Methylnaltrexone Bromide (RELISTOR) Subcutaneous Injection

National Drug Monograph ADDENDUM

December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Methylnaltrexone, a quaternary derivative of naltrexone, is a peripherally acting mu-opioid receptor antagonist with a limited ability to cross the blood-brain barrier. It was initially approved in 2008 in the US for the treatment of opioid-induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.
Indication(s) Under Review in This Document	Most recent FDA-approved indication: Treatment of OIC in adult patients with chronic noncancer pain (CNCP).
Dosage Form(s) Under Review	Single-use vial • 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe • 12 mg/0.6 mL solution for subcutaneous injection with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs Single-use pre-filled syringe • 8 mg/0.4 mL solution for subcutaneous injection • 12 mg/0.6 mL solution for subcutaneous injection
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements
Pregnancy Rating	Category C

Executive Summary	
Efficacy	• There is fair-quality evidence from one placebo-controlled trial that methylnaltrexone has a moderate effect size in achieving rescue-free bowel movement (RFBM) within 4 hours after the first dose and in achieving 3 or more RFBMs per week as an alternative to conventional laxatives in non–laxative refractory patients who had constipation associated with opioid therapy of at least 4 weeks' duration for chronic noncancer pain. • About 35% of patients had a RFBM within 4 hours following the first dose of methylnaltrexone. The median time to the first RFBM was not reported. • The comparative efficacy of methylnaltrexone is unclear, relative to alternative agents FDA-approved for OIC in CNCP (i.e., naloxegol and lubiprostone).
Safety	• Methylnaltrexone is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction (as are naloxegol and lubiprostone). • Gastrointestinal perforation occurred rarely in patients with advanced illness who were treated with methylnaltrexone; gastrointestinal perforation is also a warning / precaution for naloxegol but not for lubiprostone. • The most common adverse events were abdominal pain, diarrhea, nausea and hyperhidrosis.
Other Considerations	• Methylnaltrexone therapy was associated with improvement in quality of life of CNCP patients with OIC. • Patients should be advised to be in close proximity to toilet facilities after each dose.
Projected Place in Therapy	• Methylnaltrexone is a safe and efficacious alternative to conventional laxatives for OIC in CNCP. The main advantages of methylnaltrexone over conventional laxatives are a larger evidence base and FDA approval for OIC in CNCP.

- Patient factors, values or preferences that may influence the decision to choose methylnaltrexone over naloxegol or lubiprostone include the need for once-daily injections; a desire or need for rapid laxative effects; a requirement for the patient to be in close proximity to toilet facilities; constipation associated with methadone therapy (for which methylnaltrexone or naloxegol may be preferred over lubiprostone); and concomitant therapy with moderate or strong CYP3A4 inhibitor drugs (with which methylnaltrexone has a lower potential for interactions than naloxegol).

Background

Purpose for Review

To review clinical evidence related to the efficacy and safety of methylnaltrexone in the treatment of OIC in adults with chronic noncancer pain.

Issues to be determined:

- ✔ Evidence of need
- ✔ Does methylnaltrexone offer advantages to currently available alternatives?
- ✔ Does methylnaltrexone offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?
- ✔ Does methylnaltrexone have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other Therapeutic Options

Formulary Alternatives	Other Considerations
Surfactant Docusate capsule, rectal enema, oral liquid (OTC)	Not FDA approved and has limited efficacy for opioid-induced constipation, dosed 1 to 4 times daily, minimal safety risk, extensive history of use and available OTC, onset of action 1 – 3 days.[1]
Osmotic Agents PEG-3350 powder, oral Lactulose syrup Magnesium citrate liquid (OTC) Magnesium hydroxide susp (OTC)	Not FDA approved for opioid-induced constipation, minimal safety risk, extensive history of use and most available OTC; onset of action 1 to 3 hours PO.[1]
Stimulant Laxatives Bisacodyl EC tablet (OTC) Sennosides tablet (OTC)	Recommended first-line agents for opioid-induced constipation despite paucity of quality studies; given orally once daily(or twice daily for sennosides); most common adverse effect abdominal cramping; extensive history of use and available OTC; onset of action 6 – 12 hours PO, < 2 hours rectally.[1]
Combination Surfactant / Stimulant Docusate / Sennosides tablet (OTC)	Recommended first-line agents for opioid-induced constipation; given orally 2 – 4 times daily; onset of action 6 to 12 hours.[2,3]
Bulk-Forming Laxatives Psyllium powder, oral (OTC) Cellulose, oxidized powder, oral Calcium Polycarbophil tablet	NOT recommended for opioid-induced constipation because of potential for bowel obstruction; onset of action 1 – 3 days PO.[1]
Lubricant Mineral oil, heavy 100% (OTC)	NOT recommended for use as a laxative, acute or chronic aspiration may result in lipoid pneumonitis. [4]

Nonformulary Alternative	Other Considerations and Clinical Guidance
Peripherally acting mu-opioid receptor antagonist (PAMORA) (oral) Alvimopan capsule	PAMORA only indicated to accelerate gastrointestinal recovery following certain surgeries; increased risk of myocardial infarction with long-term use and has a REMS to limit therapy to 15 days; onset of action 4 – 7 hours. [5] Alvimopan CFU
PAMORA Naloxegol tablet	FDA-approved for opioid-induced constipation in patients with chronic noncancer pain; once daily dosing on empty stomach; drug and food interactions with CYP3A4 inhibitors; median time to onset 6–12 h. Naloxegol CFU
Chloride Channel Activator Lubiprostone capsule	FDA-approved for opioid-induced constipation in patients with chronic noncancer pain, twice daily dosing with food; common adverse effects are nausea, headache and diarrhea; onset of action < 24 hours.[6] Linaclotide and Lubiprostone CFU

Guanylate Cyclase-C Agonist Linaclotide capsule	Indicated for idiopathic constipation, once daily dosing; most common adverse effect abdominal pain; possible severe diarrhea; onset of action 22 – 24 hours. [7] Linaclotide and Lubiprostone CFU

Efficacy (OIC in CNCP)

Literature Search Summary
A literature search was performed on PubMed/Medline (2010 to Oct 2015) and the Cochrane CENTRAL database using the search terms methylnaltrexone and RELISTOR. The search was limited to studies performed in humans. Systematic reviews / meta-analyses (SRMAs) of randomized controlled trials, randomized controlled trials not reviewed in the SRMAs and long-term (≥1 year) studies published in peer-reviewed journals were included. There was no FDA Medical Review report on methylnaltrexone for OIC in CNCP.

Review of Efficacy
The overall quality of evidence of efficacy is fair; although a placebo-controlled trial evaluating methylnaltrexone for OIC in CNCP was of high quality, it has not been verified by other trials.

- **Comparative Efficacy**. The literature search found no active-controlled trials. The available systematic reviews and meta-analyses that included other laxatives were not specific for OIC in CNCP (Table 1), and one systematic review reported results by individual studies and did not perform meta-analyses.[8]

Table 1 Studies Evaluating Methylnaltrexone for OIC in CNCP

Reference	Interventions, N (K)*	Outcome Measures	Selected Efficacy Results	Comments
SRMAs of PCTs in any patient group (including CNCP, advanced illness and postsurgical)				
Ford (2013)[9]	MNTX 1610 (6) Naloxone 798 (4) Alvimopan 1693 (4) Lubiprostone — (2)	Failure to respond to therapy AEs	*RR vs. PBO (95% CI):* MNTX 0.69 (0.63–0.75) NX 0.64 (0.56–0.72) ALV 0.71 (0.65–0.78) LUB – precluded meta-analysis	Not specific for OIC in CNCP. The 6 MNTX trials included 4 for s.c. MNTX, 1 i.v., and 1 p.o. Of the 4 s.c. trials, only 1 was for OIC in CNCP.
RCT in CNCP, Not Laxative Refractory				
Michna (2011)[11]	MNTX 12 mg q.d., 150 MNTX 12 mg q.o.d., 148 PBO, 162 4 wk	BM count Time of BM RFBM within 4 h Straining Sense of complete evacuation Bristol Stool Form Scales QoL	Achieved RFBM within 4 h after first dose: 33.3% vs. 35.1% vs. 9.9%; All MNTX 34.2% vs. 9.9% ($p < 0.001$), **NNT ≈ 4** Had first BM by 8 h / 24 h, All MNTX vs. PBO: 38% / 46% vs. 12% / 25% ($p < 0.001$). Change from BL in no. of RFBMs per week: 3.1 vs. 2.1 vs. 1.5 ($p \leq 0.01$ for each dose vs. PBO). Had ≥3 RFBMs/week: 58.7% vs. 45.3% vs. 38.3%; **NNT ≈ 5 for q.d.; NNT ≈ 14 for q.o.d.**	Study is included in the SR by Siemens, et al (2015)[8] and the SRMA by Ford, et al (2013)[9]. High quality
Iyer (2011)[10]	Same as Michna (2011)	Patient-reported constipation symptoms and pain intensity scores	MNTX was superior to PBO in abdominal, rectal and stool symptoms, and global scores	Included in SR by Siemens, et al (2015)[8]

*For drugs marketed in the US. BL, Baseline; BM, bowel movement (with or without rescue laxative); RFBM, Rescue-free bowel movements

- **Efficacy Relative to Placebo**. One high-quality study showed that methylnaltrexone (12 mg once daily, the approved dosage regimen) has a moderate effect size relative to placebo, with an NNT of 4 for achieving rescue-free bowel movement (RFBM) within 4 hours after the first dose and an NNT of 5 in terms of the percentage of patients who achieved ≥3 RFBMs per week.[11]

- Methylnaltrexone did not affect pain intensity scores.[12]
- **Subgroup Response Predictor**: A post hoc analysis of the results of a multicenter, double-blind, placebo-controlled randomized clinical trial involving CNCP patients with OIC showed that an early laxative response (rescue-free bowel movements [RFBMs] within 4 hours) to 2 or more of the first 4 doses of methylnaltrexone (12 mg s.c. daily) predicted a subgroup of patients who had a beneficial overall response (≥3 RFBMs / week) during the 4-week treatment period. An overall response (≥ 3 RFBMs per week) was seen in 47 (81%) of 58 patients who had an early response to 2 or more doses compared with 34 (43%) of 79 patients ($p < 0.0001$; odds ratio 5.7) who had an early response to fewer than 2 doses.[13] Therefore, patients who had greater responses to the initial four daily doses of methylnatrexone had better responses to subsequent doses.

Potential Off-Label Use

- Treatment of acute OIC following orthopedic surgical procedures: insufficient evidence to support routine use (Phase II trial; N = 33).[14]
- Treatment of methadone-induced constipation in patients enrolled in a methadone maintenance program (DB RCT, N = 22, intravenous methylnaltrexone).[15]
- Treatment of gastrointestinal stasis in critically ill patients on fentanyl infusions who did not respond to senna and docusate within 72 hours of admission to the intensive care unit: methylnaltrexone outperformed conventional rescue therapy (sodium picosulfate and glycerin suppositories) in laxation and time to laxation (retrospective chart review, N = 15, subcutaneous methylnaltrexone).[16]
- Ineffective for relief of postoperative ileus following segmental colectomy in 2 DB RCTs (N = 1048, intravenous methylnaltrexone).[17]

Safety

For more detailed information, refer to the prescribing information.

	Comments
Boxed Warning	• None
Contraindications	• Known or suspected mechanical gastrointestinal obstruction
Warnings / Precautions	• Severe or persistent diarrhea (discontinue treatment, consult physician) • Rare cases of gastrointestinal perforation have been reported in advanced illness patients (use caution in patients with known or suspected gastrointestinal lesions). • Opioid withdrawal (consider the overall risk-benefit in patients with disruptions to the blood-brain barrier; monitor closely for symptoms of opioid withdrawal).

Long-term Safety Extension Trial

- According to the prescribing information for methylnaltrexone, a 48-week, open-label, uncontrolled trial was conducted.[18] Of 1034 adults with OIC and CNCP who entered the extension trial, a total of 624 patients (60%) completed at least 24 weeks and 477 (46%) completed 48 weeks of treatment. The adverse event profile was similar to that seen during the 4-week double-blind study. There were 4 myocardial infarctions (1 fatal), 1 stroke (fatal), 1 fatal cardiac arrest and 1 sudden death. The causal relationships between methylnaltrexone and these deaths and serious adverse events could not be established.

Safety Considerations

- Most adverse events seen during methylnaltrexone therapy were mild to moderate and comparable to those seen in the placebo group.[11]
- The most common adverse events involved the gastrointestinal tract. Abdominal pain (19.3%, 15.5%, 3.7% for methylnaltrexone 12 mg once daily, 12 mg every other day and placebo, respectively), diarrhea (6.0%, 11.5%, 3.7%) and nausea (8.7%, 11.5%, 6.2%) occurred in more patients on methylnaltrexone than on placebo.[11]
- Hyperhidrosis was reported more commonly on subcutaneous methylnaltrexone 12 mg once daily and 12 mg every other day than on placebo (6.0%, 6.1% and 1.2%, respectively).[11]
- There is a lack of long-term safety studies.

Adverse Reactions

Common adverse reactions	Incidence >5%: Abdominal pain, flatulence, nausea, dizziness, diarrhea, hyperhidrosis
Serious Adverse Reactions[11]	MNTX 12 mg q.d. (N = 150) vs. q.o.d. (N = 148) vs. PBO (N = 162): 3.3% vs. 0.7% vs. 1.2% (no significant differences)
Discontinuations Due to Adverse Reactions[11]	6.7% vs. 8.8% vs. 9.9%

Other Considerations

- The results from the placebo-controlled trial of methylnaltrexone for OIC in CNCP also showed significant improvement in patient quality of life relative to placebo. Mean improvement from baseline in the Patient Assessment of Constipation-Quality of Life (PAC-QOL) total score for methylnaltrexone 12 mg once daily, 12 mg every other day and placebo were 0.74 (33%), 0.59 (27%) and 0.39 (18%; $p \leq 0.014$ for each comparison).[11]

Dosing and Administration

- Methylnaltrexone is administered as a subcutaneous injection.
- Recommended dose for OIC in CNCP: 12 mg once daily.
- Reduce dose by one-half in severe renal impairment (CrCl <30 ml/min).
- Maintenance laxative therapy should be discontinued before starting methylnaltrexone and may be resumed if in patients who have OIC symptoms after taking methylnaltrexone for 3 days.
- Methylnaltrexone has been shown to be efficacious in patients who have taken opioids for at least 4 weeks. Sustained exposure to opioids prior to starting methylnaltrexone may increase the patient's sensitivity to the effects of methylnaltrexone.
- Patient should be within close proximity to toilet facilities once a dose is administered.

Special Populations (Adults)

	Comments
Elderly	• In clinical trials, no differences have been observed between older patients (≥65 years, N = 226) and younger patients. • Cannot rule out greater sensitivity of some older individuals.
Pregnancy	• Use of methylnaltrexone during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood brain barrier
Lactation	• Whether methylnaltrexone is secreted into human milk is unknown.
Renal Impairment	• Mild–moderate renal impairment: No dosage adjustment. • Severe renal impairment (CrCl <30 ml/min): Reduce dose by 50%.
Hepatic Impairment	• Mild–moderate hepatic impairment: No dosage adjustment. • Severe hepatic impairment: No recommendations.
Pharmacogenetics/genomics	• No data.

Projected Place in Therapy

- The incidence of OIC in US Veterans prescribed opioid therapy for CNCP is unknown. Clinical guidelines for the use of long-term opioid therapy in CNCP noted that most patients treated with opioids develop some degree of constipation.[19] In one survey, 81% of people reported constipation from opioid use, and 45% reported fewer than 3 bowel movements per week.[20] Systematic reviews of short-term, randomized trials of opioids in CNCP showed that constipation was one of the most common adverse events, reported in 41% of patients after 8 weeks of therapy in one review[21] and 15% of study patients in another review.[22] Duration of opioid therapy, female gender, older age, higher education levels, concomitant aspirin use and nonsmoker status may be predictive factors for reporting OIC.[23,24] OIC adds another disease burden that reduces quality of life in patients suffering from chronic pain[25,26] and leads to inadequate pain control because of modifications made to opioid regimens to alleviate constipation.[27]
- Since tolerance to the constipating effects of opioids does not develop, a bowel regimen should be prescribed prophylactically[28] and definitely as soon as it is deemed necessary[29] to patients receiving opioid therapy. While the mainstays of conventional bowel regimens for OIC are the stimulant laxatives, stool softeners and lifestyle changes, such

as increasing fluid intake, dietary fiber and physical activity, are also often recommended.[28] Osmotic agents such as PEG-3350 (e.g., MIRALAX) and lactulose are other options. Stool softeners are often given for constipation but there is little data to support their efficacy,[30,31] and one trial showed no additional benefit from adding docusate to sennosides for constipation in hospice patients.[32] Bulk-forming laxatives are not recommended and are relatively contraindicated for OIC because they may cause bowel obstruction.[28]

- Laxatives are considered appropriate first-line therapy for OIC because of their safety and low cost; however, none reverse the specific OIC mechanism, which is activation of enteric mu-opioid receptors. This mu-opioid receptor activation leads to decreased intestinal secretion, increased fluid absorption and decreased colonic propulsion.[33] None of the conventional laxatives are FDA approved for OIC in CNCP.
- The literature search found no evidence-based guidelines recommending the place in therapy of methylnaltrexone for OIC in CNCP. One systematic review / meta-analysis concluded that methylnaltrexone, naloxone and alvimopan are safe and effective for the treatment of OIC, whereas there was insufficient evidence for lubiprostone at the time of the report.[9]
- Taking into consideration indirect evidence from trials evaluating methylnaltrexone for OIC in patients with advanced illness, there is high-quality evidence that methylnaltrexone is safe and efficacious for OIC, although the evidence is fair quality that methylnaltrexone is a safe and efficacious alternative to conventional laxatives for OIC specifically in CNCP. The clinical trial populations represented selected groups of patients; therefore, the extent to which the efficacy and safety trial results apply to US Veterans on opioid therapy is unclear. However, there are no specific reasons to avoid a trial of methylnaltrexone in US Veterans for OIC in CNCP.
- The efficacy and safety of methylnaltrexone are counterbalanced by a lack of data on their efficacy relative to conventional laxatives, lack of long-term efficacy and safety studies, and higher drug acquisition costs.
- Patient factors, values or preferences that may influence the decision to choose methylnaltrexone over naloxegol or lubiprostone include the need for daily injections; a desire or need for rapid laxative effects; a requirement for the patient to be in close proximity to toilet facilities after each dose; constipation associated with methadone therapy (for which methylnaltrexone or naloxegol may be preferred because the efficacy of lubiprostone may be reduced by methadone and has not been established for methadone-induced constipation); and concomitant therapy with moderate or strong CYP3A4 inhibitor drugs (with which methylnaltrexone or lubiprostone has a lower potential for interactions than naloxegol).

Prepared December 2015. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Services (10P4P)

References

1 Sharkey KA, Wallace JL. Chapter 46. Treatment of Disorders of Bowel Motility and Water Flux; Anti-Emetics; Agents Used in Biliary and Pancreatic Disease. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011. http://accesspharmacy.mhmedical.com/content.aspx?bookid=374&Sectionid=41266256. Accessed December 18, 2014.

2 PERI-COLACE- docusate sodium and sennosides tablet Prescribing Information. Purdue Products. 2013.

3 McQuaid KR. Chapter 62. Drugs Used in the Treatment of Gastrointestinal Diseases. In: Katzung BG, Masters SB, Trevor AJ. eds. Basic & Clinical Pharmacology, 12e. New York, NY: McGraw-Hill; 2012. http://accesspharmacy.mhmedical.com/content.aspx?bookid=388&Sectionid=45764290. Accessed December 18, 2014.

4 Fakata KL, Tuteja AK, Lipman AG. Opioid bowel dysfunction in acute and chronic nonmalignant pain. In: Yuan C-S, ed. Handbook of Opioid Bowel Syndrome. Binghamton, NY: Haworth Medical Press; 2005:101-118.

5 Schmidt WK: Alvimopan* (ADL 8-2698) is a novel peripheral opioid antagonist. Am J Surg 2001; 182(5A suppl):11S-18S.

6 AMITIZA (lubiprostone) Prescribing Information. Bethesda, MD. Sucampo Pharma Americas. 2006.

7 Johnston JM, Lavins BJ, MacDougall JE, Lembo AJ, Schneier H, Shiff SJ, Kurtz CB, Currie MG. T1273 Time to Onset of Linaclotide Effect On the Bowel Habits in Patients with Chronic Constipation: Results from a Phase 2B Study. Gastroenterology. 2009;136(5)S1:A-537.

8 Siemens W, Gaertner J, Becker G. Advances in pharmacotherapy for opioid-induced constipation - a systematic review. Expert Opin Pharmacother. 2015 Mar;16(4):515-32

9 Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. Am J Gastroenterol. 2013 Oct;108(10):1566-74

10 Iyer SS, Randazzo BP, Tzanis EL et al. Effect of subcutaneous methylnaltrexoneon patient-reported constipation symptoms. *Value Health*. 2011; 14:177-83.

[11] Michna E, Blonsky ER, Schulman S, Tzanis E, Manley A, Zhang H, Iyer S, Randazzo B. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. J Pain. 2011 May;12(5):554-62

[12] Webster L , Brenner D , Barrett A , Paterson C , Bortey E and Forbes W. Analysis of opioid-mediated analgesia in studies with methylnaltrexone for opioid-induced constipation in patients with chronic noncancer pain. Journal of pain, 2015, 16(4 SUPPL. 1), S92

[13] Michna E , Weil AJ , Duerden M , Schulman S , Wang W , Tzanis E , Zhang H , Yu D , Manley A and Randazzo B. Efficacy of subcutaneous methylnaltrexone in the treatment of opioid-induced constipation: a responder post hoc analysis. Pain medicine (Malden, Mass.), 2011, 12(8), 1223

[14] Anissian L , Schwartz HW , Vincent K , Vincent HK , Carpenito J , Stambler N and Ramakrishna T. Subcutaneous methylnaltrexone for treatment of acute opioid-induced constipation: phase 2 study in rehabilitation after orthopedic surgery. Journal of hospital medicine, 2012, 7(2), 67

[15] Yuan CS , Foss JF , O'Connor M , Osinski J , Karrison T , Moss J and Roizen MF. **Methylnaltrexone** for reversal of constipation due to chronic methadone use: a randomized controlled trial. JAMA, 2000, 283(3), 367

[16] Sawh SB, Selvaraj IP, Danga A, Cotton AL, Moss J, Patel PB. Use of methylnaltrexone for the treatment of opioid-induced constipation in critical care patients. Mayo Clin Proc. 2012 Mar;87(3):255-9

[17] Yu CS, Chun HK, Stambler N et al.Safety and efficacy of methylnaltrexone in shortening the duration of postoperative ileus following segmental colectomy:results of two randomized, placebo controlled phase 3 trials. *Dis Colon Rectum*. 2011; 54:570-8. Cited in: Rodriguez RW. Off-label uses of alvimopan and methylnaltrexone. Am J Health Syst Pharm. 2014 Sep 1;71(17):1450-5

[18] Methylnaltrexone (RELISTOR) for Subcutaneous Injection. Raleigh, NC: Salix Pharmaceuticals; Sep 2014. Available at: http://shared.salix.com/shared/pi/relistor-pi.pdf?id=915545

[19] Chou R, Fanciullo GJ, Fine, PG, Adler JA, Ballantyne JC, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain 2009; 10 (2): 113–130

[20] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med. 2009 Jan;10(1):35-42

[21] Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. 2004 Dec;112(3):372-80

[22] Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther. 2005;7(5):R1046-51

[23] Tuteja AK, Biskupiak J, Stoddard GJ *et al*. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil* 2010;**22**:424–430 , e96.

[24] Cherny NI. Opioid analgesics: comparative features and prescribing guidelines. *Drugs* 1996;**51**:713–737

[25] Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med. 2009 Jan;10(1):35-42

[26] LoCasale RJ, Datto CJ, Margolis MK, Tack J, Coyne KS. The impact of opioid-induced constipation among chronic pain patients with sufficient laxative use. Int J Clin Pract. 2015 Sep 6. doi: 10.1111/ijcp.12718. [Epub ahead of print] PubMed PMID: 26344578

[27] Gupta S, Patel H, Scopel J, Mody RR. Impact of constipation on opioid therapy management among long-term opioid users, based on a patient survey. J Opioid Manag. 2015 Jul-Aug;11(4):325-38

[28] Veterans Health Administration, Department of Defense. VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Washington (DC): Veterans Health Administration, Department of Defense; 2010. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/

[29] Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, et al.; American Society of Interventional Pain Physicians. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. Pain Physician. 2012 Jul;15(3 Suppl):S67-116

[30] Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol* 2005;**100**:936–971

[31] Treatments for Constipation: A Review of Systematic Reviews [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Nov 17. Available from http://www.ncbi.nlm.nih.gov/books/NBK263445/

[32] Tarumi Y, Wilson MP, Szafran O *et al*. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. *J Pain Symptom Manage* 2013;**45**:2–13

[33] Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil. 2014 Oct;26(10):1386-95

Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.