapride, Small sample reported. h. The 95% CI includes the 	t					
Undesirable Ef	fects undesirable anticipated effects?						
JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
o Large o Moderate	Outcomes	Nº of participants	Certainty of the evidence	Relative effect	Anticipated absolute effects	s* (95% CI)	The panel decided that the magnitude of the harms was trivial.
 O Small ● Trivial O Varies O Don't know 		(studies) Follow up	(GRADE)	(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}	OCO VERY LOW ^{a,b,c,d}	-	The mean spontaneous bowel movement was 0	MD 0.85 higher (0.59 higher to 1.1 higher)	

The mean Bristol Stool Scale MD 0.41 higher

(0.26 higher to 0.55

higher)

705

 $\oplus \oplus \bigcirc \bigcirc$

LOW^{a,b,c,d,e}

_

was 0

Bristol Stool Scale

softer feces)

Scale from: 1 to 7 (higher score = (4 RCTs)^{2,3}

ollow up: range 9 weeks to 12 weeks							
Adverse events follow up: range 9 weeks to 16	485 (3 RCTs) ^{1,2}	$\Psi(\Lambda\Lambda)$		St	Study population		
weeks				108 per 1,000	108 per 1,000 51 fewer per 1,000 (79 fewer to 2 more)		
eferences:							
 safety of deep needling and shallow needling for functional constipation: a multicenter, randomized controlled trial. Medicine; 2014. 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. 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. 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. 							
planations: a. High risk of bias for blir	ding of particin	ants and personne	el in the Wu 20)14 study - both participa	ants 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 needlin, (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). 						ing	
d. The 95% CI may not inc			trooter t.f.	concerned	a constinution constant MD 440		
	-				g constipation reported MD = 1.16 mean change from baseline could r	not	
 (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 event in the control (mosapride) arm (n=170). 					ents		
		oth harm and ben	efit.				
g. Small sample reported.					other		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• Very low o Low o Moderate o High o No included studies		Overall, the certainty in the evidence of effects for acupuncture for the treatmen 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 i the lack of blinding in some studies.
Values Is there important uncerta	inty about or variability in how much people value the main outcomes?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Important uncertainty 	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	The panel determined that there is probably no important uncertainty in
or variability o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability	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.	how patients value the main outcomes.
o Possibly important uncertainty or variability • Probably no important uncertainty or variability o No important uncertainty or variability Balance of effect	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.	

 o Probably favors the comparison Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o Don't know 	ired	
How large are the resourc		
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.
	dence of required resources e evidence of resource requirements (costs)?	
What is the certainty of th		
What is the certainty of th JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	RESEARCH EVIDENCE No research evidence identified.	ADDITIONAL CONSIDERATIONS
JUDGEMENT o Very low o Low o Moderate o High • No included studies Cost effectiven	No research evidence identified.	ADDITIONAL CONSIDERATIONS

 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies No included studies 	No research evidence identified.	
Equity What would be the impac		
JUDGEMENT • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • Varies • Don't know	RESEARCH EVIDENCE No research evidence identified.	ADDITIONAL CONSIDERATIONS 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 accept	able 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 feasibl	e to implement?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o No	No research evidence identified.	
Probably noProbably yes		
 Probably yes 		
o Yes		
0 Varies 0 Don't know		
o 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		

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
0	0	0	0	0

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.

No monitoring and evaluation considerations.

Research priorities

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

IN-TEXT CITED REFERENCES

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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-opioidrelated 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 Constipation occurs in almost 60% of patients (McMillan et al., 2013) with cancer. o No o Probably no o Probably yes • Yes o Varies o Don't know **Desirable Effects** How substantial are the desirable anticipated effects? JUDGEMENT RESEARCH EVIDENCE ADDITIONAL CONSIDERATIONS

o Trivial o Small • Moderate	Outcomes	Nº of participants	Certainty of the evidence	Relative effect	Anticipated absolu	te effects [*] (95% CI)	The panel determined the magnitude o the desirable outcomes to be moderate
o Large o Varies o Don't know		(studies) Follow up	(GRADE)	(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	Stu	dy population	
				4.57)	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}	UERY 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}	UERY 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}	UERY 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	1075 (1 RCT) ¹	Dery Low ^{a,b,d,e}	RR 0.45 (0.14 to 1.44)	Study population		
	follow up: 8 weeks				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	Study population		
				1.02)	340 per 1,000	51 fewer per 1,000 (98 fewer to 7 more)	
	References:	1	1	1		,, ,	
	 Liu, Zhishun, Yan, Shiyan, Acupuncture for chronic 					nbin, Fu, Lixin, Sun, Jianhua. l Medicine; 2016.	

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	 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. 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.
Exp	lanations:
	 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
o Large o Moderate o Small • Trivial o Varies o Don't know	Outcomes	Nº of participants	(GRADE)	Relative effect (95% Cl)	Anticipated absolute effects [*] (95% CI)		The panel determined the magnitude of the undesirable outcomes to be trivial.
		(studies) Follow up			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)	Stud	/ 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}	UERY 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	1075 (1 RCT) ¹	000	RR 0.45 (0.14 to 1.44)	Stu	dy population	
	follow up: 8 weeks		VERY LOW ^{a,b,d,e}		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		RR 0.85 (0.71 to	Stu	Idy population	
				1.02)	340 per 1,000	51 fewer per 1,000 (98 fewer to 7 more)	
	References: 1. Liu, Zhishun, Yan, Shiyan,			-			
	 Liu, Zhishun, Yan, Shiyan, Acupuncture for chronic Wu, Xiao, Zheng, Cuihong Wei. Electroacupuncture Complementary and Alte Da, Nili, Wang, Xinjun, Liu Yangyang. The effectiven Evidence-Based Complem Explanations: Trial conducted among p Liu 2016 compares 28 set 	severe functio g, Xu, Xiaohu, for functional ernative Medic u, Hairong, Xu, less of electroa mentary and A ersons withou ssions of EA (n EA (n=58) vs. n ude a meaning	nal constipation: Ding, Pei, Xiong, F constipation: a n ine; 2017. , Xiuzhu, Jin, Xun, acupuncture for f Iternative Medici Iternative Medici es36) vs. shallow nosapride (n=67). ful difference.	a randomize Fan, Tian, Ma nulticenter, Chen, Chao unctional co ne; 2015. ctional cons (EA (n=539) Da 2016 co	ed trial. Annals of Internan, Wang, Ying, Dong, Ha randomized, control tria ming, Zhu, Dan, Bai, Jieji nstipation: a randomize tipation. . Wu 2017 compares 16	al Medicine; 2016. aoxu, Zhang, Mingmin, Wang, I. Evidence-Based	
Certainty of evider What is the overall certainty of	 Liu, Zhishun, Yan, Shiyan, Acupuncture for chronic Wu, Xiao, Zheng, Cuihong Wei. Electroacupuncture Complementary and Alte Da, Nili, Wang, Xinjun, Liu Yangyang. The effectiven Evidence-Based Complen Explanations: Trial conducted among p Liu 2016 compares 28 set (n=65) vs. weak current E The 95% CI may not includ The 95% CI includes the p Few events reported. 	severe functio g, Xu, Xiaohu, for functional ernative Medic u, Hairong, Xu, less of electroa mentary and A ersons withou ssions of EA (n EA (n=58) vs. n ude a meaning	nal constipation: Ding, Pei, Xiong, F constipation: a n ine; 2017. , Xiuzhu, Jin, Xun, acupuncture for f Iternative Medici Iternative Medici es36) vs. shallow nosapride (n=67). ful difference.	a randomize Fan, Tian, Ma nulticenter, Chen, Chao unctional co ne; 2015. ctional cons (EA (n=539) Da 2016 co	ed trial. Annals of Internan, Wang, Ying, Dong, Ha randomized, control tria ming, Zhu, Dan, Bai, Jieji nstipation: a randomize tipation. . Wu 2017 compares 16	al Medicine; 2016. aoxu, Zhang, Mingmin, Wang, I. Evidence-Based ng, Zhang, Xiaoqing, Zou, d, controlled, clinical trial. sessions of strong current EA	

• Very low o Low o Moderate o High o 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 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
 o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies o 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 requiren	nents (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.
· · · · · · · · · · · · · · · · · · ·	of required resources	
What is the certainty of the evidence	e of resource requirements (costs)?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 o Very low o Low o Moderate o High No included studies 	No research evidence identified.	
Cost effectiveness Does the cost-effectiveness of the in	itervention favor the intervention or the comparison?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
 Favors the comparison Probably favors the comparison Does not favor either the 	No research evidence identified.	
 intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies No included studies 		
 Probably favors the intervention Favors the intervention Varies 	n equity?	

 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 kee	stakeholders?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes o Yes • Varies o 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 imple	nent?	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no • Probably yes o Yes o Varies o 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
0	0	0	0	0

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).

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

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