Gastroenterology 2019;156:229–253

American Gastroenterological Association Institute Technical Review on the Medical Management of Opioid-Induced Constipation

Brian Hanson,[1,*] **Shazia Mehmood Siddique**,[2,*] Yolanda Scarlett,[3] and Shahnaz Sultan,[1] on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee

[1]Division of Gastroenterology and Hepatology, University of Minnesota and Minneapolis Veterans Affairs Healthcare System, Minneapolis, Minnesota; [2]Division of Gastroenterology and Liver Disease, University of Pennsylvania, Philadelphia, Pennsylvania; and [3]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina

Opioid medications are some of the most commonly prescribed medications for acute and chronic pain in the United States. In 2016, nearly 92 million US adults, or approximately 38% of the population, were prescribed opioids, according to results from the National Survey on Drug Use and Health.[1] As a result of the widespread use of opioids, the prevalence of opioid-related adverse effects has increased markedly. Gastrointestinal (GI) side effects, such as nausea, vomiting, gastroesophageal reflux, gastroparesis, anorexia, bloating, abdominal spasms, and constipation, are common and collectively referred to as opioid-induced bowel dysfunction. Of these adverse effects, opioid-induced constipation (OIC) is the most problematic manifestation of opioid-induced bowel dysfunction, as patients rarely develop a tolerance to OIC.[2] Up to one-third of patients may miss or decrease their analgesic medications due to GI side effects, leading to untreated chronic pain and a reduction in health-related quality of life (QOL).[3,4] The true prevalence of OIC is unknown, given the failure to recognize OIC as an adverse effect of chronic opioid use and variability in criteria used to diagnose OIC. Reported prevalence rates in the published literature range markedly, from 22% to 81%, depending on the population studied.[5–7] Health care utilization and health care costs are higher in patients with OIC. In a retrospective analysis of Medicaid patients with non-cancer pain and OIC, the annual median incremental cost increase over similar patients without constipation was $4000.[8] Similar findings have been observed in Medicare patients, privately insured patients, and patients with cancer-related pain.[9–12]

Mechanistically, OIC is mediated by activation of peripheral μ-, δ-, and κ-opioid receptors in the enteric nervous system within the GI tract. Opioid agonists bind (primarily) to the μ-opioid receptor and lead to a decrease in peristaltic activity and a reduction of mucosal secretions throughout the GI tract, resulting in delayed gastric emptying, slowed intestinal transit, and increased intestinal fluid absorption. In addition, opioids can cause disordered anal sphincter function.[13]

Until 2015, consistent criteria were not systematically used in clinical trials to make the diagnosis of OIC.[14] A multidisciplinary working group proposed a consensus definition of OIC to help inform clinical trials and defined OIC as "a change from baseline bowel habits when initiating opioid therapy that is characterized by any of the following: reduced bowel movement (BM) frequency, development or worsening of straining to pass BMs, a sense of incomplete rectal evacuation or harder stool frequency."[14] The Rome IV criteria recently defined OIC as new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include 2 or more of the following >25% of the time: straining, lumpy/hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecations, or <3 SPMs per week, with loose stools rarely present without the use of laxatives.[15,16]

Treatment of OIC requires a multifaceted approach, which includes non-pharmacologic (dietary and lifestyle modifications) and pharmacologic approaches to reduce OIC symptoms, while ensuring adequate analgesia. Several new pharmacologic therapies have been developed in recent years, many of which have unique mechanisms of action targeted specifically to the treatment of OIC. In this review, we focus on the pharmacologic management of OIC using laxatives, selective 5-HT serotonin receptor agonists, chloride channel activators, and peripherally acting μ-opioid receptor antagonists (PAMORAs).

Objectives

This technical review accompanies and informs the American Gastroenterological Association (AGA) guideline

*Authors share co-first authorship.

Abbreviations used in this paper: **AE, adverse event; AGA, American Gastroenterological Association; BFI, Bowel Function Index; BM, bowel movement; BSFS, Bristol Stool Form Scale; CI, confidence interval; FDA, Food and Drug Administration; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; OIC, opioid-induced constipation; PAC-QOL, Patient Assessment of Constipation-Quality of Life; PAMORA, peripherally acting μ-opioid receptor antagonist; PEG, polyethylene glycol; PICO, population, intervention, comparator, and outcomes; PROM, patient-reported outcome measure; QOL, quality of life; RCT, randomized controlled trial; RFBM, rescue-free bowel movement; RR, relative risk; SBM, spontaneous bowel movement.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.08.018

AGA SECTION

on the pharmacologic management of OIC and provides evidence-based information to guide patients, clinicians, and policy makers in the management of adults with OIC. The target audience for this technical review (and accompanying guideline) is gastroenterologists consulted specifically for the management of OIC. As a result, this review does not address strategies such as opioid switching, opioid rotation, opioid dose reduction, or the use of novel fixed-ratio opioid-containing combination medications, as these are outside the scope of practice of most gastroenterologists. Furthermore, this guideline does not systematically address the prevention of OIC.

The technical review panel included gastroenterologists with clinical and research expertise, a methodologist with experience in evidence appraisal and guideline development, and 2 trainee methodologists. Financial and nonfinancial conflicts of interest of all participants were managed according to AGA policies and no member of this technical review panel had any conflicts of interest. The panel held periodic telephone conferences and one face-to-face meeting to conduct this work. Methods for deriving focused clinical questions, systematically reviewing and rating the quality of evidence for each outcome, and rating the overall quality of evidence were based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, which has been described in more detail previously.[17]

Methods

Rapid Review Process

In light of the recent development of several new agents for the management of OIC, the AGA clinical guideline committee proposed this topic as a rapid review with the goal of reducing the time from topic proposal to guideline publication and expediting the process. While the panel generally followed the steps outlined by the AGA clinical guideline committee, the following "shortcuts" were taken: (1) initial review of titles and abstracts was done by 1 of 3 authors (BH, SS, SS) and only the excluded titles and abstracts were reviewed by a second author. This reduced the title and abstract review process time, but did not reduce the sensitivity for full-text review; (2) data extraction for each study was performed by only 1 of 3 authors (BH, SS, SS); and (3) risk of bias assessment was initially determined by a single author (BH or SS) and when concerns arose, a second author was consulted (SS).

Formulation of Clinical Questions and Determining Outcomes of Interest

Using the PICO format, which frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcomes (O), the panel prioritized the questions to be addressed by this guideline (see Table 1). The final set of questions and statements was approved by the AGA Governing Board.

Members of the technical review and guideline committee selected patient-important outcomes for each question a priori. The panel rated the relative importance of each outcome for decision making on a scale of 1–10. Outcomes receiving a score

Table 1.PICO Questions

Population(s)	Intervention(s)	Comparator	Outcome(s) a priori	Studies
Adults with OIC (ambulatory, adult outpatients on chronic opioids with constipation defined by clinical symptoms [<3 SBMs], physician diagnosis, or other study-specific diagnostic criteria)	Osmotic or stimulant laxatives Osmotic: PEG PAMORAs: naloxegol, alvimopan, naldemedine, methylnaltrexone Secretagogues: lubiprostone Selective 5HT4 agonist: prucalopride	Placebo or usual care or active comparator	SPMs, number per week Lack of straining during defecation BM within prespecified time frame, time to laxation RFBMs Reduction/cessation of laxatives Reduction in painful defecation Stool frequency Stool consistency (BSFS) PAC-QOL PROM AEs leading to treatment discontinuation (ie, allergic reactions, death, cardiac events, abdominal pain, diarrhea, incontinence, nocturnal BMs) Reversal of analgesia or exacerbation of chronic pain Cost-effectiveness	RCT Observational studies (for the harm outcome) Systematic review/meta-analysis

of 7–10 were considered critical (for decision making), 4–6 as important (for decision making), and 1–3 less important (for decision making). This initial list of outcomes was then further refined during the evidence review by the technical review panel. Ultimately, the following outcomes were considered critical or important for decision making and therefore included in the evidence profiles: spontaneous bowel movement (SBM) response using the responder definition—defined as ≥3 SBMs/wk and ≥1 SBM/wk over baseline for a predefined number of weeks (critical); increase in stool frequency (important); improvement in stool consistency (Bristol Stool Form Scale) (important); reduction in painful defecation/lack of straining (important); QOL (important); and adverse events (AEs) leading to treatment discontinuation (important). One additional outcome was included for methylnaltrexone: laxation response (important), which was defined as a spontaneous or rescue-free bowel movement within 4 hours of first dose of intervention.

Outcome Definitions

Over the last few decades, clinical trials for constipation and OIC have changed their efficacy end points. Earlier trials included end points such as increase in BM frequency (measured as change from baseline to the end of the treatment period) or time to laxation (measured in hours). Newer trials placed more emphasis on SBMs, denoting BMs without intake of any "rescue" medication (such as a laxatives) 24 hours before the BM and combined end points that capture longer-term sustained improvements in SBMs over a defined time period. This is consistent with outcomes used in studies of pharmacologic therapies for chronic idiopathic constipation. Based on guidance from the Food and Drug Administration (FDA) and European Medicines Agency, contemporary OIC clinical trials primarily use a "responder analysis" as their primary end point, where response is defined as ≥3 SBMs and ≥1 SBM/wk over baseline for a specified duration or number of weeks (eg, at least 75% of the total duration of the study or for 9 of 12 weeks). A BM was classified as spontaneous if no laxative had been used in the prior 24 hours. This responder outcome defines a minimum SBMs per week for response (minimum threshold of at least 1 additional SBM over baseline), excludes BMs achieved with rescue laxatives, and specifies that the improvement must be sustained to establish clinically meaningful improvement. If the FDA responder outcome was not available, an effort was made to determine whether the reported study outcome was similar enough to the responder definition to inform the pooled effect estimate. For example, rescue-free bowel movement (RFBM), defined as ≥3 RFBMs/wk for the duration of the study (without an accompanying increase in weekly RFBMs) or ≥3 RFBMs/wk and an increase of ≥1 RFBM/wk from baseline for at least 3 of the first 4 weeks, was used for some studies of methylnalteroxe.

Additional patient-important outcomes included improvement in stool consistency, reduction in straining, or lack of painful defecation. Stool consistency was assessed using the Bristol Stool Form Scale (BSFS) and reduction/lack of straining or painful defecation were assessed on a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining); mean differences (MDs) in change from baseline for the intervention and placebo arms were reported. The majority of trials did not provide specific cutoffs or define a minimal clinically important difference in outcomes for these scales. Furthermore, no responder definition was used to analyze differences between groups. QOL was frequently assessed using the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire, which comprises 28 questions and 4 subscales, including physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction. Each element is scored on a scale of 0–4 (least to the greatest effect), and higher scores indicate reduced QOL. A 1-point improvement in PAC-QOL scores has been validated as a relevant definition of response for treatment group comparisons.[18,19]

While our initial list of relevant outcomes included patient-reported outcome measures (PROMs), such as the Patient Assessment of Constipation-Symptoms, Bowel Function Index (BFI), and Bowel Function Diary, few published clinical trials utilized these outcomes consistently, limiting the ability to pool effects for these PROMs across studies.

The BFI has recently been endorsed as a tool to identify patients likely to benefit from OIC treatment.[20] This PROM draws from previously developed severity measures (Rome Criteria and Patient Assessment of Constipation-Symptoms).[21] Developed to evaluate the effects of oxycodone prolonged release (PR)/naloxone PR, an opioid agonist/antagonist combination for chronic pain, BFI has been used in 7 randomized controlled trials (RCTs). BFI has also been validated in one small non-intervention trial.[22] BFI measures a sense of incomplete evacuation, ease of defecation, and personal judgment of the patient regarding constipation over the previous 7 days. Using a numeric analogue scale, a score of 0–100 is assigned by the patient to each of the 3 components. Higher scores indicate more severe symptoms. These 3 scores are then averaged to achieve the final BFI score. Scores ≤28.8 have been demonstrated to include 95% of all non-constipated patients. A change in BFI ≥12 has been proposed as a clinically meaningful change.[23]

Recent consensus recommendations (2014) recommend the BFI as a simple, relevant, and easy-to-administer tool to identify individuals who may benefit from OIC therapy.[20] A score of ≥30 was selected by this panel based on the fact that 95% on non-constipated patients would fall in the range below this number. BFI may identify patients with OIC and provide an easy-to-use measure for patient selection and monitoring for response, but it must be noted it was not developed for this purpose, and it was validated from an enriched population of patients enrolled in clinical trials for the treatment of OIC.

For SBM response, the threshold for a clinically meaningful benefit, based on consensus among panel members, was set at a number needed to treat of approximately 10, that is, 10 more responders for every 100 treated patients compared to placebo. The threshold for clinically meaningful harm was set at a number needed to harm of approximately 5—5 more AEs leading to treatment discontinuation for every 100 treated patients compared to placebo. For outcomes such as improvement in stool consistency or reduction in straining/painful defecation, a non-contextualized approach relying on statistical significance was used to inform judgments about the quality or certainty of the evidence.[24]

Literature Search/Search Strategy and Study Selection

A search of the medical literature was conducted by an information specialist using the following databases: MEDLINE (1950 to February 2017), EMBASE and EMBASE Classic (1947 to February 2017), and the Cochrane Central Register of Controlled Trials, and health technology assessments to identify RCTs using a combination of controlled vocabulary and text words. This search was updated to look for additional studies that were published from February 2017 to May 2018 (just after the public comment was terminated). Trials examining the effect of pharmacologic therapies (laxatives, methylnaltrexone, naloxegol, alvimopan, naldemedine, prucalopride, and lubiprostone) in adult patients with OIC (with and without cancer) were eligible for inclusion. Studies were restricted to English language and letters, notes, case reports, and comments were excluded. Abstracts of the papers identified by the initial search were evaluated independently by 1 of 3 investigators for appropriateness. Hand searching was not performed. Full-text version of all potentially relevant studies were obtained and evaluated in detail. Bibliographies of all identified relevant studies were used to perform a recursive search. Articles were assessed independently by 1 of 3 investigators using predefined eligibility criteria.

Trials using any dose of pharmacologic therapy were considered eligible. Studies that recruited patients with organic or chronic idiopathic constipation were ineligible. A diagnosis of OIC was based on a history of constipation associated with the onset of opioid analgesic use or constipation as defined by the Rome IV criteria (<3 SBMs/wk and 1 additional constipation-related symptom ≥25% of the time in the presence of opioid therapy). The specific definitions of OIC used as part of study inclusion criteria in individual studies is included Table 2. Only trials with at least a 4-week duration of treatment were considered, with the exception of methylnaltrexone (2-week minimum), as earlier clinical trials of methylnaltrexone were generally shorter in duration. Studies evaluating efficacy of pharmacologic therapies in postoperative settings were excluded. First or senior authors of studies were contacted to provide additional information on trials where required.

Data Extraction

Data was extracted by 2 of 4 panel members (BH, SS, SS) to a Microsoft Excel spreadsheet. The following clinical data were extracted for each trial, where available: setting, number of centers, country of origin, dose and duration of therapy, concomitant medications, criteria used to diagnose OIC, outcome measures, and AEs. Risk of bias assessment (randomization, allocation concealment, blinding, intention-to-treat analysis) was assessed by a single author (BH or SS) and reviewed with a second author (SS) when necessary.

Analytic Approach

For each outcome and in every comparison, a pooled effect estimate was calculated (when possible) and expressed as a relative risk (RR) for categorical variables and mean differences (MDs) for continuous variables. The DerSimonian and Laird method for random-effect or fixed-effects models (when pooling <3 clinical trials) was applied to determine the overall effect size with 95% confidence intervals (CIs). AE data were also summarized with RRs. Heterogeneity between studies was assessed using a χ^2 test of homogeneity with a .10 significance level and the I^2 statistic. No predefined subgroup analysis were specified or performed. When applicable, publication bias was evaluated using funnel plot asymmetry. All percentage of outcomes reported in the trials were converted to absolute numbers and a minimal attempt at determining extractable values from graphics or figures was made to avoid subjective interpretation. Review Manager (RevMan), version 5.3 (RevMan for Windows 2008, the Nordic Cochrane Center, Copenhagen, Denmark) was used to conduct all statistical analyses and generate Forest plots and funnel plots.

Quality or Certainty of the Evidence

Risk of bias for individual studies was assessed using the Cochrane risk of bias tool. The GRADE system framework was used to assess the quality of evidence (also known as certainty in the body of evidence or confidence in the estimated effects).[24,25] In this approach, evidence from RCTs starts at high quality and can be downgraded due to concerns about risk of bias in the body of evidence, indirectness (addressing a different but related population, intervention, or outcome from the one of interest), imprecision (of boundaries of 95% CIs), inconsistency (or heterogeneity), and/or publication bias, and end up with high-, moderate-, low-, very low-quality evidence. Due to inherent limitations in observational studies, evidence derived from observational studies starts at low quality and is potentially downgraded based on the aforementioned factors (to very low quality), or can be upgraded (in rare circumstances) on the basis of a large effect, dose–response gradient or opposing confounding (to moderate or high quality). The quality of the evidence was first evaluated for each outcome and then across outcomes for each PICO. Any disagreements about judgments regarding the quality of the evidence were resolved by discussion. Additionally, for each question, an evidence profile, using the GRADEpro Guideline Development Tool (www.gradepro.org) was prepared.

Results

The search strategy generated 1601 citations, 46 of which were retrieved for further assessment (see Figure 1). Of these, 26 were excluded for several reasons, leaving a total of 20 eligible trials. One study assessed laxative use, 3 studies assessed naloxegol, 3 studies assessed alvimopan, 3 studies assessed naldemedine, 2 studies assessed methylnaltrexone, 3 studies assessed lubiprostone, and 2 studies assessed prucalopride. All studies were published in English. Details of the individual clinical trials are provided in Table 2. The risk of bias assessments and Forest plots for each of the clinical questions are also available in the Supplementary Materials.

Question: Should Laxatives Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Osmotic and stimulant laxatives promote evacuation of the colon through stimulation of fluid and electrolyte transport and/or increase propulsive motility.

Table 2. Characteristics of Included Studies and Definitions of Opioid-Induced Constipation and Outcomes

Study	Setting	Patient group	OIC definition	Intervention	Evidence profile outcome definitions: SBM response	Change in SBM frequency	Reduction in straining	Stool consistency improvement	QOL	AEs
Laxatives										
PEG										
Freedman, 1997[26]	Single-center in a US outpatient methadone program	Chronic non-malignant pain, not laxative refractory (n = 57)	Enrollment into the drug-dependency program with a complaint of constipation in patients who previously sought laxative use	Lactulose 30 mL nightly, or PEG-3350 (dose not reported) nightly for 7 wk	—	—	—	Weekly stool mean of patient reported hard, soft, or loose stools	—	—
PAMORAs										
Naloxegol										
Chey, 2014[35] KODIAC-04 KODIAC-05	Europe and US, 115 secondary and tertiary care centers Europe and US, 142 secondary and tertiary centers	Chronic non-malignant pain, at least 50% with inadequate laxative response (n = 641) Chronic non-malignant pain, at least 50% with inadequate laxative response (n = 696)	Stable opioid use (total daily dose of 30–1000mg of morphine, or equivalent, for ≥4 wk) AND <3 SBMs/wk associated with ≥1 of the following: hard/lumpy stools, straining, sensation of obstruction, or incomplete evacuation in ≥25% of BMs	Naloxegol 12.5 mg or 25 mg oral daily for 12 wk	≥3 SBMs/wk and an increase from baseline of ≥1 SBM for ≥9 of 12 wk and for ≥3 of the final 4 wk	Mean change in SBMs/wk from baseline	5-point scale, ranging from 1 (no straining) to 5 (extreme amount of straining), compared to baseline	BSFS at the end of treatment, compared to baseline	—	AE leading to treatment discontinuation
Webster, 2013[36]	54 sites in 4 countries (Germany, US, Romania, Canada), setting not reported	Chronic non-malignant pain, not laxative refractory (n = 207)	Opioid use (total daily dose of 30–1000 mg of morphine, or equivalent, for ≥2 wk) AND <3 SBMs/wk associated with ≥1 of the following: hard/lumpy stools, straining, sensation of obstruction, or incomplete evacuation in ≥25% of BMs	Naloxegol 5 mg, 25 mg, or 50 mg oral daily for 4 wk	—	—	—	—	PAC-QOL	AE leading to treatment discontinuation
Webster, 2014[38]	Multicenter	Chronic non-malignant pain, not laxative refractory (n = 534)	Stable opioid use (total daily dose of 30–1000 mg of morphine, or equivalent) AND <3 SBMs/wk on average with ≥1 of the following symptoms in ≥25% of BMs: BSFS type 1 or 2; moderate, severe or very severe straining; or incomplete BM.	Naloxegol 25 mg oral daily	—	—	—	—	—	AE leading to treatment discontinuation

Table 2. Continued

Study	Setting	Patient group	OIC definition	Intervention	Evidence profile outcome definitions: SBM response	Change in SBM frequency	Reduction in straining	Stool consistency improvement	QOL	AEs
Alvimopan Irving, 2011[40]	Multi-national, 153 secondary and tertiary care centers	Chronic non-malignant pain, laxative status not reported (n = 485)	Stable opioid use (≥1 full opioid agonist at a stable dose of at least 30 mg/d oral morphine equivalents except for codeine at least ~20 mg morphine equivalents for ≥1 month) AND <3 SBMs/wk and ≥1 of the following: sense of incomplete evacuation after passing stool, straining, lumpy hard stools or small pellets in ≥25% of BMs	Alvimopan 0.5 mg daily or 0.5 mg bid for 12 wk	≥3 SBMs/wk over the treatment period and average increase of ≥1 SBM/wk from baseline	Mean change in SBMs/wk from to baseline	4-point scale (no, mild, moderate, or severe straining) with a responder having a mean straining score ≤2 over the treatment period	4-point scale (1 = watery/ loose, 2 = semi-solid/ soft, 3 = lumpy hard, 4 = small pellets) with a responder having an average score of between 1.72 and 2.25	—	AE leading to treatment discontinuation
Jansen, 2011[41]	Multi-national (North America and Europe), 148 secondary and tertiary care centers	Chronic non-malignant pain, laxative status not reported (n = 518)	Stable opioid use (≥1 full opioid agonist at a stable dose of at least 30 mg/d oral morphine equivalents except for codeine at least ~20 mg morphine equivalents for ≥1 month) AND <3 SBMs/wk and ≥1 of the following: sense of incomplete evacuation after passing stool, straining, lumpy hard stools or small pellets in ≥25% of BMs	Alvimopan daily or 0.5 mg bid for 12 wk	≥3 SBMs/wk during therapy with an increase of ≥1 SBM/ wk from baseline	Mean change in SBMs/wk from baseline	4-point scale (no, mild, moderate, or severe straining) with a responder having a mean straining score ≤2 over the treatment period	4-point scale (1 = watery/ loose, 2 = semisolid/ soft, 3 = lumpy hard, 4 = small pellets) with a responder having an average score of between 1.72 and 2.25	—	AE leading to treatment discontinuation; cardiovascular events
Webster, 2008[42]	9 countries, 113 secondary and tertiary care centers	Chronic non-malignant pain, not laxative refractory (n = 522)	Stable opioid use (a full opioid agonist other than meperidine and propoxyphene at a dose of ≥30 mg/d oral morphine equivalents) AND <3 SBMs and >0 SBMs/wk and ≥1 of the following: sensation of incomplete evacuation, straining, lumpy hard stools or small pellets for ≥25% of BMs	Alvimopan 0.5 mg bid, 1 mg daily or 1 mg bid orally for 6 wk	≥3 complete SBMs/wk	—	4-point scale (no, mild, moderate, or severe straining) with a responder having a mean straining score ≤2 over the treatment period	4-point scale (1 = watery/ loose, 2 = semisolid/ soft, 3 = lumpy hard, 4 = small pellets) with a responder having an average score of between 1.72 and 2.25	PAC-QOL	AE leading to treatment discontinuation; cardiovascular events

Table 2. Continued

Study	Setting	Patient group	OIC definition	Intervention	Evidence profile outcome definitions: SBM response	Change in SBM frequency	Reduction in straining	Stool consistency improvement	QOL	AEs
Naldemidine										
Hale, 2017[30] COMPOSE I COMPOSE II	COMPOSE I Europe and US, 68 outpatient sites in 7 countries COMPOSE II Europe and US, 69 outpatient sites in 6 countries	Chronic non-malignant pain, not laxative refractory (n = 547) COMPOSE II Chronic non-malignant pain, not laxative refractory (n = 553)	Stable opioid dose (total daily dose ≥30mg oral morphine equivalents for 1 mo) AND ≤4 SBMs/wk with ≥1 of: hard/lumpy stools, straining, sensation of obstruction, or incomplete evacuation in ≥25% of BMs	Naldemedine 0.2 mg daily for 12 wk	≥3 SBMs/wk with an increase of ≥ 1 BM/wk from baseline for at least 9 of 12-wk treatment period, AND at least 3 of the last 4 wk of the total 12-wk treatment period	Mean change in SBMs/wk from baseline at the last 2 wk of treatment	Change in the frequency of SBMs without straining per week from baseline to the last 2 wk of the treatment period	—	—	AE leading to treatment discontinuation
Webster, 2018[32]	Europe and US, 69 sites	Chronic non-malignant pain, laxative refractory (n = 244)	Stable opioid dose (total daily dose ≥30mg oral morphine equivalents for 1 month) AND <3 SBMs/wk despite laxative use and ≥1 of the following in ≥25% of BMs: straining, incomplete evacuation, and/or hard/small stools, defined as BSFS <3	Naldemedine 0.1 mg, 0.2 mg, 0.4 mg daily for 28 d	≥3 SBMs/wk in the last 2 wk of the treatment period and an increase of ≥1 SBM/wk from baseline	Mean change in SBMs/wk from baseline to the last 2 wk of treatment	Change in weekly frequency of SBMs without straining from baseline to the last 2 wk of the treatment period	Change in weekly frequency of SBMs rated 3 or 4 on the BSFS from baseline to the last 2 wk of the treatment period	—	AE leading to treatment discontinuation
Methylnaltrexone										
Michna, 2011[44]	USA, multiple sites, setting not reported	Chronic non-malignant pain, not laxative refractory	Stable opioid dose equivalent of >50 mg/d of morphine for ≥2 wk AND <3 rescue-free BMs/wk associated with ≥1 of: hard or lumpy stools, straining, or incomplete evacuation	Methylnaltrexone 12 mg sc daily or on alternate days for 4 wk	≥3 rescue-free BMs/wk	Mean change in weekly SBM frequency from baseline during wk 1 to 4	4-point straining scale; change from baseline in % of those with "none" or "mild" straining during first 2 wk of treatment	BSFS; change from baseline over 4 wk	PAC-QOL	AE leading to treatment discontinuation
Rauck, 2016[46]	Country not reported, Multicenter, setting not reported	Chronic non-malignant pain, laxative refractory	Stable opioid dose equivalent to ≥50mg/d of morphine for ≥2 wk AND <3 rescue-free BMs/wk associated with ≥1 of BSS 1 or 2, straining or incomplete evacuation on 25% of BMs	Methylnaltrexone 150 mg, 300 mg, or 450 mg orally daily × 4 wk, then as required for 8 wk	≥3 rescue-free BMs/wk with an increase of ≥1 BM/wk from baseline for 3 of first 4 wk	Mean change in weekly number of rescue free BMs from baseline during wk 1 to 4	—	—	—	AE leading to treatment discontinuation

Table 2. Continued

Study	Setting	Patient group	OIC definition	Intervention	Evidence profile outcome definitions: SBM response	Change in SBM frequency	Reduction in straining	Stool consistency improvement	QOL	AEs
Thomas, 2008[48]	USA and Canada, 27 sites, primary and secondary care	Advanced illness (life expectancy 1 month or more), laxative refractory	Stable opioid regimen for ≥2 wk, <3 BMs in previous week AND no clinically meaningful BM within 48 hours before first study dose	Methylnaltrexone 0.15 mg/kg sc daily on alternate days for 2 wk	≥3 rescue-free BMs/wk	—	5-point scale; change from baseline	6-point scale; change from baseline	Global Clinical Impression of Change Scale	AE leading to treatment discontinuation
Secretagogues										
Lubiprostone										
Cryer, 2014[50]	US and Canada, 79 secondary and tertiary centers	Chronic non-malignant pain, not refractory (n = 418)	Stable dose of any full agonist opioid for ≥30 d AND <3 SBMs/wk and ≥1 of the following: hard/very hard stools, sensation of incomplete evacuation, moderate to very severe straining in >25% of BMs	24 μg orally bid for 12 wk	—	Mean change in SBMs/wk from baseline at week 12 and overall	Mean change from baseline on a 5-point scale ranging from 0 (absent) to 4 (very severe)	Mean change from baseline on a 5-point scale ranging from 0 (very loose) to 4 (very hard)	—	AE leading to treatment discontinuation
Jamal, 2015[51]	US and Europe, 103 sites, primary and secondary care	Chronic non-malignant pain, laxative status unknown (n = 431)	Stable opioid dose ≥30 d AND <3 SBMs/wk and ≥1 of the following: hard/very hard stools, sensation of incomplete evacuation, moderate to very severe straining in > 25% of BMs	24 μg orally bid for 12 wk	≥3 SBMs/wk f or ≥9 of the 12 treatment wk and an increase of ≥1 SBM/wk from baseline for all treatment wk	Mean change in SBMs/wk from baseline at wk 8,12, and overall	Not defined	Not defined	PAC-QOL, EQ-5D	AE leading to treatment discontinuation
Spierings 2016[53]	Multicenter	Chronic non-malignant pain, laxative status unknown (n = 437)	Stable dose of any full agonist opioid for ≥30 d AND <3 SBMs/wk and ≥1 of the following: hard/very hard stools, sensation of incomplete evacuation, moderate to very severe straining in >25% of BMs	24 μg orally bid for 12 wk	≥3 SBMs/wk for at least 50% of treatment wk[a]	Mean change in SBMs/wk from baseline at week 8	Mean change from baseline on a 5 point scale ranging from 0 (absent) to 4 (very severe)	Mean change from baseline on a 5 point scale ranging from 0 (very loose) to 4 (very hard)	—	—
Selective 5HT4 agonists										
Prucalopride										
Sloots, 2010[49]	Multi-national, 60 secondary and tertiary care centers	Chronic non-malignant pain, not laxative refractory (n = 196)	Constipation secondary to chronic daily opioid use with ≤2 SBMs/wk resulting in the sensation of complete evacuation	2 mg or 4 mg orally daily for 4 wk	≥3 SBMs/wk averaged over 4 wk	Mean change in SBMs/wk from baseline frequency over 4 wk	—	Not defined	PAC-QOL	AE leading to treatment discontinuation
NCT01117051	Leuven, Belgium	Chronic non-malignant pain (n = 77)	Not reported	1 mg or 2 mg prucalopride once daily	≥3 SBMs/wk over 12 wk	—	—	—	—	—

bid, twice a day; sc, subcutaneous.

[a]Results for this responder outcome were not published and data is not available from ClinicalTrials.gov.

Key message. There is limited direct evidence on the efficacy of laxatives in OIC. However, there is indirect evidence of the benefit for laxatives in patients with chronic idiopathic constipation (a condition that presents similarly to OIC with respect to clinical symptoms) and there is a large body of evidence on the efficacy of laxatives, especially osmotic laxatives such as polyethylene glycol (PEG)-3350, in promoting a dose-dependent effect on laxation, supporting its use as a bowel cleansing agent for colonoscopy. Furthermore, laxatives were routinely used as rescue therapy in the majority of clinical trials for OIC in patients that failed to respond to the active medication. The indirect evidence and the use of laxatives in OIC trials helped to increase our certainty in the effectiveness of laxatives for the management of OIC (***moderate-quality evidence***).

Effect estimates. Based on abstract and full-text review, only 1 double-blind RCT, with 57 patients who participated in a methadone outpatient program, was identified.[26] The majority of articles evaluating the use of laxatives included patients with constipation not specifically attributed to OIC. In this study by Freedman et al,[26] patients were randomized to placebo, lactulose, or PEG-3350 and were followed over a 7-week period, however, no specific definition of OIC was provided, no specific dose of methadone was defined, and no specific BM frequency for constipation was used. The primary end point was weekly stool consistency defined by patients' self-reported diaries. The investigators found that both lactulose and PEG were superior to placebo in improving bowel consistency. The authors reported more AEs with PEG, specifically diarrhea but no change in electrolyte imbalances. Notably, there were no drug-related AEs that resulted in withdrawal from the study.

Two additional studies of laxative use in OIC patients were identified, however, these were open-label, single-center cohort studies.[27,28] In the small study by Twycross et al,[28] 20 cancer patients with OIC received sodium picosulfate. Seventy-five percent reported a satisfactory BM response, but only 7 patients remained in the study at the end of the 14-day treatment period. In the second study by Wirz et al,[27] 358 cancer patients with OIC received sodium picosulfate, PEG, or lactulose. The authors reported that only 12.6% of patients who received PEG, 11.1% of patients who received sodium picosulfate, and 15.5% of patients who received lactulose, had a stool-free interval longer than 72 hours.

With limited data on laxative use in OIC patients, the panel sought additional sources of indirect evidence. As mentioned previously, given the similarities in clinical presentation between patients with OIC and chronic idiopathic constipation and similarities in clinical trials and outcome assessment (SBM response, SBM frequency, and stool consistency), evidence supporting the efficacy of laxatives in chronic idiopathic constipation patients was used to inform this PICO question. The panel identified an existing systematic review and meta-analyses from 2011 conducted by Ford et al[29] examining the efficacy of laxatives in chronic idiopathic constipation. In this systematic review, the authors identified 7 RCTs evaluating 1411 patients (laxatives, n = 876; placebo, n = 535) treated with stimulant or osmotic laxatives and laxatives were found to be superior to placebo for SBM response and change in BM frequency. The pooled RR, for SBM response was 2.24 (95% CI, 1.93–2.61). For BM frequency, the MD between the laxative and placebo groups was an increase of 2.55 (1.53 more to 3.57 more). Laxatives were also associated with a reduction in straining (RR, 1.52; 95% CI, 1.18–1.96). For improvement in stool consistency or reduction in passage of hard stools, the RR was 1.55 (95% CI, 1.33–1.82). QOL was not reported. Total number of AEs was not different between the 2 groups. These findings are also supported by a more recent systematic review and network meta-analysis of chronic idiopathic constipation by Nelson et al,[4] where the authors demonstrated equal efficacy of bisacodyl and sodium picosulfate for SBM response and change in complete SBM from baseline. Because these studies were conducted in patients with chronic idiopathic constipation and not specifically OIC patients, we rated down for indirectness reflecting less certainty that these results were applicable to patients with OIC, despite the relatively large magnitude of effects.

Finally, additional evidence to support the effectiveness of laxatives in OIC patients was based on the observation that laxatives were used as rescue therapy in the majority of the OIC clinical trials. In these trials, if individuals in either the intervention or placebo groups had no response (ie, SBM within a specified time frame, which ranged 48 to 72 hours) laxatives such as bisacodyl or enemas were used.

Quality of evidence. Applying the results from patients with chronic idiopathic constipation to the OIC population, we rated down for indirectness, as there was less certainty that these results were generalizable to OIC patients. For BM frequency, we additionally rated down for inconsistency. The evidence is summarized in Table 3. ***The overall quality of evidence for the use of laxatives for OIC was moderate.***

Question: Should Naldemedine Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Naldemedine, an orally available opioid antagonist received approval by the FDA in March 2017 for the treatment of OIC in adult patients with chronic non-cancer pain. Naldemedine is administered as an oral once-daily medication at a dose of 0.2 mg.

Key message. In patients with OIC, naldemedine improves SBM response and SBM frequency and possibly improves straining and stool consistency (***high-quality evidence***).

Effect estimates. Four RCTs (3 phase 3 trials and 1 phase 2b trial) including 2463 patients (naldemedine, n = 1233; placebo, n = 1230) compared naldemedine to

Table 3. Evidence Profile of Laxatives for the Treatment of Opioid-Induced Constipation

Laxatives: stimulant and osmotic laxatives												
Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laxatives	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
SBM response (defined as ≥ 3 SBMs/wk or ≥3 stools/wk)												
7	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	525/876 (59.9)	143/535 (26.7)	2.24 (1.93–2.61)	33 more per 100 (from 25 more to 43 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change in BM frequency												
6	Randomized trials	Not serious	Serious[b]	Serious[a]	Not serious	None	805	464	MD 2.55 more (1.53 more to 3.57 more)		⊕⊕◯◯ LOW	IMPORTANT
Reduction in straining[c]												
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	49/58 (84.5)	33/60 (55.0)	1.52 (1.18–1.96)	29 more per 100 (from 10 more to 53 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Stool consistency improvement (measured as hard/pellet stools[c]												
3	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	123/138 (89.1)	76/131 (58.0)	RR 1.55 (1.33–1.82)	32 more per 100 (from 19 more to 48 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
QOL[d]												
AEs leading to treatment discontinuation[e]												IMPORTANT

[a]Estimates were derived from Ford et al,[29] which included 7 studies of osmotic (n = 5) and stimulant (n = 2) laxatives. We rated down for indirectness because the population consisted of non-OIC patients.
[b]We rated down for heterogeneity I2 = 100%.
[c]Data were extracted from the primary studies cited in the systematic review by Ford et al.[29]
[d]Not reported.
[e]Total number of AE was reported and no differences were found between groups.

placebo for the treatment of patients with OIC.[30–32] The phase 3 studies (COMPOSE-1 and COMPOSE-2) by Hale et al[30] were identical multicenter parallel trials (analyzed and reported in a single article) evaluating the efficacy of naldemedine vs placebo in adult patients with non-cancer pain and OIC. OIC was defined as ≤4 SBMs over the 14-day qualifying period, with ≤3 SBMs in a given week and at least 1 bowel symptom (presence of straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage) in ≥25% of BMs. Naldemedine 0.2 mg or placebo was administered orally once a day for 12 weeks. Response to treatment was defined using the standard SBM responder end point: patients reporting ≥3 SBMs/wk and an increase from baseline of ≥1 SBM/wk for that week (a positive response week) for at least 9 weeks of the 12-week treatment period and at least 3 of the last 4 weeks of the 12-week treatment period. In the 4-week phase 2b dose-ranging study by Webster et al,[31] OIC was defined as <3 SBMs/wk despite laxative use and ≥1 of the following in ≥25% of BMs: straining, incomplete evacuation, and/or hard/small stools, defined as BSFS score <3.[31] Patients were administered once-daily oral naldemedine: 0.1 mg, 0.2 mg, or 0.4 mg and response to treatment was defined using the standard SBM responder end point, but the response rate was measured over the entire 4 weeks of the study duration. Long-term safety and efficacy of naldemedine (0.2 mg) were evaluated in a 52-week multicenter phase study in patients with OIC and chronic noncancer pain.[32] In this study by Webster et al, OIC was defined as ≤4 SBMs over the 14-day qualifying period and ≤3 SBMs in a given week; only 50% of patients were on a routine laxative regimen (using an over-the-counter laxative at least once per week). The authors reported on AEs over a follow-up period of 52 weeks, as well as change in BM frequency and QOL (using the PAC-QOL).

Overall, 318 (52.1%) of 610 patients who received naldemedine had response to therapy compared with 210 (34.6%) of 607 patients who received placebo (over a follow-up period of 12 weeks). Compared with placebo, naldemedine was associated with a higher rate of response (RR, 1.51; 95% CI, 1.32–1.72). Based on a placebo response rate of approximately 35%, if 100 patients were treated with naldemedine, 18 more patients would have response (95% CI, 11 more to 25 more). Naldemedine was associated with an increase in the frequency of SBMs per week; the MD between the naldemedine and placebo groups was an increase of 1.38 (95% CI, 1.03 more to 1.73 more). An SBM was defined as a BM occurring without the use of rescue laxative medication in the previous 24 hours. Change in BM frequency from baseline over a treatment period of 52 weeks was reported in the COMPOSE-3 study. Naldemedine was associated with an increase in BM frequency per week; MD was 0.95 more (95% CI, 0.57 more to 1.33 more). Change in frequency of SBMs without straining was reported across the 3 studies. Naldemedine was associated with an increase in the number of SBMs without straining: MD was 0.82 more (95% CI, 0.44 more to 1.21 more). Change in frequency of SBMs rated 3 or 4 on the BSFS was only reported in the phase 2b study. Use of naldemedine was associated with an MD of 1.51 more SBMs (95% CI, 0.51 more to 2.51 more). Improvement in QOL (using the PAC-QOL) was only reported in the long-term 52-week study; naldemidine was not associated with a clinically meaningful improvement in QOL.

AEs leading to treatment discontinuation occurred in 82 (6.1%) patients receiving naldemedine and 53 (4.3%) patients receiving placebo. The pooled RR was 1.44 (95% CI, 1.03–2.03). Based on a placebo AE rate of 4.3%, the use of naldemedine would result in 2 more AEs per 100 patients (95% CI, from 0 more to 4 more).

Quality of evidence. All 3 studies were at low risk of bias. The quality or certainty of the evidence for SBM response, SBM frequency, change in frequency of BMs without straining, and change in frequency of SBMs rated 3 or 4 on the BSFS, QOL, and AEs leading to treatment discontinuation was rated as high. For long-term efficacy as measured by change in BM frequency, there was moderate-quality evidence because we rated down for imprecision. The evidence is summarized in Table 4. ***The overall quality of evidence for the use of naldemedine for OIC was high.***

Other considerations. Naldemedine has been studied in patients with cancer pain and OIC in a phase 2b and 2 phase 3 trials (COMPOSE-4 and COMPOSE-5).[33] For our analysis, we chose not to combine results from trials of naldemedine in cancer patients (which were generally of short duration, <4 weeks) with results from trials in non-malignant pain patients so as to minimize heterogeneity. However, the findings from these trials are summarized.

In a 4-week phase 2b dose ranging study in 225 patients, OIC was defined as ≤5 SBMs with straining, incomplete evacuation, and/or hard stools in ≥25% of BMs during the 2 weeks before randomization. Inclusion criteria were patients with any cancer that did not directly affect GI function, on stable doses of opioids for ≥2 weeks, and an Eastern Cooperative Oncology Group performance status ≤2. Patients were randomized in 1:1:1:1 fashion (naldemedine 0.1 mg, n = 55; naldemedine 0.2 mg, n = 58; naldemedine 0.4 mg, n = 56; placebo, n = 56). SBM responder rates ranged from 56.4% to 82.1% among patients receiving naldemedine vs 37.5% in the placebo group. In the phase 3 study, 193 patients with OIC and cancer were randomized to receive naldemedine 0.2 mg or placebo for 2 weeks, followed by a 12-week open-label extension study to evaluate the safety of naldemedine. The definition of OIC and inclusion criteria were similar to the dose-ranging study; 71.1% of patients receiving naldemedine achieved the responder outcome vs 34.4% in the placebo arm. In addition, patients receiving naldemedine had more frequent SBMs per week and less straining than at baseline; the MD across groups in SBMs per week was 3.62 (95% CI, 2.13–5.12) and for SBMs without straining per week was 2.67 (95% CI, 1.20–4.15). Nine of 97 (9.3%) patients in the naldemedine arm withdrew as a result of AEs vs only 1 of 96 (1.0%) patients receiving placebo. In the open-label extension study, of the 131 patients receiving naldemedine, 12 patients withdrew secondary to AEs.

Table 4. Evidence Profile of Naldemedine for the Treatment Opioid-Induced Constipation

Naldemedine 3 RCTs (Hale[30] 2017 COMPOSE-1 and COMPOSE-2; Webster[32] 2018 COMPOSE-3) and 1 phase 2 study (Webster[31])

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naldemedine	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
SBM response (at least 3 SBMs/wk and an increase from baseline of 1 SBM/wk; follow-up 4–12 wk)												
3	Randomized trials Hale Webster	Not serious	Not serious	Not serious	Not serious	None	318/610 (52.1)	210/607 (34.6)	1.51 (1.32 to 1.72)	18 more per 100 from 11 more to 25 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in SBM frequency (change from baseline in mean number of SBMs/wk; follow-up 4–12 wk)												
3	Randomized trials Hale Webster	Not serious	Not serious	Not serious	Not serious	None	608	566	MD 1.38 more (1.03 more to 1.73 more)		⊕⊕⊕⊕ HIGH	IMPORTANT
Change in frequency of BMs without straining (frequency (from baseline to the last 2 weeks of the treatment period)[a]												
3	Randomized trials Hale Webster	Not serious	Not serious	Not serious	Not serious	None	608	566	MD 0.82 more (0.44 more to 1.21 more)		⊕⊕⊕⊕ HIGH	IMPORTANT
Change in BM frequency (change from baseline in mean number of SBMs/wk; follow-up 52 wk)[b]												
1	Randomized trials Webster	Not serious	Not serious	Not serious	Serious[d]	None	621	620	MD 0.95 more (0.57 more to 1.33 more)		⊕⊕⊕◯ MODERATE	IMPORTANT
Change in frequency of SBMs rated 3 or 4 on the BSFS[c]												
1	Randomized trials Webster	Not serious	Not serious	Not serious	Not serious	None	59	20	MD 1.51 more (0.51 more to 2.51 more)		⊕⊕⊕⊕ HIGH	IMPORTANT
QOL (based on PAC-QOL, MCID 1 point; follow-up 52 wk)												
1	Randomized trials Webster	Not serious	Not serious	Not serious	Not serious	None	621	620	MD .30 (0.16 to 0.44)		⊕⊕⊕⊕ HIGH	IMPORTANT
AEs leading to treatment discontinuation (follow-up 4–52 wk)												
3	Randomized trials Hale Webster	Not serious	Not serious	Not serious	Not serious	None	82/1340 (6.1)	53/1226 (4.3)	1.44 (1.03–2.03)	2 more per 100 (from 0 more to 4 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

NOTE. All results and analyses are presented for the 0.2-mg dose.
[a]For change in frequency of BMs without straining, mean difference in change from baseline from the 2 studies showed a statistically significant difference, however, it is unclear if this represents a clinically meaningful improvement.
[b]In the COMPOSE-3 study BM frequency (not SBM were reported). The actual mean and SD were not provided at end of treatment (wk 52) however, estimates for mean (±SE) change from baseline were gleaned from graphs (then converted to SD to allow for calculation of mean difference between groups.
[c]For change in frequency of SBMs rated 3 or 4 on the BSFS, mean difference in change from baseline from the 2 studies showed a statistically significant difference, however, it is unclear if this represents a clinically meaningful improvement.
[d]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.

Question: Should Naloxegol Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Naloxegol is a pegylated derivative of the μ-opioid receptor antagonist naloxone. The pegylation alters its distribution, limiting penetration across the blood–brain barrier, while retaining peripheral opioid-blocking action.[34] Naloxegol was the first once-daily oral PAMORA to receive FDA approval in 2014 at a dose of 25 mg daily, for the treatment of OIC in adult patients with chronic, non-cancer pain. Naloxegol has not been approved for use in patients with OIC and cancer pain.

Key message. In patients with OIC, naloxegol improves SBM response and SBM frequency and possibly improves straining, and stool consistency (***moderate-quality evidence***).

Effect estimates. Three RCTs (2 phase 3 trials and 1 phase 2 trial) including 1559 patients compared naloxegol (n = 971) to placebo (n = 541) for treatment of patients with OIC.[35,36] The phase 3 studies (KODIAC-04 and KODIAC-05) by Chey et al[35] were identical multicenter, double-blind, parallel trials (analyzed and reported in a single article). Patients were randomized to naloxegol 12.5 mg, 25 mg or placebo daily for 12 weeks. The phase 2 study by Webster et al[37] was a multicenter, randomized, double-blind dose-escalation study with 4 sequential dose cohorts (naloxegol 5 mg, 25 mg, 50 mg, and 100 mg); however, the study was terminated early and naloxegol 25 mg was identified as a safe and tolerable dose. A 52-week open-label extension study (KODIAC-08), which included 804 patients (naloxegol, n = 534; usual care, n = 270), was also used for data regarding AEs.[38]

The 3 trials had similar inclusion and exclusion criteria and defined OIC as <3 SBMs/wk with accompanying symptoms (hard or lump stools, straining, or a sensation of incomplete evacuation or anorectal obstruction in ≥25% of BMs during the screening period) in the setting of a stable opioid regimen. Patients with uncontrolled pain despite opioid therapy or concomitant medication use that could impact bowel habits were excluded from the studies. The phase 2 trial had more strict exclusion criteria with specific restrictions on patients with renal, cardiac, GI, and hepatic disease, as well as, patients with <6 months' life expectancy.

The responder end point, defined as ≥3 SBMs/wk with an increase from baseline of ≥1 SBMs/wk for at least 9 of 12 weeks, and for at least 3 of the 4 final weeks (overall 12-week response rate) was used in the phase 3 studies. The 4-week phase 2 study by Webster et al[36] did not report a responder outcome and only reported median change in SBMs per week compared to placebo over a 4-week period, which precluded pooling these data with the phase 3 studies.

Naloxegol (25 mg) was associated with a higher rate of response to therapy (RR, 1.43; 95% CI, 1.19 to 1.71) compared with placebo among patients. Overall, 187 (41.9%) of 446 patients who received naloxegol had response to therapy compared to 131 (29.4%) of 446 patients who received placebo. Assuming a placebo response rate of approximately 30%, naloxegol use would result in 13 more patients with response per 100 (95% CI, 6 more to 21 more). Naloxegol was associated with an increase in SBM frequency compared to placebo. Across the 2 studies, the MD was 1.02 (95% CI, 0.67 to 1.37) with the lower boundary crossing our threshold of a clinically meaningful difference. Mean increases of 0.54 (95% CI, 0.12 to 0.96) and 0.52 (95% CI, 0.06 to −0.98) were observed with the 12.5-mg dose. Reduction in straining with BMs was assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining) and the MD in change from baseline for the intervention and placebo arms was reported across the 2 studies: MD of −0.24 (95% CI, −0.35 to −0.14). Stool consistency was assessed using the BSFS **(**types 1–7, with 1 denoting small, hard, lumpy stool and 7 denoting watery stool). Across the 2 studies, naloxegol (25 mg) was associated with a decrease of 0.33 (95% CI, 0.20 to 0.46) on the scale. QOL was only reported in the 4-week phase 2 study. No clinically meaningful improvement in median PAC-QOL scores was observed between the intervention and placebo groups (median total PAC-QOL scores was 1.1 vs 1.7 for the 25-mg cohort).

AEs leading to treatment discontinuation were pooled from the 3 studies[35,36] mentioned, as well as, a randomized open-label study comparing naloxegol to usual care.[38] REFS. Overall, 141 patients of 1500 (9.4%) patients discontinued therapy due to AEs compared with 34 of 809 (4.2%) patients who received placebo. The pooled RR, was 2.33 (95% CI, 1.62–3.35). In absolute terms, compared to placebo, naloxegol use was associated with 6 more AEs leading to treatment discontinuation per 100 patients (95% CI, 3 more to 10 more). In the 52-week study of naloxegol 25 mg daily, the most common treatment-emergent AEs were abdominal pain (17.8% in naloxegol vs 3.3% in placebo), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%), headache (9.0% vs 4.8%), flatulence (6.9% vs 1.1%), and upper abdominal pain (5.1% vs 1.1%). Additionally, pain scores and mean daily opioid doses remained stable.

Quality of evidence. All studies were considered low risk of bias. For SBM response and change in SBM frequency, we rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference. For reduction in severity of straining and improvement in stool consistency, statistically significant differences were noted, however, it was unclear if these represented clinically meaningful improvements. For stool consistency, we also rated down for inconsistency For AEs leading to treatment discontinuation, we rated down for imprecision. The evidence is summarized in Table 5. ***The overall quality of evidence for the use of naloxegol for OIC was moderate.***

Other considerations. Additionally, a subgroup analysis of the phase 3 studies was conducted[39] to examine those with inadequate response to laxatives. The original study specified randomization to include similar numbers of patients with inadequate laxative response in all groups. Overall SBM response rates were improved in the treatment groups for naloxegol 25 mg and 12.5 mg

in the inadequate laxative response groups compared to placebo.

Question: Should Alvimopan Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Alvimopan is an oral once-daily PAMORA. It binds the GI tract μ-opioid receptors, antagonizing the opiate effects on GI motility and secretion. Alvimopan has restricted ability to cross the blood–brain barrier and therefore does not affect opioid analgesic effects or induce opioid withdrawal symptoms. While alvimopan has been studied in OIC,[40–42] it is currently only FDA approved for in-hospital management of postoperative ileus. The use of alvimopan for OIC is considered off-label. Moreover, alvimopan is currently not available in the doses used in clinical trials for OIC.

Key message. Alvimopan has been studied in patients with OIC and chronic non-cancer pain, but it is not FDA-approved for OIC and the equivalent doses used in clinical trials of OIC are not currently available. A full evidence review of alvimpoan is, however, included in the Supplementary Material.

Question: Should Methylnaltrexone Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Methylnaltrexone is a PAMORA; it is the only PAMORA that has 2 indications: advanced illness, including active cancer, and chronic non-malignant pain. It was the first drug of its kind to be approved by the FDA and European Medicines Agency for the treatment of OIC in terminally ill patients in 2008. It has subsequently been approved for the treatment of OIC in patients with non-cancer pain and is available in 2 formulations (subcutaneous injection and oral tablet). Because of its quaternary amine structure, it is restricted from crossing the blood–brain barrier. Methylnaltrexone is also unique among the PAMORAs as not being metabolized via the CYP3A4 system, which decreases the potential for drug–drug interactions.

Key message. In patients with OIC, methylnaltrexone possibly improves RFBM response, RBM frequency, and straining (***low-quality evidence***).

Effect estimates. As outlined in the Methods section, different criteria were used for the selection of studies to inform this clinical question, that is, studies of short duration (minimum of 2 weeks) and studies performed in advanced cancer/terminal illness were also reviewed. In the first analysis, we combined studies[43–48] that evaluated methylnaltrexone for the treatment of OIC in chronic non-cancer pain and patients with advanced illness/terminal illness/cancer (evidence profile in the Supplementary Materials). In a secondary analysis, only studies in OIC patients with chronic non-cancer pain were included. Methylnaltrexone is the only PAMORA to be FDA approved for the management of OIC in patients with both populations. Earlier clinical trials of methylnaltrexone were conducted in advanced cancer/terminally ill patients using the subcutaneous formulation and because the safety and efficacy of methylnaltrexone were established before development of the oral tablet, the FDA approved the oral formulation based on only 1 phase 3 randomized placebo-controlled study.[44] One additional study evaluated the subcutaneous formulation in OIC patients with chronic non-cancer pain.[46]

The secondary analysis examining the efficacy of methylnaltrexone in patients with chronic non-cancer pain will be discussed (consistent with the review of the evidence in this technical review for other PAMORAs in patients with OIC and chronic non-cancer pain). The majority of studies measured RFBMs, defined as BMs without prior use (within last 4 to 24 hours) of any rescue medications or laxatives, which is conceptually similar to SBM response, defined as BM that occurred when no laxative had been used in the prior 24 hours. The pooled effect estimate for RFBM response was based on 2 RCTs, including 713 patients (methylnaltrexone, n = 350; placebo, n = 363).[40,41] In the 4-week RCT by Rauck et al,[41] oral methylnaltrexone was compared to placebo in adult OIC patients with chronic non-malignant pain. A responder was defined as a patient having $\geq$3 RFBMs/wk and an increase of $\geq$1 RFBM/wk from baseline for at least 3 of the first 4 weeks. In the 4-week RCT by Michna et al,[40] OIC patients with chronic non-malignant pain were randomized to receive subcutaneous methylnaltrexone vs placebo and a responder was defined as a patient with $\geq$3 RFBMs/wk (with no requirement of an increase in $\geq$1 RFBM/wk from baseline over the duration of the study). Overall, 191 of 350 (54.6%) patients who received methylnaltrexone had response to therapy compared with 139 of 363 (38.3%) patients who received placebo; the pooled effect estimate was 1.43 (95% CI, 1.21–1.68).

An additional outcome, laxation response, was included in the evidence synthesis for methylnaltrexone. This was defined as a BM within 4 hours of a subcutaneous or oral dose of methylnaltrexone (and no laxative use for at least 4–24 hours prior). Compared with placebo, methylnaltrexone was associated with higher rate of laxation response (RR, 3.16; 95% CI, 2.18–4.58; based on 2 RCTs). Of 350 patients who received methylnaltrexone, 97 of 350 (27.7%) had laxation response compared with 32 of 363 (8.8%) treated with placebo. Based on a placebo response rate of approximately 8.8%, if 100 patients were treated with methylnaltrexone, 19 more patients would have response (95% CI, 10 more to 32 more).

Methylnaltrexone may or may not be associated with a clinically meaningful increase in RFBM frequency (measured as change from baseline until end of treatment in mean number of weekly RFBMs). The MD between groups in RFBM frequency ranged from an increase of 0.5 more to 1.60 more. With respect to other outcomes, such as reduction in straining, improvement in stool consistency, and improvement in QOL, only Michna et al[40] reported on these outcomes. Using a straining scale, compared with placebo, methylnaltrexone was associated with an increase in RFBMs with straining rated as “none” or “mild” during 2 weeks of treatment (week 3: methylnaltrexone 29% compared with

Table 5. Evidence Profile of Naloxegol for the Treatment Opioid-Induced Constipation

Naloxegol 2 RCTs (Chey[35]) and 1 phase 2 RCT (Webster[36]) and one OLE study (Webster[38])												
Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Naloxegol	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
SBM response rate (at least 3 SBMs/wk and an increase from baseline of 1 SBM for at least 9 of 12 wk and for at least 3 of the final 4 wk)												
2	Randomized trials Chey (KODIAC-04) Chey (KODIAC-05)	Not serious	Not serious	Not serious	Serious[a]	None	187/446 (41.9)	131/446 (29.4)	1.43 (1.19 to 1.71)	13 more per 100 (from 6 more to 21 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change in SBM frequency (change from baseline in mean number of SBMs/wk)[b]												
2	Randomized trials Chey (KODIAC-04) Chey (KODIAC-05)	Not serious	Not serious	Not serious	Serious[b]	None	438	442	MD 1.02 more (0.67 more to 1.37 more)		⊕⊕⊕◯ MODERATE	IMPORTANT
Reduction in severity of straining (assessed using a 5-point scale ranging from 1 (no straining) to 5 (extreme amount of straining)[c]												
2	Randomized trials Chey (KODIAC-04) Chey (KODIAC-05)	Not serious	Not serious	Not serious	Not serious	None	438	442	MD –0.24 (–0.35 to –0.14)		⊕⊕⊕⊕ HIGH	IMPORTANT
Stool consistency (assessed using the BSFS (with 1 denoting small, hard, lumpy stool and 7 denoting watery stool)[d]												
2	Randomized trials Chey (KODIAC-04) Chey (KODIAC-05)	Not serious	Serious[e]	Not serious	Not serious	None	438	442	MD 0.33 (0.20 to 0.46)		⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of Life[f]												
AE leading to treatment discontinuation												
4	Randomized trials Chey (KODIAC-04) Chey (KODIAC-05) Webster Webster	Not serious	Not serious	Not serious	Serious[g]	None	141/1500 (9.4)	34/809 (4.2)	2.33 (1.62 to 3.35)	6 more per 100 (from 3 more to 10 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

NOTE. All results and analyses presented in this evidence profile are for the 25-mg cohort.
[a]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference (defined as a number needed to treat of 10 per 100).
[b]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference (defined as an increase of at least 1 SBM).
[c]For reduction in severity of straining, MD in change from baseline from the 2 studies showed a statistically significant difference, however, it is unclear if this represents a clinically meaningful improvement.
[d]For stool consistency, MD in change from baseline from the 2 studies showed a statistically significant difference, however, it is unclear if this represents a clinically meaningful improvement.
[e]We rated down for inconsistency, as I2 was 73%.
[f]QOL was only reported in the 4-week phase 2 study. Median total PAC-QOL score was 1.1 vs 1.7 for the 25-mg cohort.
[g]Data pooled from the Chey studies as well as a 4-week phase 2 study (Webster) and open-label extension study (Webster). We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.

placebo 14.4%; MD, 14.6%). For stool consistency, the authors reported an "improvement from baseline in average Bristol Stool Form Scale score of 1.4 in the methylnaltrexone arm vs 0.9 in the placebo arm" (MD, 0.5). For QOL, mean improvement in the total PAC-QOL scores from baseline of approximately 0.74 compared with 0.39 in the placebo arm was reported (MD, 0.35).

Data on AEs was pooled from 2 RCTs. AEs leading to discontinuation occurred in 17 of 350 (4.9%) patients receiving methylnaltrexone and 10 of 363 (2.8%) patients receiving placebo (RR, 1.77; 95% CI, 0.82–3.80).

Quality of evidence. We rated down for indirectness across all outcomes because (i) the study duration was short in the Michna et al study (4 weeks) and Rauck et al study (4 weeks followed by as needed dosing for 8 weeks) as compared to 12 weeks for the FDA SBM responder endpoint, (ii) we included studies using different formulations (Rauck et al: 450 mgs oral methylnaltrexone and Michna et al: 12 mgs subcutaneous methylnaltrexone). As the majority of patients with OIC are on long-term chronic opioids and the studies were of short duration, there was uncertainty about the efficacy of methylnaltrexone beyond 4 weeks. For RFBM response, in addition to rating down for indirectness we also rated down for imprecision as the lower boundary of the CI crossed our threshold of a clinically meaningful difference. For RFBM frequency we rated down for indirectness and imprecision because a MD of 1 RFBM was deemed clinically significant and across the range of effects there was a possibility of no clinically meaningful improvement. For outcomes where no raw data or results were reported, narrative information on the outcome was included but the certainty of the evidence was not rated. For AE, the quality of the evidence was low; we rated down for imprecision because our CI crossed our threshold of a clinically meaningful difference. The evidence is summarized in Table 6. ***The overall quality of evidence for the use of methylnatrexone for OIC is low.***

Other considerations. Our first analysis of methylnaltrexone included trials of OIC patients with terminal illness or advanced cancer as well as patients with OIC and non-cancer pain. Additional studies that informed some of the outcomes for this analysis include: a 2-week RCT by Thomas et al. where subcutaneous methylnaltrexone was compared to placebo in terminally ill (mostly cancer) adult patients with OIC who were allowed to continue baseline laxatives and a responder was defined as a patient with >3 RFBMs per week.[48] Notably, the evidence profile includes a revised effect estimate (see footnote) for the outcome of RFBM (RR 1.56, 95% CI, 1.31–1.87) based on additional unpublished data received from Salix after the public comment period. For the outcome of laxation response (defined as a BM within 4 hours of initial dose), 3 additional studies were used to inform the outcome: the 2-week study by Bull et al[43] (N=230) that compared oral methylnaltrexone with placebo in patients with advanced illness (life expectancy > 1 month), the RCT by Slatkin et al[47] (N=154) in patients with OIC in hospice and palliative care centers that received a single dose of methylnaltrexone (0.15 mgs/kg or 0.3 mgs/kg, and the 1-week RCT by Porteney et al[45] (N=33) that compared subcutaneous methylnaltrexone with placebo in laxative refractory patients. Laxation response was defined as a BM within 4 hours of initial dose.

Since the analyses for the other PAMORA drugs focused only on OIC in non-cancer patients, we performed a second analysis of methylnaltrexone in non-cancer patients and used this meta-analysis to inform the guideline recommendation. The primary analysis is available in the supplementary materials.

Question: Should Prucalopride Be Used in the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Prucalopride is a highly selective 5-HT4 agonist currently approved by the European Medicines Agency and the European Commission for use in females with laxative refractory chronic constipation. Although prucalopride has been studied in patients with OIC, it has yet to be FDA-approved for OIC or any other indication.

Key message. In patients with OIC, we are uncertain of the effects of prucalopride on improving SBM response and SBM frequency (***low-quality evidence***).

Effect estimates. Only one 4-week phase 2 study of prucalopride in 196 patients with OIC was identified from the literature review.[43] In the study by Sloots et al,[43] OIC was defined as patients who endorsed chronic daily opioid use and ≤2 SBMs/wk with complete evacuation. A total of 196 OIC patients were randomized to receive placebo or prucalopride 2 mg or 4 mg orally daily for 4 weeks. Responders were defined as patients with an average of ≥3 SBMs/wk averaged over 4 weeks. The authors also reported the proportion of patients with an average increase of ≥1 SBM/wk, averaged over 4 weeks. This responder definition is slightly different than in other studies, where a responder is defined as a patient ≥3 SBMs/wk over the treatment period and an average increase from baseline of ≥1 SBM/wk).

In an effort to incorporate all available evidence on the use of prucalopride in OIC patients, we also searched for ongoing or completed trials on ClinicalTrials.gov. One additional 12-week study of prucalopride was titled "Prucalopride Effects on Subjects With Chronic Non-Caner Pain Suffering From Opioid Induced Constipation" (ClinicalTrials.gov ID: NCT01117051). According to ClinicalTrials.gov, this study was terminated early (2014) by Movetis after recruitment of only 174 patients. In the trial, a responder was defined as a patient with an average frequency of ≥3 SBMs/wk over 12 weeks follow-up. Despite the limitations of using the results posted on ClinicalTrials.gov, we extracted the available data and pooled the results from this trial with the phase 2 study.[49]

Overall, 126 (58.3%) of 216 patients who received prucalopride had response to therapy compared with 62 (41.6%) of 149 patients who received placebo. The pooled RR, was 1.36 (95% CI, 1.08–1.70). Based on a placebo rate of 41.6%, if 100 patients were treated with prucalopride, 15 more patients would have a response (95% CI, 3 more to 29 more). Improvement in SBM frequency was reported in the

Table 6. Evidence Profile of Methylnaltrexone for the Treatment of Opioid-Induced Constipation

Methylnaltrexone: 2 RCTs: Michna, 2011[40] and Rauck, 2016[41]											
Certainty assessment							Patients, n (%)		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylnaltrexone	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
RFBM Response (defined as ≥3 RFBMs/wk; follow-up 4 wk)												
2	Randomized trials Michna Rauck	Not serious	Not serious	Serious[a]	Serious[b]	None	191/350 (54.6)	139/363 (38.3)	RR 1.43 (1.21 to 1.68)	16 more per 100 (from 8 more to 26 more)	⊕⊕◯◯ LOW	CRITICAL
Laxation response (defined as a BM within 4 hours and no laxative in the prior 24 hours)												
2	Randomized trials Michna Rauck	Not serious	Not serious	Serious[a]	Not serious	None	97/350 (27.7)	32/363 (8.8)	RR 3.16 (2.18 to 4.58)	19 more per 100 (from 10 more to 32 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in RFBM frequency[c]												
3	Randomized trials Rauck Michna	Not serious	Not serious	Serious[a]	Serious[c]	None	MD 1.60 more with 12 mg sc qd (Michna) MD 0.5 more with 450 mg (Rauck)				⊕⊕◯◯ LOW	IMPORTANT
Reduction in straining assessed using a straining scale 0 (none) to 4 (very severe)												
1	Randomized trials Michna						See footnote[d]					IMPORTANT
Stool consistency assessed using the BSFS												
	Randomized trials Michna						See footnote[e]					IMPORTANT
Quality of Life												
	Randomized trials Michna						See footnote[f]					IMPORTANT

Table 6. Continued

Methylnaltrexone: 2 RCTs: Michna, 2011[40] and Rauck, 2016[41]												
Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylnaltrexone	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
AEs leading to treatment discontinuation												
2	Randomized trials Michna Rauck	Not serious	Not serious	Serious[a]	Serious[g]	None	17/350 (4.9)	10/363 (2.8)	1.77 (0.82–3.80)	2 more per 100 (from 0 more to 8 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

qd, once daily; sc, subcutaneous.
[a]We rated down for indirectness for the following reasons: the outcomes were measured differently across the 2 studies, the studies used different formulations (Rauck et al used 450 mgs oral methylnaltrexone and Michna et al used 12 mgs subcutaneous methylnaltrexone) and the range of follow up across the studies was short (only 4 weeks, as compared to 12 weeks for the SBM response outcome used in studies of other PAMORAs).
[b]We rated down for imprecision because 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 for change in RFBM frequency; MD in the Michna study was 1.60 more with the 12-mg subcutaneous daily dose and Rauck was 0.5 more with the 450-mg dose. No CIs or SDs were provided.
[d]For reduction in straining, in the study by Michna et al, the authors concluded that compared with placebo, methylnaltrexone led to more RFBM with "none" or "mild" straining (MD 14.6% more). No raw data provided.
[e]The Michna study reported "improvement from baseline in average Bristol Stool Form Scale score of 1.4 in the methylnaltrexone arm versus 0.9 in the placebo arm" (MD 0.5) Baseline data not provided.
[f]In the study by Michna, methylnaltrexone group showed an improvement in the total score of 0.74 (12 mg subcutaneous once daily) compared with 0.39 in the placebo group (baseline QOL scores of patients not provided).
[g]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.

study by Sloots et al[43]; MD from baseline was 2.2 (2 mg), 2.5 (4 mg) in the intervention arms vs 1.5 in the placebo arm.

Improvement of individual symptoms, such as reduction in painful defecation or lack of straining, were not reported. For improvement in stool consistency, the authors reported that prucalopride increased the percentage of stools with normal consistency and decreased the percentage of hard stools, although the data were not provided. QOL was measured using the PAC-QOL instrument, however, only the Satisfaction subscale was reported. A responder was defined as a patient achieving ≥1 point increase. Overall, 28.5% of patients (37 of 130) in the prucalopride arm had a response compared with 18.2% of patients (12 of 66) in the placebo arm (RR, 1.57; 95% CI, 0.88–2.80). In absolute terms, with a baseline risk of 18.2%, 10 more patients would experience an improvement in satisfaction on the PAC-QOL scale (95% CI, 2 fewer to 33 more).

AEs leading to treatment discontinuation occurred in 8 of 130 (6.2%) patients who received prucalopride compared to 7 of 66 (10.6%) patients who received placebo. There was no statistically significant difference in AEs between therapy and placebo, aside from abdominal pain, which occurred at a higher rate in those receiving prucalopride 4 mg (25.0%) than those in the 2-mg (12.1%) and placebo (9.1%) groups. The RR was 0.58 (95% CI, 0.22–1.53).

Quality of evidence. Publication bias was a concern, as the trial titled "Prucalopride Effects on Subjects with Chronic Non-Caner Pain Suffering from Opioid Induced Constipation" (ClinicalTrials.gov ID: NCT01117051) was terminated by the manufacturer Movetis in 2014 before recruitment was completed and the study results were never published. For SBM response and SBM frequency, we rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference or because we could not exclude a non-clinically meaningful difference. The quality of evidence for QOL was low (after rating down for imprecision). For AEs, we rated down due to few events. The evidence is summarized in Table 7. ***The overall quality of evidence for the use of prucalopride for OIC is low.***

Question: Should Lubiprostone Be Used the Management of Opioid-Induced Constipation in Patients With Non-Cancer Pain?

Lubiprostone is an oral chloride channel activator that increases chloride influx in the lumen of the GI tract, resulting in acceleration of intestinal transit. Lubiprostone was approved by the FDA in 2013 for the treatment of OIC.

Key message. In patients with OIC, we are uncertain of the effects of lubiprostone on improving SBM response, SBM frequency, straining, stool consistency and QOL (***low-quality evidence***).

Effect estimates. Three large phase 3 RCTs including 1284 patients (lubiprostone, n = 647; placebo, n = 637) compared the use of lubiprostone to placebo for the treatment of OIC.[44–46] These studies evaluated the efficacy of lubiprostone vs placebo in adult patients with non-cancer pain on stable opiate doses for at least 30 days before enrollment. OIC was defined as an average of <3 SBMs/wk without the use of a laxative or stool softener during the screening period and ≥1 of the following symptoms for ≥25% of SBMs during the same period: hard/very hard stools, sensation of incomplete evacuation, or moderate/severe straining. Lubiprostone 24 μg twice daily with meals and 8 ounces of fluid were administered for 12 weeks in each study.

A standard SBM responder definition (patient experiencing ≥3 SBMs/wk for at least 9 of 12 treatment weeks and ≥1 SBM/wk over all treatment weeks) was used in only of 2 of the 3 trials.[45,46] Cryer et al[50] defined an overall responder as a patient who was in the study for at least 8 weeks, achieved at least a moderate response (≥3 SBMs/wk) for at least 50% of the study weeks, however, this outcome was not reported in the published article. The authors did report change in SBM frequency from baseline to week 8. Lastly, Spierings et al[52] reported a change in SBM frequency from baseline at week 8, but did not report an overall responder outcome in the published article. A review of study on ClinicalTrials.gov found the authors did in fact define and measure an overall response outcome. An overall responder was defined as ≥3 SBMs/wk for >50% of the study weeks. These studies varied in duration from 8 to 12 weeks.

Across 2 studies, 166 of 437 (38.0%) patients randomized to lubiprostone were responders compared with 141 of 431 (32.7%) patients randomized to placebo. As compared with placebo, lubiprostone use was not associated with an SBM response; the pooled RR was 1.15 (95% CI, 0.97 to 1.37). In absolute terms, using a placebo response rate of 32.7%, lubiprostone therapy would result in 5 more responses per 100 patients (95% CI, 1 fewer to 12 more). With respect to change in SBM frequency, lubiprostone was not associated with an increase in SBM frequency: MD in SBM frequency was 0.80[45] and 0.60.[44] In the Spierings et al[52] study, a difference of –0.10 (95% CI, –0.78 to 0.58) was reported between the 2 groups.

All 3 trials assessed stool consistency and reduction in straining. Stool consistency was reported on a 5-point scale (0, very loose to 4, very hard) and straining was reported using a 5-point scale (0, absent to 4, very severe). Only Spierings et al[52] provided numerical data for change in stool consistency. Less straining was noted between the lubiprostone group vs placebo (MD, –0.30; 95% CI, –0.47 to –0.13). The other 2 studies reported improvement in average stool consistency from hard at baseline to normal with lubiprostone and reduction in straining from moderate to severe at baseline to mild to moderate with lubiprostone therapy, however, no comparative data were provided between the treatment and placebo groups. One study[45] assessed health-related QOL using PAC-QOL and EuroQoL-5 Dimensions, but found no statistical difference over the 12-week study. PAC-QOL median change from baseline was –0.861 in lubiprostone arm and –0.695 in placebo arm; a difference of –0.166 was noted between the treatment and placebo arms. The EuroQoL-5 Dimensions did not change from baseline in both arms.

AEs were reported in the 3 large RCTs and in 1 open-label extension trial.[52] AEs leading to discontinuation of

Table 7. Evidence Profile of Prucalopride for the Treatment of Opioid-Induced Constipation

Selective 5HT4 agonists: prucalopride 1 RCT and unpublished data: Sloots 2010[43] (phase 2 study; 4 wk), data from NCT01117051 (12 wk)

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prucalopride	Placebo	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
SBM response (defined as an average of ≥3 SBMs/wk) (follow-up: 4 wk)												
2	Randomized trials Sloots NCT01117051	Not serious	Not serious	Not serious	Serious[a]	Publication bias[b]	126/216 (58.3)	62/149 (41.6)	RR 1.36 (1.08 to 1.70)	15 more per 100 (from 3 more to 29 more)	⊕⊕◯◯ LOW	CRITICAL
Change in SBM frequency												
1	Randomized trials Sloots	Not serious	Not serious	Not serious	Serious[c]	Publication bias[b]			MD 0.7 more with 2 mg MD 1.0 more with 4 mg		⊕⊕◯◯ LOW	IMPORTANT
Reduction in painful defecation/lack of straining (not reported)												
Stool consistency							See footnote[d]					
QOL improvement as measured by PAC-QOL (responder defined as patient achieving improvement or 1 or greater point on satisfaction subscale)												
1	Randomized trials Sloots	Not serious	Not serious	Not serious	Serious[e]	Publication bias[b]	37/130 (28.5)	12/66 (18.2)	RR 1.57 (0.88 to 2.80)	10 more per 100 (from 2 fewer to 33 more)	⊕⊕◯◯ LOW	IMPORTANT
AEs leading to treatment discontinuation												
1	Randomized trials Sloots	Not serious	Not serious	Not serious	Serious[f]	Publication bias[b]	8/130 (6.2)	7/66 (10.6)	RR 0.58 (0.22 to 1.53)	4 fewer per 100 (from 6 more to 8 fewer)	⊕⊕◯◯ LOW	IMPORTANT

[a]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.
[b]Publication bias was a concern as there were no other published studies since the Sloot study. On ClinicalTrials.gov a study titled "Prucalopride Effects on Subjects with Chronic Non-Caner Pain Suffering from Opioid Induced Constipation" was found (NCT01117051), but this study was terminated early (2014) by Movetis after recruitment of 174 patients.
[c]We rated down for imprecision as there were no CIs or SDs provided.
[d]No quantitative data reported. Authors state prucalopride increased the percentage of stools with normal consistency and decreased the percentage of hardness of stools (data not shown).
[e]We rated down for imprecision because the CI crossed the line of no effect.
[f]We rated down for imprecision due to few events.

Table 8. Evidence Profile of Lubiprostone for the Treatment of Opioid-Induced Constipation

Secretagogues: Lubiprostone 3 RCTs: Jamal 2015,[45] Cryer 2014,[44] Spierings 2016[53]												
Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lubiprostone	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
SBM response (defined as ≥3 SBMs/wk for at least 9 of 12 treatment weeks and at least ≥1 SBM improvement/wk for all weeks)												
2	Randomized trials Jamal Spierings	Not serious	Not serious	Not serious	Serious[a]	selective reporting bias[b]	166/437 (38.0)	141/431 (32.7)	1.15 (0.97–1.37)	5 more per 100 (from 1 fewer to 12 more)	⊕⊕◯◯ LOW	CRITICAL
Change in SBM frequency defined as mean increase in weekly SBM from baseline												
3	Randomized trials Jamal Cryer Spierings	Not serious	Not serious	Not serious	Serious[c]	Selective reporting bias[d]	MD 0.8 more (Jamal) and 0.6 more (Cryer). MD 0.10 less (0.78 less to 0.58 more) (Spierings)				⊕⊕◯◯ LOW	IMPORTANT
Reduction in straining was scored on a 5-point scale ranging from 0 (absent) to 4 (very severe)												
1	Randomized trials Spierings	Not serious	Not serious	Not serious	Not serious[e]	Selective reporting bias[f]	MD of –0.30 (–0.47 to –0.13) (Spierings)				⊕⊕⊕◯ MODERATE	IMPORTANT
Stool consistency was assessed using a 5-point scale ranging from 0 (very loose) to 4 (very hard; little balls)												
1	Randomized trials Spierings	Not serious	Not serious	Not serious	Not serious[g]	Selective reporting bias[f]	MD of –0.20 (–0.37 to –0.03) (Spierings)				⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of Life (assessed with the PAC-QOL; MID 1 point)												
1	Randomized trials Jamal	Not serious	Not serious	Not serious	Serious[h]	Selective reporting bias[6]	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				⊕⊕◯◯ LOW	IMPORTANT

Table 8. Continued

Secretagogues: Lubiprostone 3 RCTs: Jamal 2015,[45] Cryer 2014,[44] Spierings 2016[53]												
Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lubiprostone	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
AEs leading to treatment discontinuation[i]												
3	Randomized trials Jamal Cryer Spierings	Not serious	Not serious	Not serious	Serious[j]	None	41/643 (6.4)	19/632 (3.0)	2.13 (1.25 to 3.61)	3 more per 100 (from 1 more to 8 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

[a]We rated down for imprecision because the CIs did not cross our threshold of a clinically meaningful difference.
[b]We rated down for selective outcome reporting bias. The Cryer study did not report results on the responder outcome and the Spierings 2017 study did not report the responder outcome from the 12-week OPAL study; data to inform the SBM responder outcome were obtained from Clinical.Trials.gov (NCT00597428).
[c]We rated down for imprecision, as there were no CIs or SDs reported and there was uncertainty about the range of possible effects.
[d]We rated down due to issues with how the data were analyzed/reported. The Spierings data were obtained from ClinicalTrials.gov.
[e]An increase in SBM frequency was found, however, it is unclear if this is a clinically meaningful improvement.
[f]In the Jamal and Cryer studies, the authors reported a statistically significant improvement in this outcome, however, they did not provide any quantitative information for this outcome.
[g]An improvement in stool consistency was found, however, it is unclear if this is a clinically meaningful improvement.
[h]We rated down for imprecision as there were no CIs or SDs reported and there was uncertainty about the range of possible effects.
[i]Data on AEs was pooled from the 12-week Jamal, Cryer, and Spierings studies. An open-label extension study published by Spierings 2016 showed that only 23/439 (5.2%) participants discontinued the medication due to AE over 9 months of follow-up.
[j]We rated down for imprecision due to few events.

treatment occurred in 41 of 643 (6.4%) patients receiving lubiprostone and 19 of 632 (3.0%) patients receiving placebo (RR, 2.13; 95% CI, 1.25–3.61). In the open-label extension study by Spierings et al,[52] only 23 of 439 (5.2%) participants discontinued the medication due to AEs over 9 months of follow-up.

Quality of evidence. Overall, there was concern about selective reporting bias across the studies, which lowered our confidence in the effect estimates. For SBM response, we rated down for imprecision (the range of effects did not cross our threshold of a clinically meaningful response). For SBM frequency, we rated down because there was uncertainty about the range of possible effects, as we could not pool across studies. For improvement in stool consistency, reduction in straining, and QOL, it was unclear if the differences reported were clinically meaningful improvements. For AEs, the quality of the evidence was moderate. The evidence is summarized in Table 8. ***The overall quality of evidence for the use of lubiprostone for OIC is low.***

Evidence Gaps

Our review of the literature identifies several areas where lack of high quality studies limited our ability to adequately inform specific clinical questions or inform patient important outcomes relevant for decision-making. For example, we found limited data for laxatives in OIC. Given the ease of availability (over the counter), lower cost, and favorable safety profile, laxatives are commonly used as first-line treatment for patients with OIC.[20,21] Large RCTs conducted in OIC patients (diagnosed using Rome criteria) evaluating the efficacy of osmotic, stimulant or lubricating laxatives (administered in scheduled doses as single agents or in combination) are needed to fill this evidence gap. These studies should evaluate all patient-important outcomes including SBM response, SBM frequency, stool consistency, straining and quality of life. Furthermore, while only a limited number of clinical trials explicitly defined and recruited laxative refractory patients, the majority of studies recruited patients who had been using laxatives for management of constipation in the setting of chronic opioid use and were required to discontinue its use once enrolled in the clinical trial. Future studies of OIC should specify if subgroups of patients are laxative-refractory, have explicit criteria for defining this subgroup and evaluate response based on laxative refractory status. In this technical review, only studies of naloxegol specified laxative refractory cohorts and reported on results based on this subgroup.

Our review also highlighted several areas for improvement in clinical trial designs of future studies of OIC. Future RCTs should use FDA responder criteria as the primary outcome, which is defined as $\geq$ 3 SBM and $>$ SBM per week over baseline for a specified duration or number of weeks. Given the fact that many patients are long-term chronic users of opioids, trials with treatment durations of at least 12–16 weeks would provide more clinically meaningful data. There is a also need for more consistent use of PROMs, such as PAC-SYM, for the evaluation of other constipation-related symptoms; many of the clinical trials reported improvement of symptoms such as straining or painful defecation using four or five point Likert-type scales that had not been previously validated and no minimal clinically important differences have been published. Furthermore, authors frequently reported mean changes in scores in place of a responder analysis that may be more clinically meaningful. Finally, there is a need for head-to-head trials comparing different drugs, comparative effectiveness studies, cost effective analyses and health care utilization studies would contribute significantly to clinical application of these therapies and help us to further understand the impact of available therapies on reducing the burden of OIC.

Conclusions

The widespread use of opioids for the management of chronic pain has led to a rising incidence in opioid-related adverse effects. Opioid-induced constipation is the most common detrimental side effect of long-term opioids and appropriate prevention, identification, and treatment of OIC is critical in improving the quality of life of chronic opioid users. This technical review was used to inform the accompanying guideline on the pharmacologic management of OIC and outlines several effective medications available to manage OIC. The review focused on laxatives, PAMORAs (naldemedine, naloxegol, alvimopan, and methylnaltrexone, selective 5-HT agonists (prucalopride), and intestinal secretagogues (lubiprostone). Indirect evidence (moderate quality) supports the use of over-the-counter laxatives but there is insufficient data comparing the efficacy of laxatives versus prescription medications targeted to treat OIC. There was evidence to support the use of naledemedine (high quality evidence), naloxegol (moderate quality), and methylnaltrexone (low quality) for OIC but limited evidence to support the use of lubiprostone (low quality) and prucalopride (low quality). The findings in this review are consistent with other recent systematic reviews of therapies for the management of OIC.[54,55] Interestingly, in the recent network meta-analysis by Luthra et al,[54] naldemedine was found to be the most effective drug when SBM response using the responder definition (which we deemed a critical patient-important outcome for our review) was used in the analysis. This technical review informed the development of the first GI society guideline on OIC targeted for gastroenterologists (see accompanying guideline).

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.08.018.

References

1. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in u.s. adults: 2015 national survey on drug use and health. Ann Intern Med 2017;167:293–301.

2. Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. Ther Adv Chronic Dis 2016;7:121–134.
3. Hjalte F, Ragnarson Tennvall G, Welin KO, et al. Treatment of severe pain and opioid-induced constipation: an observational study of quality of life, resource use, and costs in Sweden. Pain Ther 2016;5:227–236.
4. Nelson AD, Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. Therap Adv Gastroenterol 2015; 8:206–220.
5. Abramowitz L, Beziaud N, Labreze L, et al. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. J Med Econ 2013;16:1423–1433.
6. Cowan DT, Wilson-Barnett J, Griffiths P, et al. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med 2003;4:340–351.
7. Ducrotte P, Milce J, Soufflet C, et al. Prevalence and clinical features of opioid-induced constipation in the general population: A French study of 15,000 individuals. United European Gastroenterol J 2017;5:588–600.
8. Olufade T, Kong AM, Princic N, et al. Comparing healthcare utilization and costs among Medicaid-insured patients with chronic noncancer pain with and without opioid-induced constipation: a retrospective analysis. Am Health Drug Benefits 2017;10:79–86.
9. Candrilli SD, Davis KL, Iyer S. Impact of constipation on opioid use patterns, health care resource utilization, and costs in cancer patients on opioid therapy. J Pain Palliat Care Pharmacother 2009;23:231–241.
10. Fernandes AW, Kern DM, Datto C, et al. Increased burden of healthcare utilization and cost associated with opioid-related constipation among patients with noncancer Pain. Am Health Drug Benefits 2016;9:160–170.
11. Kwong WJ, Diels J, Kavanagh S. Costs of gastrointestinal events after outpatient opioid treatment for noncancer pain. Ann Pharmacother 2010;44:630–640.
12. Wan Y, Corman S, Gao X, et al. Economic burden of opioid-induced constipation among long-term opioid users with noncancer pain. Am Health Drug Benefits 2015;8:93–102.
13. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterol Res Pract 2014; 2014:141737.
14. Gaertner J, Siemens W, Camilleri M, et al. Definitions and outcome measures of clinical trials regarding opioid-induced constipation: a systematic review. J Clin Gastroenterol 2015;49:9–16.
15. Drossman DA. Functional gastrointestinal disorders: what's new for Rome IV? Lancet Gastroenterol Hepatol 2016;1:6–8.
16. Drossman DA, Hasler WL. Rome IV-Functional GI disorders: disorders of gut-brain interaction. Gastroenterology 2016;150:1257–1261.
17. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol 2013;11:329–332.
18. Dubois D, Gilet H, Viala-Danten M, et al. Psychometric performance and clinical meaningfulness of the Patient Assessment of Constipation-Quality of Life questionnaire in prucalopride (RESOLOR) trials for chronic constipation. Neurogastroenterol Motil 2010;22:e54–e63.
19. Marquis P, De La Loge C, Dubois D, et al. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol 2005;40:540–551.
20. Argoff CE, Brennan MJ, Camilleri M, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. Pain Medicine (United States) 2015;16:2324–2337.
21. Rentz AM, Yu R, Muller-Lissner S, et al. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12:371–383.
22. Rentz AM, van Hanswijck de Jonge P, Leyendecker P, et al. Observational, nonintervention, multicenter study for validation of the Bowel Function Index for constipation in European countries. Curr Med Res Opin 2011;27:35–44.
23. Ueberall MA, Muller-Lissner S, Buschmann-Kramm C, et al. The Bowel Function Index for evaluating constipation in pain patients: definition of a reference range for a non-constipated population of pain patients. J Int Med Res 2011;39:41–50.
24. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. J Clin Epidemiol 2017;87:4–13.
25. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336: 924–926.
26. Freedman MD, Schwartz HJ, Roby R, et al. Tolerance and efficacy of polyethylene glycol 3350/electrolyte solution versus lactulose in relieving opiate induced constipation: a double-blinded placebo-controlled trial. J Clin Pharmacol 1997;37:904–907.
27. Wirz S, Nadstawek J, Elsen C, et al. Laxative management in ambulatory cancer patients on opioid therapy: a prospective, open-label investigation of polyethylene glycol, sodium picosulphate and lactulose. European journal of cancer care 2012;21:131–140.
28. Twycross RG, McNamara P, Schuijt C, et al. Sodium picosulfate in opioid-induced constipation: Results of an open-label, prospective, dose-ranging study. Palliative Medicine 2006;20:419–423.
29. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209–218.
30. Hale M, Wild J, Reddy J, et al. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicentre, phase 3, double-blind, randomised, parallel-group trials. Lancet Gastroenterol Hepatol 2017;2:555–564.

31. Webster LR, Yamada T, Arjona Ferreira JC. A phase 2b, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of naldemedine for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Med 2017;18:2350–2360.
32. Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. Pain 2018;159:987–994.
33. Katakami N, Harada T, Murata T, et al. Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer. J Clin Oncol 2017;35:3859–3866.
34. Leppert W, Woron J. The role of naloxegol in the management of opioid-induced bowel dysfunction. Therap Adv Gastroenterol 2016;9:736–746.
35. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. New England Journal of Medicine 2014;370:2387–2396.
36. Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain 2013;154:1542–1550.
37. Webster L, Chey W, Tack J, et al. Long-term safety and tolerability of naloxegol in patients with opioid-induced constipation. American journal of gastroenterology 2013;108:S568–S569.
38. Webster L, Chey WD, Tack J, et al. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Alimentary pharmacology & therapeutics 2014;40:771–779.
39. Tack J, Lappalainen J, Diva U, et al. Efficacy and safety of naloxegol in patients with opioid-induced constipation and laxative-inadequate response. United European Gastroenterology Journal 2015;3:471–480.
40. Irving G, Penzes J, Ramjattan B, et al. A randomized, placebo-controlled phase 3 trial (study sb-767905/013) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. Journal of Pain 2011;12:175–184.
41. Jansen JP, Lorch D, Langan J, et al. A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain 2011;12:185–193.
42. Webster L, Jansen JP, Peppin J, et al. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain 2008;137:428–440.
43. Bull J, Wellman CV, Israel RJ, et al. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. J Palliat Med 2015;18:593–600.
44. Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. J Pain 2011;12:554–562.
45. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. J Pain Symptom Manage 2008;35:458–468.
46. Rauck R, Slatkin NE, Stambler N, et al. Randomized, Double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. Pain Practice 2016;17:17.
47. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol 2009;7:39–46.
48. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008;358:2332–2343.
49. Sloots CEJ, Rykx A, Cools M, et al. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci 2010;55:2912–2921.
50. Cryer B, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Medicine 2014;15:1825–1834.
51. Jamal MM, Adams AB, Jansen JP, et al. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol 2015;110:725–732.
52. Spierings ELH, Drossman DA, Cryer B, et al. Efficacy and safety of lubiprostone in patients with opioid-induced constipation: phase 3 study results and pooled analysis of the effect of concomitant methadone use on clinical outcomes. Pain Med 2018;19:1184–1194.
53. Spierings ELH, Rauck R, Brewer R, et al. Long-term safety and efficacy of lubiprostone in opioid-induced constipation in patients with chronic noncancer pain. Pain Practice 2016;16:985–993.
54. Luthra P, Burr NE, Brenner DM, et al. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut 2018.
55. Nee J, Zakari M, Sugarman MA, et al. Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2018.

Reprint requests
Address requests for reprints to: Shahnaz Sultan, MD, MHSc, Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, 516 Delaware Street, SE 1-124C, MMC 36, Minneapolis, Minnesota 55455. e-mail: ssultan@umn.edu; fax: (612) 625-5620.

Conflicts of interest
All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland and pertinent disclosures are published with the report.

Final Search Strategy–Opioid-Induced Constipation

Search date: February 18, 2017; May 17, 2018[a]

Limits: English language, humans; removed case reports, editorials, letters, notes, comments

Databases searched: Embase Classic+Embase 1947 to 2017 February 17; May 17*, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Wiley Cochrane

Embase, Ovid MEDLINE(R)

No.	Searches	Results
1	exp Analgesics, Opioid/ use ppez or exp Opiate/ use emczd	179190
2	(opioid* or opiate*).ti,ab.	199930
3	1 or 2	292693
4	exp Constipation/	89379
5	(constipa* or colonic inertia).ti,ab.	54938
6	4 or 5	105515
7	3 and 6	7809
8	((opioid* or opiate*) adj3 constipation).ti,ab.	1290
9	7 or 8	7809
10	exp Cathartics/ use ppez or exp Laxatives/ use ppez or exp Laxative/ use emczd	196392
11	(cathartic* or laxative* or bowel evacuant* or purgative*).ti,ab.	15503
12	exp Polyethylene Glycols/ use ppez or exp macrogol 3350/ use emczd	60804
13	(PEG 3350 or Miralax or macrogol 3350).ti,ab.	831
14	exp Methylcellulose/	14300
15	(methylcellulose or senna or Psyllium or metamucil or bisacodyl).ti,ab.	15095
16	exp Lubiprostone/ use ppez	147
17	(Amitiza or lubiprostone).ti,ab.	667
18	(linaclotide or linzess).mp.	876
19	exp Serotonin 5-HT4 Receptor Agonists/ use ppez	253
20	exp serotonin 4 agonist/ use emczd	836
21	exp prucalopride/ use emczd	861
22	(prucalopride or resotran* or Resolor).mp.	1178
23	exp mu opiate receptor antagonist/ use emczd	1410
24	(Peripherally-Acting Mu-Opioid Receptor Antagonist* or PAMORA*).mp.	232
25	exp naloxegol/ use emczd	167
26	exp 17 methylnaltrexone/ use emczd	828
27	(naloxegol or methylnaltrexone or Relistor or Movantik).mp.	1503
28	exp alvimopan/ use emczd	633
29	(alvimopam or Entereg).mp.	133
30	exp naloxone plus oxycodone/ use emczd	224
31	(Targin or Targiniq or Targinact).mp.	131
32	exp Naloxone/ use ppez	23682
33	exp Oxycodone/ use ppez	1730
34	32 and 33	175
35	exp naldemedine/ use emczd or exp axelopran/ use emczd	29
36	(TD-1211 or naldemedine or axelopran).mp.	55
37	or/10-31	281091
38	or/34-37	281245
39	9 and 38	2302
40	limit 39 to english language	2082
41	animals/ not (humans/ and animals/)	5511710
42	40 not 41	2073
43	remove duplicates from 42	1630
44	limit 43 to (editorial or letter or note or case reports or comment) [Limit not valid in Embase, Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	115
45	Case Report/	4077671
46	43 not (44 or 45)	1451
47	(Meta Analysis or Controlled Clinical Trial).pt.	166578
48	Meta - Analysis/ use ppez or Meta - Analysis as Topic/ use ppez or exp Technology Assessment, Biomedical/ use ppez	98883
49	(meta analy* or metaanaly* or health technolog* assess*).mp.	343139
50	Meta Analysis/ use emczd or "Meta Analysis (Topic)"/ use emczd or Biomedical Technology Assessment/ use emczd	193878

Continued

No.	Searches	Results
51	exp Randomized Controlled Trial/	928762
52	exp Random Allocation/ use ppez or exp Double - Blind Method/ use ppez or exp Control Groups/ use ppez or exp Placebos/ use ppez	245166
53	exp Randomization/ use emczd or exp RANDOM SAMPLE/ use emczd or Double Blind Procedure/ use emczd or exp Triple Blind Procedure/ use emczd or exp Control Group/ use emczd or exp PLACEBO/ use emczd	768043
54	(random* or RCT or RCTs or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.	2442149
55	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pub med or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab.	528788
56	or/47-55	3573646
57	46 and 56	559

[a]This search was re-run to capture any additional references published between February 17, 2017 and May 17, 2018. A total of 20 citations were found and 1 met our inclusion criteria.

Wiley Cochrane Library

Date Run: 18/02/17; 18/05/17[a]

Description:

ID	Search	Hits
#1	MeSH descriptor: [Analgesics, Opioid] explode all trees	6025
#2	(opioid* or opiate*):ti,ab	11048
#3	#1 or #2	14427
#4	MeSH descriptor: [Constipation] explode all trees	1120
#5	(constipa* or colonic inertia):ti,ab	3701
#6	#4 or #5	3940
#7	#3 and #6	423
#8	((opioid* or opiate*) near/3 constipation):ti,ab	151
#9	#7 or #8	423
#10	MeSH descriptor: [Cathartics] explode all trees	640
#11	MeSH descriptor: [Laxatives] explode all trees	129
#12	(cathartic* or laxative* or bowel evacuant* or purgative*):ti,ab	829
#13	MeSH descriptor: [Polyethylene Glycols] explode all trees	2621
#14	(PEG 3350 or Miralax or macrogol 3350):ti,ab	71
#15	MeSH descriptor: [Methylcellulose] explode all trees	265
#16	(methylcellulose or senna or Psyllium or metamucil or bisacodyl):ti,ab	649
#17	MeSH descriptor: [Lubiprostone] explode all trees	17
#18	(Amitiza or lubiprostone):ti,ab	66
#19	(linaclotide or linzess):ti,ab	74
#20	MeSH descriptor: [Serotonin 5-HT4 Receptor Agonists] explode all trees	29
#21	(prucalopride or resotran* or Resolor):ti,ab	81
#22	(Peripherally-Acting Mu-Opioid Receptor Antagonist* or PAMORA*):ti,ab	38
#23	(naloxegol or methylnaltrexone or Relistor or Movantik):ti,ab	87
#24	(alvimopam or Entereg):ti,ab	2
#25	(Targin or Targiniq or Targinact):ti,ab	6
#26	(TD-1211 or naldemedine or axelopran):ti,ab	11
#27	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26	4549
#28	MeSH descriptor: [Naloxone] explode all trees	1756
#29	MeSH descriptor: [Oxycodone] explode all trees	465
#30	#28 and #29	41
#31	#27 or #30	4583
#32	#9 and #31	152

[a]This search was re-run to capture any additional references published between February 17, 2017 and May 17, 2018. A total of 20 citations were found and 1 met our inclusion criteria.

Supplementary Table 1. Evidence Profile of Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Patients With Non-Cancer Pain and Advanced Illness/Cancer Pain

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methylnaltrexone	Placebo/ usual care	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
RFBM response (defined as ≥3 RFBMs/wk)												
3	Randomized trials Rauck[41] Thomas[42] Michna[40]	Not serious	Not serious	Serious[a]	Serious[b]	None	485/963 (50.4)	171/434 (39.4)	1.33 (1.16–1.52)	13 more per 100 (from 6 more to 20 more)	⊕⊕◯◯ LOW	CRITICAL
Laxation response												
5	Randomized trials Rauck Bull Slatkin Porteney Thomas	Not serious	Not serious	Serious[a]	Not serious	None	220/602 (36.5)	48/396 (12.1)	3.50 (2.65–4.62)	30 more per 100 (from 20 more to 44 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Change in RFBM frequency[c]												
3	Randomized trials Rauck Michna	Not serious	Not serious	Serious[a]	Serious[c]	None	MD 1.60 more with 12 mg sc qd and 0.60 more with 12 mg sc qod (Michna) MD 0.5 more with 300 mg/450 mg and 0.1 more with 150 mg (Rauck)				⊕⊕◯◯ LOW	IMPORTANT
Reduction in straining assessed using a straining scale 0 (none) to 4 (very severe)							See footnote[d]					
QOL							See footnote[e]					
AEs leading to treatment discontinuation												
4	Randomized trials Bull Michna Rauck Thomas	Not serious	Not serious	Serious[a]	Serious[f]	None	49/1080 (4.5)	20/548 (3.6)	1.51 (0.83–2.71)	2 more per 100 (from 1 fewer to 6 more)	⊕⊕◯◯ LOW	IMPORTANT

qd, once daily; qod, every other day; sc, subcutaneous.
[a]We rated down for indirectness because we included studies in terminally ill and cancer patients with OIC and different doses and formulation of methylnaltrexone.
[b]We rated down for imprecision because 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. Mean change in RFBM frequency: (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 Porteney study was excluded as it was a combined 1-wk RCT and 3-wk open label study. No CIs or standard deviations were provided.
[d]In the study by Michna et al, the authors concluded that compared with placebo, methylnaltrexone led to more RFBM with none or mild straining (MD 11% to 15% more). No raw data provided.
[e]In the study by Michna et al, methylnaltrexone group showed an improvement in the total score of 0.74 (12 mg sc qd) and 0.39 (12 mg sc qod).
[f]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.

Supplementary Table 2. Evidence Profile of Alvimopan for the Treatment of Opioid-Induced Constipation in Patients With Non-Cancer Pain

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alvimopan	Placebo	RR (95% CI)	Absolute (95% CI)	Quality	Importance
SBM response (at least 3 SBMs/wk over the treatment period and increase of at least 1 SBM/wk)												
3	Randomized trials Irving Jansen Webster	Serious[a]	Not serious[b]	Not serious	Serious[c]	None	685/1060 (64.6)	224/465 (48.2)	1.36 (1.08 to 1.70)	17 more per 100 (from 4 more to 34 more)	⊕⊕◯◯ LOW	CRITICAL
Change in SBM frequency (mean change in weekly SBM frequency compared with baseline)												
2	Randomized trials Irving Jansen	Serious[d]	Not serious	Not serious	Serious[e]	None	MD 0.87 more (Irving) and 1.50 more (Jansen) with 0.5 mg bid MD 1.01 more (Irving) and 1.41 more (Jansen) with 0.5 mg qd				⊕⊕◯◯ LOW	IMPORTANT
Reduction in straining assessed using a 4-point scale ranging from 1 (no straining) to 4 (severe straining). Response defined as an average score of less than or equal to 2												
3	Randomized trials Irving Jansen Webster	Serious[a]	Not serious[f]	Not serious	Not serious[g]	None	357/1060 (33.7)	89/465 (19.1)	1.83 (1.16–2.87)	16 more per 100 (from 3 more to 36 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Improvement in stool consistency assessed using a 4-point scale (1 = watery/loose stools, 2 = semisolid/soft, 3 = lumpy hard stools, and 4 = small pellets). Response defined an average score between 1.75 and 2.25 (inclusive) or normal stool (semisolid/solid)												
3	Randomized trials Irving Jansen Webster	Serious[a]	Serious[h]	Not serious	Not serious[g]	None	480/1060 (45.3)	154/465 (33.1)	1.39 (1.03–1.88)	13 more per 100 (from 1 more to 29 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
QOL improvement as measured by the PAC-QOL (MID 1 point)							See footnote[i]					
AEs leading to treatment discontinuation												
3	Randomized trials Irving Jansen Webster	Not serious	Not serious	Not serious	Serious[j]	None	127/1060 (12.0)	37/465 (8.0)	1.30 (0.75–2.26)	2 more per 100 (from 2 fewer to 10 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Supplementary Table 2. Continued

Certainty assessment							Patients, n (%)		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alvimopan	Placebo	RR (95% CI)	Absolute (95% CI)	Quality	Importance
Cardiovascular events												
2	Randomized trials Jansen Webster	Not serious	Not serious	Not serious	Serious[k]	None	12/739 (1.6)	4/301 (1.3)	1.22 (0.40–3.76)	0 more per 100 (from 1 fewer to 4 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

bid, twice a day; qd, once daily.
[a]There was unclear reporting of allocation concealment and blinding across the studies.
[b]There was heterogeneity across the two studies but we didn't rate down for inconsistency (I^2=77%) as the confidence intervals were overlapping.
[c]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference (defined as a NNT of 10 per 100).
[d]There was unclear reporting of allocation concealment and blinding across the studies and issues with how the data were analyzed/reported; no standard deviations or 95% confidence intervals were reported thus data could not be pooled. The Webster study was excluded because they reported change in SBM frequency during the first 3 weeks (of the 6 week) treatment period.
[e]We rated down for imprecision as there was uncertainty about whether the effect estimates were statistically significant.
[f]There was heterogeneity across the two studies (I^2=77%) but we didn't rate down for inconsistency as the confidence intervals were overlapping.
[g]Across the two studies showed a statistically significant difference was found using the responder definition, however it is unclear if this represents a clinically meaningful improvement.
[h]There was heterogeneity across the two studies (I^2=75%) but we didn't rate down for inconsistency as the confidence intervals were overlapping.
[i]Only the Webster et al study reported on QOL. Compared with placebo statistically significant improvements were noted in the overall PAC-QOL score and for most of the subscales.
[j]We rated down for imprecision because the CI crossed our threshold of a clinically meaningful difference.
[k]We rated down for imprecision because of few events.