

**Peripherally Acting Mu-Opioid Receptor Antagonists
For Opioid-Induced Constipation
Utah Medicaid Pharmacy and Therapeutics Review**

56:92 GI Drugs, Miscellaneous

Methylnaltrexone (Relistor[®])

Naloxegol (Movantik[®])

Final Report

December 2015

Review prepared by:
Vicki Frydrych, BS, PharmD, Clinical Pharmacist

University of Utah College of Pharmacy
Copyright © 2015 by University of Utah College of Pharmacy
Salt Lake City, Utah. All rights reserved.

Abbreviations:

ALV - Alvimopan
AUC – Area under the curve
BBB – Blood brain barrier
C_{max} – Maximum concentration
CrCl – Creatinine clearance
EAPC – European Association for Palliative Care
ENS – Enteric nervous system
GI – Gastrointestinal
ITT – Intent to treat
LES – Lower esophageal sphincter
LIR – Laxative inadequate response
LOS – Length of stay
LTCF – Long-term care facility
MACE – Major adverse cardiovascular event (death, myocardial infarction or stroke)
MEU – Morphine equivalent units
MNTX – Methylnaltrexone
NAL – Naloxegol
NMS – Neuroleptic malignant syndrome
NNH – Number needed to harm
NNT – Number needed to treat
OBD – Opioid bowel disorder
OIC – Opioid-induced constipation
OR – Odds ratio
PAC-QoL – Patient assessment of constipation – quality of life questionnaire
PAC-SYM – Patient assessment of constipation-symptoms questionnaire
PAMORA – Peripherally acting μ -opioid receptor antagonist
PBO – Placebo
RFBM – Rescue-free bowel movement
SAE – Serious adverse event
SBM – spontaneous bowel movement
UC – Usual care

Table of Contents

Executive Summary.....	4
Introduction.....	6
Background.....	6
Prevention and Treatment.....	7
<i>Table 1: Agents Used for Opioid-Induced Constipation.....</i>	<i>10</i>
<i>Table 2: Guidelines for Prevention and Treatment of Constipation/OIC Mentioning PAMORAs.....</i>	<i>11</i>
Mechanism of Peripheral Activity.....	12
Comparison of Agents.....	12
<i>Table 3: Comparison of PAMORA Agents for Opioid-Induced Constipation.....</i>	<i>13</i>
Pharmacokinetics.....	14
Meta-Analysis.....	14
<i>Table 4: Meta-Analysis, Systematic Reviews, Cochrane Reviews and Pooled Analysis of PAMORAs for Opioid-Induced Constipation.....</i>	<i>15</i>
Safety Information.....	16
<i>Table 5: Summary of Safety Information.....</i>	<i>17</i>
Pharmacodynamics: Effects on Cardiac Repolarization.....	18
Special Populations.....	18
Methods.....	18
Clinical Evidence: Naloxegol.....	19
Clinical Evidence: Methylnaltrexone.....	20
Conclusion.....	23
Appendix: Evidence Tables.....	24
Bibliography.....	32

Executive Summary:

Introduction: Constipation is a common side effect of opioid analgesics. Opioid-induced constipation reflects a condition beyond having fewer stools and includes abdominal bloating, the sensation of incomplete bowel movements, straining, gas, abdominal discomfort and hard, dry stools. The prevalence of constipation in the non-malignant pain population receiving opioids is reported to be as high as 81%. Many patients find these symptoms to be more troublesome than their pain. Laxatives are used to prevent and treat opioid-induced constipation but are effective in less than 50% of patients. This is not unexpected, as they do not target the cause, opioid activity at μ -opioid receptors in the enteric nervous system. Many patients discontinue or reduce the dose of their opioid to alleviate symptoms and to have a bowel movement. Opioid induced constipation adversely affects a patient's quality of life and satisfaction with their pain management regimen. Additionally, it is associated with a significant increase in health care resource utilization and costs.

Two peripherally acting μ -opioid receptor antagonists are indicated for treatment of opioid-induced constipation, naloxegol (Movantik®) for oral use and methylnaltrexone (Relistor®) administered subcutaneously. These opioid analogs have been modified to prevent them from crossing the blood brain barrier, which would lead to a loss of analgesia and the potential development of withdrawal symptoms.

Clinical Efficacy: Pivotal randomized, double-blind, placebo-controlled efficacy trials for naloxegol (2 studies) and methylnaltrexone (2 trials) document their ability to reverse opioid-induced constipation in ~50% of patients. In naloxegol trials, the primary endpoint was ≥ 3 spontaneous bowel movements per week and an increase from baseline of ≥ 1 spontaneous bowel movement per week in nine or more of the 12 weeks of study and three or more of the final 4 weeks. Methylnaltrexone trials evaluated the percentage of patients having ≥ 3 spontaneous bowel movements per week during the 4 weeks of study. Both agents demonstrated statistical superiority compared to patients treated with placebo. Long-term efficacy was demonstrated with both agents.

Safety: These agents are generally well tolerated. Adverse events were most commonly gastrointestinal in nature, typically mild to moderate, more common at higher dosages and most often occurring early in therapy. The adverse events reported most often with both agents were abdominal pain, diarrhea, nausea and vomiting. Significant adverse events occurred similarly among treatment groups. In treated patients, the majority of discontinuations of therapy related to gastrointestinal adverse events. No significant loss of analgesia or symptoms reflective of opioid-withdrawal were observed. Post-marketing surveillance revealed gastrointestinal perforation in 7 patients treated with methylnaltrexone that had underlying pathology. Currently, both agents carry a contraindication for use in patients at risk of gastrointestinal perforation.

Summary: A laxative bowel regimen started prophylactically is appropriate for all patients receiving opioid-therapy. Because laxatives do not counter the pharmacologic mechanism of opioid-induced constipation they are often ineffective. The peripherally acting μ -opioid receptor antagonists are a new class of agents that reverse the effects of opioids on receptors within the enteric nervous system producing laxation in ~50% of patients in clinical trials. The fact that

only 50% of patients respond well to this therapy may reflect the multi-factorial cause of constipation in many patients with chronic pain.

The evidence supports the use of naloxegol and methylnaltrexone in the treatment of opioid-induced constipation in patients without risk of bowel perforation who have received an opioid for a minimum of 4-weeks with an inadequate response to laxatives (i.e. stimulant laxative and osmotic laxative/stool softener). In clinical trials, these agents increase the number of spontaneous bowel movements and reduce time to laxation. Methylnaltrexone data suggests the NNT to prevent OIC is in the range of 3-6 and this is likely also true for naloxegol. No significant loss of analgesia or opioid withdrawal symptoms have been noted. Currently, there is no evidence supporting use of these agents beyond 12 months or validating superiority over other pharmacologic therapies. Naloxegol is available orally, while methylnaltrexone is administered subcutaneously. Adverse events of mild to moderate intensity are most commonly gastrointestinal in nature, including abdominal pain, nausea, vomiting, diarrhea and flatulence. No serious adverse events have been reported. These agents are comparable in efficacy and safety and offer clinicians an additional treatment option for opioid-induced constipation.

Introduction: The introduction of peripherally acting μ -opioid receptor antagonists brings attention to an under-diagnosed and under-treated complication of pain management, opioid-induced constipation. Less than half of patients report no constipation or successful prevention or treatment with laxatives. Opioid-induced constipation affects quality of life, health care resource utilization, adherence, absorption concerns for medications/nutrients, adverse events and the potential for serious complications. This review presents evidence concerning the safety and efficacy of both naloxegol (Movantik[®]) and methylnaltrexone (Relistor[®]) in the treatment of opioid-induced constipation in chronic non-malignant pain patients, and methylnaltrexone (Relistor[®]) in the treatment of pain in palliative-care patients with advanced-illness whom have failed laxative therapy.

Background:

Chronic pain is reported by at least one in five American adults, ranging from 2-40% (mean of 15%) and affecting 100 million adults.^{1,2,3} An increase in therapeutic opioid use in the US is also well documented.^{4,5,6,7,8,5,9,10} Currently, narcotic analgesics are the third most commonly prescribed category of pharmaceuticals.¹⁶

Clinically, opioids produce analgesia, confusion, sedation, nausea, vomiting, hypotension, pruritus, urinary retention, respiratory depression, miosis, euphoria, dysphoria, delirium, seizures, motor and cognitive impairment, bowel dysfunction as well as dependence.¹¹⁻¹⁴

Opioid bowel dysfunction (OBD) presents with an array of symptoms associated with short or long term use of opioids and may include; dry-mouth, gastro-esophageal reflux, vomiting, bloating, abdominal distension and pain, anorexia, hard, dry stools, straining or incomplete evacuation.^{12,15,11}

Opioid-induced constipation is generally considered to be constipation resulting as a side effect of taking opioids for pain management.^{15,16} However, there is a need for a universal definition that could be used in patient care and research a definition of OIC was developed by a Multidisciplinary Working Group of US and international basic science and clinical experts in pain medicine, palliative care, gastroenterology, and gut neurobiology. The number of bowel movements daily or weekly is insufficient to capture patients with OIC. By consensus, OIC was defined as, “A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development of worsening or straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.”¹⁷ The Working Group recommends the development of treatment guidelines and quality of life measures specific for OIC.¹⁷

Opioid-induced constipation (OIC) is only one manifestation of OBD and is characterized by infrequent stools, straining, hard, dry stools and incomplete evacuation. Many patients consider it the most bothersome of opioid adverse effects.¹⁸⁻²⁰ For some patients, constipation is less troublesome than bloating, straining, gas, or abdominal pain.^{12, 21}

Opioid receptors are located both centrally and peripherally, are stimulated endogenously by endorphins, enkephalins, dynorphins and exogenously by morphine and other μ -opioid receptor agonists.^{17,22, 12,16} Central opioid effects are mediated by opioid receptor subtypes, mu (μ), delta

(δ), and kappa (κ). Analgesia occurs predominately through central μ -opioid receptor stimulation.²³⁻²⁵ A number of the adverse effects of opioids are caused by central, μ -opioid receptor stimulation, including sedation, drowsiness, sleep disturbances, cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams, nightmares, myoclonus, hyperalgesia and tolerance.^{26,19}

Central stimulation of opioid receptors affects circulating catecholamines and central sympathetic outflow reducing autonomic vasomotor tone and inhibiting nitric oxide generation (inhibitory neurotransmitter).¹⁵ Peripherally, opioids act directly on the enteric nervous system (ENS) at μ -opioid receptors.^{16, 17,22,27,28, 29-31, 32} Motility, absorption, secretion and blood flow are affected. The net effect on the gastrointestinal tract is an increase in segmental longitudinal and circular intestinal smooth muscle contraction, a decrease in peristaltic activity, inhibition of water and electrolyte secretions, stimulation of fluid absorption, increased anal and pyloric sphincter tone and decreased rectal sensitivity, predisposing to OIC.^{33,17,22,27,28,29-31,32,34,35,29-31} It is important to remember that non-opioid constipation is a common, under-diagnosed disorder and the development of constipation during opioid therapy does not equal causation.

Concurrent with the increased use of opioids, more patients are presenting with opiate bowel dysfunction.³⁶ The prevalence of opioid-induced constipation in non-malignant patients treated with opioids, ranges from 15-81% and increases with duration of use.^{11,36-40} Symptoms are often severe and up to a third of patients stop their opioid in order to have a bowel movement.^{41,15,36,38,42-45,66,67} In the population of cancer patients receiving opioids for pain, opioid-induced constipation is estimated to occur in >85% of patients and in those receiving palliative-care it exceeds 94%.^{46,47, 48-55}

The consequences of chronic constipation impact a patient's activities of daily living and quality of life. Patients with advanced cancer who receive chronic opioid therapy often report that the constipation causes them more distress than their cancer.^{56,22,52} Many trade constipation relief for pain relief, which places them at risk of inadequate pain control and the possible development of withdrawal symptoms.^{11,15,37,41,57,16,58}

Inpatient and direct costs are significantly increased in the presence of chronic pain, exceeding \$60 billion annually.^{1,59} Opioid-induced constipation adversely affects work productivity, daily activities, quality of life, overall health-related quality of life (HRQoL), complicates pain management and increases health care resource utilization (e.g. admission rates, physician and alternate care provider visits, emergency department visits, pharmacy and laboratory costs)^{37,41,60,16,43,60-62,90,91}

Prevention and Treatment

When prevention fails (see below), the goal of treatment of opioid-induced constipation (OIC) is to increase the frequency of spontaneous bowel movements (SBMs) and provide symptom improvement (e.g., straining, stool consistency, feeling of complete evacuation) without impacting pain control. Constipation is common, significant, often the most troubling and persistent side effect of opioid therapy, and should be anticipated.^{63-66,67,15,36,68,56}

Lifestyle modifications are recommended as the first-line, non-pharmacologic intervention for patients receiving opioids, although most often inadequate to prevent or treat OIC. Modifications may include increasing water and fluid intake, increasing exercise, increasing or adding dietary fiber or fiber-supplements and optimizing toileting habits.^{11,12,15,16,45,69}

Pharmacologic Interventions (See Table 1) Prevention and treatment of OIC includes several approaches. Although μ -opioid receptor antagonists seem reasonable options to antagonize the effects of opioids on the ENS their ability to cross the blood brain barrier (BBB) results in the reversal of central mediated analgesia rendering these agents without merit.^{22,70,71,70-73} This limitation led to the development of opioid antagonists that do not cross the BBB, the PAMORAs.¹⁵

Rotating opioids has been proposed as a modality to limit OIC. Some opioids are associated with less constipation (e.g. fentanyl) and transdermal administration appears to reduce the development of constipation. Unfortunately, rotating opioids may predispose to dosing errors, over-dosage, prescribing errors or other adversities. In fact prescriber or patient errors during rotation have been implicated in opioid over-dosage and death.⁷⁴⁻⁷⁶ Another strategy to combat constipation is via opioid dose reductions.⁷⁷ This is performed by the addition of a non-opioid co-analgesic (e.g. hydrocodone/acetaminophen, oxycodone/acetaminophen), the addition of an adjuvant analgesic (appropriate to the pain syndrome and mechanism), the application of therapy targeting the cause of the pain, the application of regional anesthesia or neuro-ablative interventions.⁶³ Because OIC develops at a lower dose than required for the treatment of pain, reducing the dose of the opioid may be ineffective to solve OIC.²⁰

Laxatives are traditionally the first medication used to prevent or treat constipation in patients receiving opioids. The adage, “the hand that prescribes opioid shall also prescribe laxatives” is implemented with either oral (or rectal) products, often in combination, and may include; bulk forming laxatives, lubricant laxatives, osmotic laxatives, stimulant laxatives or stool softeners.^{11,78,63-66} Laxatives may be contraindicated, particularly in palliative-care patients with neutropenia or thrombocytopenia.²³ In patients with limited fluid intake, bulk-forming laxatives may lead to pseudoobstruction.¹⁵ Despite the number of nonspecific laxative agents available for treatment or prevention of OIC, laxative failure is common and up to 81% of patients still report constipation with symptoms refractory to even the most aggressive laxative regimens.^{15,23,79,11} Laxative use and overuse may result in electrolyte disturbances, tolerance or dependence to the laxative, kidney stones, kidney failure or the potential for drug-drug or drug-nutrient interactions limiting utility.²² Rescue modalities (e.g., enemas, colonic investigation, and manual disimpaction) are often administered when other options fail. These modalities are often unpleasant, distressing and may carry risks.

The results of an international study involving 489 non-malignant patients receiving opioids found an inadequate response to a single laxative agent in 94% of patients, while 27% failed to respond to two or more laxative agents.⁸⁰ In fact, only 46% of non-malignant patients receiving an opioid had a desired response 50% of the time compared with a laxative response of 84% in control subjects.¹⁵ A prospective, longitudinal, multi-national study in patients with chronic non-malignant pain and self-reported OIC found most used a laxative at least 4 times in the prior 2 weeks with an inadequate response.⁸¹

The National Hospital Ambulatory Medical Care Survey (NHAMCS) data from 2010 found that <1% of patients given a prescription for an opioid were also given a prescription for a laxative. This contrasted with discharge laxative prescriptions for 42% of patients presenting with constipation, demonstrating that most patients receiving opioids are not prescribed laxatives.⁸²

A meta-analysis failed to demonstrate the benefit of one laxative or combination over another in the treatment of OIC. No differences were noted between lactulose and senna, lactulose/senna vs magnesium hydroxide/liquid paraffin, or between misrakasnehan and senna.⁸³ Laxative failures are common in OIC and not unexpected as these agents do not target the underlying mechanism of OIC, activation of μ -opioid receptors of the GI tract.^{12, 18,84}

Lubiprostone, a chloride channel activator was approved by the FDA (April, 2013) for use in opioid-induced constipation. The primary response measure, an increase of ≥ 1 SBM/week and at least 3 SBMs per week for at least 9 of 12 weeks of study varied in three trials from 15.3% to 27.1% with lubiprostone compared to placebo response rates of 13% to 18.9%. Lubiprostone may not be as effective in patients taking methadone. First dose dyspnea was noted which tended to resolve within 3 hours but can occur with continued dosing. The most common adverse events when used to treat OIC were nausea and diarrhea. This agent should not be used in the setting of possible mechanical bowel obstruction. Dosing is initiated at lower doses in the presence of hepatic impairment.

Pro-kinetic medications initiate or enhance peristalsis and facilitate bolus transport. Dopamine antagonists (e.g. metoclopramide) stimulate peristalsis by releasing acetylcholine. Substituted benzamides (e.g. cisapride) release acetylcholine by acting on 5HT₄ receptors and motilides such as erythromycin enhance peristalsis by acting on motilin receptors or by releasing motilin.⁸⁵ These agents are not considered safe for long term use due to the potential for tardive-dyskinesia.^{13,14}

Table 1: Agents Used for Opioid-Induced Constipation^{13,14,86}

Pharmacologic Class	Agents	Time to Laxation	Comments	FDA Approved or Clinical Efficacy Established in OIC
Laxatives				
Stimulant	Bisacodyl Tab Bisacodyl Suppository	0.25-1 hour 0.25-1 hour	Abdominal cramps, nausea, vomiting, dependence	No
	Senna Casanthranol Cascara	8-12 hours		
Stool Softeners, Surfactant	Docusate	12-72 hour	Nausea, diarrhea, bitter taste	No
Combination Stimulant – Surfactant	Docusate-casanthranol	8-12 hour	See separately	No
Osmotic Laxatives	PEG	0.5-1 hour	Dissolve in 4-8 oz. fluid, flatulence, nausea, bloating, cramping, diarrhea, rectal bleeding, do not use with symptoms of bowel obstruction, risk of electrolyte disturbances	No
	Lactulose	24-48 hour		
	Glycerin (PR)	0.5-1 hour		
Bulk Forming, Fiber	Psyllium	12-72 hours	Abdominal pain, flatulence, bloating, rectal pain, requires adequate fluid intake (minimum 8 oz.), caution in fluid restricted patients, rectal bleeding, do not use with gastrointestinal strictures, stenosis, may interfere with absorption of medications, bulk may distend abdomen and cause pain or aggravate constipation	No
	Methylcellulose			
	Polycarbophil			
Emollient	Mineral Oil		Not recommended as a laxative; aspiration may cause lipid pneumonia, caution in the elderly, cramps, diarrhea, nausea, vomiting, anal leakage, interferes with absorption of fat soluble vitamins and medications	No
Saline	Magnesium citrate; Magnesium hydroxide; Magnesium sulfate; Sodium phosphate and bisphosphates	0.5-1 hour	Abdominal cramping, watery diarrhea, electrolyte imbalance, use caution in patients with heart failure or kidney insufficiency, may cause magnesium/aluminum toxicity	No
	Phosphate enema	5-15 min		
Other Agents				
Stimulate Peristalsis:	Metoclopramide		Tardive dyskinesia, extrapyramidal reactions, neuroleptic malignant syndrome, fluid retention, limit duration of use, nausea, diarrhea, fatigue, restlessness Diarrhea, potential changes in gut flora (Not marketed)	No
	Erythromycin			
	Cisapride			
Chloride Channel Activator: Increases intestinal fluid and transit times	Lubiprostone	< 24 hours	Nausea, headache, diarrhea, flatulence, abdominal pain, headache; take with food and water, swallow whole; monitor dyspnea; hepatic dosing recommendations; confirm absence of GI obstruction; dyspnea has been reported within 1 hour of first dose	Yes

Peripherally acting μ -opioid receptor antagonist agents (PAMORAs) are newer agents that specifically block the peripheral effects of opioids on μ -opioid receptors in the enteric nervous system to treat OIC. It has been suggested that up to 50% of patients with OIC may benefit from treatment with a PAMORA, however, PAMORA resistant constipation may be found in patients with other etiologies which may include medications, advanced age, immobility or advanced illness.^{87,88} Currently two agents are FDA-approved for the treatment of opioid-induced constipation. Naloxegol (Movantik®) was approved in 2014 for the treatment of opioid-induced constipation in adult patients with chronic non-malignant pain. Methylnaltrexone (Relistor®) was initially approved in 2008 for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy was not sufficient, and expanded in 2014 to include the treatment of opioid-induced constipation in adult patients with chronic, non-malignant pain. The use of PAMORAs are being incorporated within guidelines for management of constipation in patients receiving opioids.^{63,83,89} (See **Table 2**)

Table 2: Guidelines for Prevention and Treatment of Constipation/OIC Mentioning PAMORAs

American Society for Interventional Pain Physicians ⁹⁰	Insufficient data for PAMORAs in chronic, non-malignant pain syndromes.
Use of Opioid Analgesics in the Treatment of Cancer Pain: Evidence-Based Recommendations from the EAPC ^{78,91}	Laxative Failure: Methylnaltrexone
NICE: Opioids in Palliative Care: Strong Opioids for Pain Relief (Clinical Guideline CG140) – A Guideline Summary ⁹²	Laxative Failure: Methylnaltrexone
NICE: Naloxegol for Treating Opioid-Induced Constipation (Constipation Pathway TA345). ⁹³	Laxative Failure: Naloxegol
Palliative Care for the Patient with Incurable Cancer or Advanced Disease. (Part 2: Pain and Symptom Management.) ⁹⁴	Treatment: Methylnaltrexone
The Canadian Consensus Development Group Consensus Recommendations for the Management of Constipation in Patients with Advanced Progressive Illness. ⁶⁴	Laxative Failure: Methylnaltrexone
Expert Working Group of the European Association of Palliative Care Network ⁶³	Laxative Failure: Methylnaltrexone

Mechanism of Peripheral Activity

Naloxegol is a PEGylated derivative of naloxone which acts as a μ -opioid receptor antagonist. PEGylation reduces permeability across the blood brain barrier. Preclinical studies documented a 15-fold reduction in CNS penetration in comparison to unconjugated naloxone. CNS penetration is further limited, as the molecule is a substrate for the P-glycoprotein (P-gp) transporter.^{95, 22,96} The efflux transporter acts a defense mechanism. The transporter is located on the endothelial cells of brain capillaries and limits the accumulation of toxins, xenobiotics and drugs into the brain. By PEGylation and as a substrate for the P-gp transporter, therapeutic doses of naloxegol do not cause antagonism at central μ -receptors.⁹⁶

Methylnaltrexone is a quaternary compound created by N-methylation of an alkyl-substituent on the nitrogen atom of the tertiary opioid antagonist, naltrexone. N-methylation results in a positive charged-derivative (in solution) with limited ability to cross the blood-brain barrier due to both polarity and low lipid solubility.^{23,97,98,99-102} The inability of methylnaltrexone to cross the BBB has been confirmed in humans. No loss of analgesia or opioid withdrawal symptoms was noted.²⁸

Comparison of PAMORA Agents

Both agents are FDA approved for use in non-malignant patients with opioid-induced constipation. Methylnaltrexone is additionally indicated for opioid-induced constipation in patients with advanced illness who are receiving palliative care, when the response to laxative therapy has been insufficient. The average opioid exposure in clinical trials was 4 weeks for each agent which may increase sensitivity to the medications. Laxatives should be discontinued before use, but may be initiated after 3 days of sub-optimal response. For methylnaltrexone, with a rapid onset of laxation, it is recommended that patients be in close proximity to toilet facilities.

Naloxegol is indicated once daily, in the morning, on an empty stomach, as a 25 mg tablet, swallowed whole. A 12.5 mg tablet is available for those that do not tolerate the 25 mg dosage. Methylnaltrexone is indicated for non-malignant patients as a 12mg, SQ, once daily dosage and for use in palliative-care patients dosed via weight. Methylnaltrexone is available in 8 and 12 mg prefilled syringes and as 12 mg/0.6 ml vials, available individually or in kits containing needle, syringe, and alcohol pads. Once drawn into a syringe, it is stable at room temperature for 24 hours (**See Table 3**)

Table 3: Comparison of PAMORA Agents for Opioid-Induced Constipation

Generic Name Brand Name	Naloxegol (Movantik®) ⁹⁶	Methylnaltrexone (Relistor®) ¹⁰³										
Manufacturer	AstraZeneca (Approved 2014)	Salix (Approved 2008, 2014)										
FDA-Approved Indications	Treatment of opioid-induced constipation in adult patients with chronic non-malignant pain	Treatment of opioid-induced constipation in adult patients with chronic non-malignant pain Treatment of opioid-induced constipation in adult patients with advanced illness that are receiving palliative care, when response to laxative therapy has not been sufficient. (Use beyond 4 months has not been studied in the advanced illness population).										
Route of Administration	Oral	Subcutaneous: Rotate administration: upper arm, abdomen and thigh										
Dosage and Administration	<p>Discontinue if/when treatment with the opioid is discontinued</p> <p>In non-malignant pain and OIC</p> <p>Dosage: 25 mg once daily in the morning. If poorly tolerated, reduce dosage to 12.5 mg once daily</p> <ul style="list-style-type: none"> • Take on an empty stomach 1 hour before or 2 hours after the first meal • High fat meal: ↑ Cmax (30%) and AUC (45%) • Swallow tablets whole, do not crush or chew • Avoid grapefruit or grapefruit juice during treatment 	<p>Discontinue if/when treatment with the opioid is discontinued Be within close proximity to toilet facilities once administered</p> <p>In non-malignant pain and OIC</p> <p>Dosage: 12 mg subcutaneously once daily</p> <ul style="list-style-type: none"> • Inject one dose daily • Reevaluate continued need whenever opioid regimen is changed <p>In advanced illness and OIC (weight-based dosing)</p> <ul style="list-style-type: none"> • Inject every other day, as needed, no more frequently than one dose per 24-hours: <table border="1" data-bbox="1213 896 1633 1101"> <thead> <tr> <th>Weight of Adult Patient</th> <th>SQ Dose</th> </tr> </thead> <tbody> <tr> <td>Less than 38 kg</td> <td>0.15 mg/kg</td> </tr> <tr> <td>38 to ≤ 62 kg</td> <td>8 mg</td> </tr> <tr> <td>62 kg to 114 kg</td> <td>12 mg</td> </tr> <tr> <td>More than 114 kg</td> <td>0.15 mg/kg</td> </tr> </tbody> </table> <p>From vial: Administer with a 1 mL syringe, 27 gauge x ½ inch needle.</p>	Weight of Adult Patient	SQ Dose	Less than 38 kg	0.15 mg/kg	38 to ≤ 62 kg	8 mg	62 kg to 114 kg	12 mg	More than 114 kg	0.15 mg/kg
Weight of Adult Patient	SQ Dose											
Less than 38 kg	0.15 mg/kg											
38 to ≤ 62 kg	8 mg											
62 kg to 114 kg	12 mg											
More than 114 kg	0.15 mg/kg											
How Supplied	<ul style="list-style-type: none"> • 25 mg tablet • 12.5 mg tablet 	<ul style="list-style-type: none"> • Single-use vial: One 12 mg/0.6 mL vials (Solution drawn into syringe stable 24 hrs.) • 8 mg/0.4 mL single-use pre-filled syringes with needle guard system • 12 mg/0.6 mL single-use pre-filled syringes with needle guard system 										
Storage	Store between 20-25 °C	Store at 20-25 °C room temperature; Protect form light.										

Pharmacokinetics

Naloxegol: Following a 25 mg oral dose, C_{max} is achieved in less than 2 hours with a secondary peak observed 0.4 to 3 hours later in a majority of subjects, suggesting enterohepatic recycling. AUC demonstrated a dose-proportional increase with minimal accumulation following multiple daily doses. The steady state volume of distribution is ~968 to 2140 L with 4.2% plasma protein binding. Metabolism is primarily via the CYP3A enzyme system through N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain producing six metabolites. The elimination half-life ranges from 6 to 11 hours. Elimination is via the feces (68%) and urine (16%) with 16% and <6% excreted unchanged, respectively.

Methylnaltrexone: Following a 12 mg SQ dose, C_{max} is achieved at ~0.5 hours. AUC demonstrated dose-proportional increases but did not accumulate following once daily dosing for seven days. The steady state volume of distribution is ~1.1 L/kg with 11%-15.3% plasma protein binding. Five distinct metabolites are recovered; methyl-6-naltrexol isomers (5%) and methylnaltrexone sulfate (1.3% of total) appear to be the primary metabolism pathways. The elimination half-life is ~8 hours. The majority of the drug is eliminated unchanged in the urine (54%) and feces (17%). The renal clearance of methylnaltrexone is 4-5 fold higher than creatinine clearance suggesting active renal secretion.

Meta-Analyses

Currently, there are no comparative trials of the two FDA-approved agents, naloxegol and methylnaltrexone, in the treatment of OIC. It is difficult to compare these agents across clinical trials as the clinical endpoints or the manner in which they were analyzed, differed.¹⁰⁴ A number of systematic reviews, meta-analysis or Cochrane reviews have been published evaluating the utility of methylnaltrexone, naloxegol and/or alvimopan across studies (See Table 4).

McNicol et al, found the agents effective at reversing opioid-induced oral-cecal transit increases but not statistically beneficial in the treatment of OIC when the data was adjusted for heterogeneity.¹⁰⁵ Becker et al, noted differences across studies in the diagnosis of constipation and questioned the external validity of the data.¹⁰⁶ Sonu et al, noted that although the agents are effective in producing laxation in comparison to placebo, 52% to 62% of patients remained constipated.¹⁰⁷ Ford et al, noted a failure rate with these agents of 46%, a relative risk of failure of 0.69 and a number needed to treat (NNT) to prevent OIC of 4 with a number needed to harm (NNH) of 14. Their subgroup analysis of the methylnaltrexone (MNTX) studies yielded similar findings.¹⁰⁸ Magee et al, calculated the odds ratio (OR) for improvement of OIC to be 3.1 with a NNT of 5.6.¹⁰⁹ Lastly, Candy reported an OR for rescue-free laxation within 4 hours of 6.95 and within 24 hours of 5.42.⁸³

Table 4: Meta-Analysis, Systematic Reviews, Cochrane Reviews and Pooled Analysis of PAMORAs for Opioid-Induced Constipation

Author	Methods	Results
McNicol 2008 ¹⁰⁵	<p>The efficacy and safety of peripheral μ-opioid receptor antagonists in the treatment of opioid bowel dysfunction was assessed from 22 articles [2352 opioid antagonist-treated patients: ALV (8 studies), MNTX (6 studies), naloxone (7 studies) and nalbuphine (1 study).] Three studies were excluded, two with insufficient data reported and 1 study with outcome measures that could not be combined with other trials.</p> <p>Reversal of opioid-induced oral-cecal transit increases identified six of ten studies pooled for analysis (5 MNTX and 1 ALV). The majority of the studies were done in healthy volunteers. A single study evaluated transit time changes in patients receiving chronic methadone therapy.</p> <p>Four trials were assessable for constipation (1 each methylalntrexone and alvimopan and 2 with naloxone).</p>	<p>Both alvimopan and methylalntrexone were efficacious in reversing opioid-induced increases of gastrointestinal transit times.</p> <p>MNTX studies: GI transit time was reduced 59 minutes vs. PBO (95% CI: -75 to -42). Data was presented on a forest plot and demonstrated weak efficacy.</p> <p>PAMORAs resulted in a NNT of 2.7 (95% CI: 1.9 to 4.8). Statistical significance was lost with a random effects model. Adverse events across trials were similar MNTX vs. PBO and rated as mild to moderate.</p>
Becker 2007 ¹⁰⁶	<p>A systematic review initially identified 20 trials addressing the use of opioid antagonists in the treatment of opioid-induced constipation. After excluding for small sample size or non-randomized, single blind design, 9 studies using MNTX and 6 studies of ALV were analyzed. Most studies were performed in healthy volunteers, with nonmalignant pain or involving patients in methadone programs.</p>	<p>Inconsistency in the diagnosis of constipation questioned the external validity of the well-performed studies.</p>
Sonu 2015 ¹⁰⁷ (Abstract)	<p>Two randomized, placebo-controlled, clinical trials using MNTX and NAL were reviewed to determine the probability of relief from opioid-induced and chronic idiopathic constipation.</p>	<p>Statistical significance to relieve OIC was found, vs. PBO</p> <p>Patients remaining constipated: MNTX 52% and naloxegol low/high dose 62%/58</p>
Ford 2013 ¹¹⁰	<p>A meta-analysis identified 14 studies reflecting 4,101, of whom 2,719 received a μ-opioid receptor antagonist for the treatment of OIC (MNTX in 6 studies, naloxone in 4 studies and ALV in 4 studies).</p>	<p>PAMORAs failed in 46.4% of patients vs. PBO patients of 64.1% Treatment resulted in a lower RR of failure compared with placebo (RR=0.69; 95% CI 0.63 to 0.76). The NNT was 4 (95% CI 3 to 6) and the NNH was 14 (95% CI 9-33)</p> <p>The RR of any adverse event (RR=1.11; 95% CI 1.04 to 1.20). MNTX Subgroup treated 1-12 days (n=1,095): a failure to respond 48.7% compared with 64.5% with PBO. RR of failure vs. PBO 0.67 (95% CI, 0.56 to 0.72) with a NNT of 3 MNTX Subgroup treated > 2 days RR of failure vs. PBO was 0.79 (95% CI 0.7 to 0.88). Trend toward more AEs in MNTX vs. PBO (RR 1.24; 95% CI 0.98 to 1.57).</p>
Magge 2012 ¹⁰⁹	<p>Data was extracted and pooled from a review of 3 MNTX studies.</p>	<p>Odds ratio (OR, 95% CI) for global improvement was 3.1 (1.97-5.05) with a NNT of 5.6 (4-9)</p>
Candy 2011 ⁸³	<p>A meta-analysis of 287 palliative care patients enrolled in two randomized, controlled trials assessed the efficacy of MNTX SQ vs placebo to treat OIC.</p>	<p>The odds ratio for rescue-free bowel movement within 4 hours was 6.95 (95% CI: 3.83 to 12.61) and within 24 hours was 5.42 (5% CI 3.12 to 9.42).</p>

Safety Information

These agents are generally well tolerated. The most common adverse events noted in clinical studies related to the gastrointestinal system (nausea, abdominal pain, diarrhea, flatulence). Other common adverse events included, hyperhidrosis, tremor, headache, dizziness and hot flush at greater than 1%. Caution should be used in patients without an intact blood brain barrier (BBB).

Both agents are contraindicated in patients with impaired structural integrity of the GI tract based on methylnaltrexone data. In reviewing post-marketing, Adverse Event Reporting System (AERS) data, reflecting approximately one year of usage (4/08 to 10/09), Mackey identified 7 cases of gastrointestinal perforation in patients receiving methylnaltrexone. Each patient had a pathological or anatomic abnormality in the upper or lower GI tract, including; metastatic colon cancer with previous hemicolectomy, peptic ulcer, bevacizumab use, volvulus, ALS, peptic ulcer and bowel obstruction. Abdominal pain preceded perforation in four of patients and occurred following the first dose in four patients.¹¹¹

Naloxegol is metabolized through the CYP 3A4 and is contraindicated in combination with strong CYP3A4 inhibitors due to the potential for increased exposure to naloxegol and the risk of opioid withdrawal reactions. It is recommended to avoid concomitant use of naloxegol with moderate CYP3A4 inhibitors, grapefruit products, or CYP3A4 inducers (**See Table 5**).

Table 5: Summary of Safety Information

Generic Name Brand Name	Naloxegol (Movantik®) ⁹⁶	Methylnaltrexone (Relistor®) ¹⁰³
Adverse Events	Most common adverse events in clinical trials occurring in $\geq 3\%$ of patients and at an incidence greater than placebo are abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, and hyperhidrosis.	Chronic Non-malignant Pain: Most common adverse events in clinical trials occurring at $\geq 1\%$ and at an incidence greater than placebo are abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor and chills. Advanced Illness: Most common adverse events in clinical occurring at an incidence $\geq 5\%$ and at an incidence greater than placebo are abdominal pain, flatulence, nausea, dizziness, and diarrhea.
Warnings, Precautions	Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if symptoms develop. Opioid withdrawal symptoms have occurred during treatment and more frequently in patients receiving methadone. Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal.	Gastrointestinal Perforation: Cases have been reported in adult patients with OIC and advanced illness in conditions affecting structural integrity of the gastrointestinal tract. Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if symptoms develop. Severe or persistent diarrhea: Discontinue Opioid withdrawal symptoms have occurred during treatment. Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor opioid withdrawal symptoms.
Contraindications	Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to potential for gastrointestinal perforation (based on methylnaltrexone data). Patients concomitantly using strong CYP3A4 inhibitors (e.g. clarithromycin ketoconazole), due to increased exposure and potential for precipitating opioid withdrawal. Patients who have had a known serious/severe hypersensitivity reaction	Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction due to the potential for gastrointestinal perforation.
Drug Interactions	Avoid use with other opioid antagonists. Potential for additive opioid antagonism and risk of withdrawal. <u>Strong CYP3A4 Inhibitors:</u> Contraindicated (e.g. ketoconazole, itraconazole, clarithromycin) <u>Moderate CYP3A4 inhibitors:</u> Avoid use. If use is unavoidable, reduce the dosage to 12.5 mg/day and monitor for adverse reactions (e.g. diltiazem, erythromycin, verapamil) <u>CYP3A4 Inducers:</u> Not recommended (e.g. rifampin, carbamazepine, St. John's Wort) Avoid grapefruit juice or grapefruit during treatment.	Avoid use with any other opioid antagonists. Potential for additive opioid antagonism and risk of withdrawal. Weak, clinically, non-significant inhibitor of CYP2D6
Post-Marketing Experience		Gastrointestinal: perforation, cramping, vomiting General: Diaphoresis, flushing, malaise, pain, cases of opioid withdrawal

Pharmacodynamics

Effects on Cardiac Repolarization

A third PAMORA was studied for use in the treatment of OIC. In a study evaluating the utility of Alvimopan in OIC, 518 patients receiving opioids for non-malignant pain were treated with Alvimopan 0.5mg twice a day.^{141,40} A non-significant finding of myocardial infarction in 7 of 538 alvimopan treated patients prompted a conservative response from the FDA, although all seven of the patients were at high risk of cardiovascular disease.^{112,113, 22} Further development of alvimopan for OIC was discontinued.^{113,114} Adolor Pharmaceuticals “based this determination principally on its assessment of the cost and timeline for an additional Phase III study relative to the remaining commercial life of alvimopan in OBD.”¹¹⁵

Because it was unknown if cardiac adverse effects reflected a class effect, both methylnaltrexone and naloxegol studies were designed to look specifically for cardiac adverse effects, especially major adverse cardiovascular events (MACE - cardiovascular death, myocardial infarction or stroke effects). Neither naloxegol nor methylnaltrexone demonstrated any effect on cardiac repolarization, QTc interval prolongation, blood pressure pulse, platelet aggregation or metabolic changes in pre-clinical or clinical trials.^{116 95,96, 131,151}

Special Populations

Neither agent has been tested in children or pregnancy (category C), and exposure through lactation is unknown. Both agents appear safe and effective in the geriatric population. Mild to moderate hepatic dysfunction was not associated with clinically significant effects.^{96,103,117}

Adjustments for renal impairments are indicated for both methylnaltrexone and naloxegol. For methylnaltrexone, severe renal impairment (CrCl<30mL/min) did not change Cmax. However, a two-fold increase in total exposure and an 8 to 9-fold decrease in renal clearance was documented prompting the recommendation to reduce the dosage by 50% in this population.¹⁰³

Naloxegol pharmacokinetics in mild, moderate and severe renal impairment did not differ from normal controls except in two patients (one each moderate and severe renal impairment). It is postulated that the increased exposure in these two patients (AUC 1.7 to 2.2-fold increase and Cmax 1.1 to 1.8-fold increase) reflects the effects of renal impairment on gut metabolism, or the downregulation of CYP3A enzyme expression in the gut and liver since naloxegol is primarily eliminated by this enzyme system. At CrCl <60 mL/min, a starting dose of 12.5 mg is recommended which may be increased to 25 mg with consideration of adverse effects.^{96,118}

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2014), Embase (1970 – 2015), the Cochrane Library, the National Institute for Health and Care Institute (NICE), NIH Clinical Trials website, the FDA website, Agency for Healthcare Research and Quality (AHRQ), the Academy of Managed Care Pharmacy (AMCP) and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English were included. Trials evaluating the efficacy of μ -opioid receptor antagonists in opioid-induced constipation are included.

Clinical Evidence - Naloxegol

Naloxegol for Opioid-Induced Constipation in Non-Malignant Pain

Dose-Escalation Study

A phase 2, randomized, double blind, placebo-controlled, dose-escalation study involving 207 patients with chronic, non-malignant pain, randomized to 4 weeks treatment with placebo or 5, 25 or 50 mg of naloxegol solution once daily was performed. The primary endpoint of a change in spontaneous bowel movements from baseline was achieved with 25 and 50 mg naloxegol (2.9 vs 1.0; $p=0.0020$ and 3.3 vs 0.5; $p=0.0001$, respectively). The effect was maintained through the 4-weeks of randomized treatment, with the exception of the 25 mg dose during the second week of treatment. The median change in bowel movements over the entire 4 weeks documented superiority for both the 25 and 50 mg doses of naloxegol compared to placebo (3.0 vs 0.8; $p=0.002$ and 3.5 vs 1.0; $p=0.0001$, respectively) while doses of 5 mg did not demonstrate a difference from placebo. Effects were maintained across opioid dosage strata (30-100 MEU/day or >100 MEU/day). The median time to the first bowel movement was significantly shorter than placebo for the 25 and 50 mg cohorts (6.6 vs 48.6 hours; $p=0.0012$ and 2.9 vs 44.9 hours; $p=0.0016$, respectively). PAC and PAC-QOL scores were better at individual time points, but not consistent throughout the study. Naloxegol was generally well tolerated. Common adverse events were abdominal pain, diarrhea and nausea which were mild and transient in the 5 and 25 mg doses and more frequent and severe in the 50 mg dose resulting in higher discontinuation rates. Daily opioid doses remained constant and no changes in opioid withdrawal scores were noted. This phase II dose escalation study confirmed that oral doses of 25 and 50mg QD significantly increased the number of SBMs in patient with OIC over a wide range of opioid doses without interference of central mediated analgesia. Adverse events were mainly gastrointestinal, and more significant with the 50 mg dose. Gastrointestinal adverse events occurred most often during the first week of therapy and resolved by the second week. It is postulated that this may reflect increased bowel functioning following inactivity.^{20,119}

Pivotal Trials

Two identical randomized, placebo-controlled, parallel-group studies (Study-04 and Study-05) evaluated the effects of naloxegol (12.5 or 25 mg) or placebo in outpatients with non-malignant pain and opioid induced constipation during a 12-week randomized treatment period.¹²² Criteria for enrollment included outpatients aged 18-75 years, receiving daily doses of 30-1000mg MEU, with non-malignant pain who met the definition of opioid-induced constipation (<3SBMs per week with one symptom; hard-lumpy stools, straining or the sensation of incomplete evacuation/anal obstruction present $\geq 25\%$ of bowel movements over the prior 4 weeks). The study included a 2-week period of laxation documentation to confirm the presence of opioid-induced constipation and serve as a baseline. For the primary endpoint (defined as ≥ 3 SBMs per week with an increase of ≥ 1 SBM/week for 9 of the 12 weeks, including 3 of the final four weeks of the study and improvement in at least one measure on the Bristol Stool Scale), naloxegol 25mg performed better than placebo in the ITT population of both studies: Study-04, 44.4% vs 29.4%, and $p=0.001$; Study-05, 39.7% vs 29.3%, $p=0.02$. The number needed to treat at 25 mg was 6.7 in Study-04 and 9.7 in Study-05. Patients with an inadequate response to laxatives during the 2-week prescreening period also responded well to naloxegol 25mg: Study-04, 48.7% vs 28.8%, $p=0.002$; Study-05, 46.8% vs 31.4%, $p=0.01$. Naloxegol 12.5mg performed

significantly better than placebo in the ITT population of Study-04: 40.8% vs 29.4%, $p=0.02$; as well as the inadequate response to laxative subset, 42.6% vs 28.8%, $p=0.03$ but not statistically superior in Study-05. The time to the first spontaneous bowel movement and the mean number of days per week with one or more spontaneous bowel movements was higher with naloxegol 25mg vs placebo in both studies ($p<0.001$) and with naloxegol 12.5mg in Study-04 ($p<0.001$). In Study-04 the response time varied from placebo to naloxegol from 35.8 hours to 5.9 hours, respectively and in Study-05, from 37.2 hours to 12 hour. Pain scores, changes in opioid dose and opioid withdrawal symptoms were similar among groups and studies. Gastrointestinal adverse effects occurred more commonly in patients receiving naloxegol 25mg than naloxegol 12.5mg or placebo and led to more discontinuations in this group. Abdominal pain, diarrhea, flatulence, nausea and vomiting typically occurred shortly after initiating treatment and were of mild to moderate severity. Serious adverse events and major cardiovascular events were similar across treatment groups.¹²⁰

Long-term Safety

A long-term safety and tolerability study in 804 patients compared the use of naloxegol 25mg once daily to usual care (UC; a laxative regimen chosen by the investigator based upon clinical experience) over a 52-week period. Patients were rolled into the study from Study-04 and Study-05 or without prior NAL exposure. The completion rate for the naloxegol group was 58.1% and for the UC group 67.3%. Adverse events occurring more commonly in the NAL versus UC group (81.8%, 72.2%) and included abdominal pain (17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%) and headache (9.0% vs 1.1%). There were no differences between groups with regard to serious adverse events or cardiovascular adverse events. Most naloxegol adverse events occurred early, were mild to moderate in intensity and resolved during or after naloxegol therapy. Discontinuation rates were similar between the earlier studies and this study. Patients discontinuing therapy with naloxegol reported diarrhea, abdominal pain or vomiting as the reasons. Pain scores and mean daily opioid doses remained stable throughout the study and no attributable opioid withdrawal symptoms occurred in either treatment arm.^{121,122}

Clinical Evidence - Methylnaltrexone

Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness

Pivotal Trials in Advanced Illness

Methylnaltrexone was added to standard care in two pivotal studies and demonstrated to be more effective than standard care in the relief of opioid-induced constipation in patients with advanced illnesses. Laxation occurred following the first dose and within 30 minutes in ~50% of patients. A similar rate of response was noted over the first 4 administered doses. Overall, MNTX was well tolerated with the most commonly reported adverse events, abdominal pain, nausea and vomiting. No loss of analgesia or withdrawal symptoms were reported.^{23,123,124} The additional finding that the higher dose of MNTX was less well tolerated and without significant efficacy advantage suggests that patients not responding to the initial doses will likely not respond to dosage increases or continued administration and therefore should not be continued on the medication.¹²⁵

Thomas et al, explored the use of MNTX 0.15 mg/kg or PBO every other day for 14 days in 133 patients with advanced illness (defined as a terminal cancer or end-stage disease with a life

expectancy of >1 month) and opioid-induced constipation. Patients had received opioids for ≥ 2 weeks (utilizing a stable dosage), were using laxatives and had gone ≥ 3 days without relief of opioid-induced constipation (defined as ≤ 3 SBM in the preceding week and no “meaningful” BM within 24 hours of the first dose of study drug, or no “meaningful” BM within 48 hours of study drug.) At baseline, patients were receiving a median dose of 100 mg MEU/day and a median use of 2 classes of laxatives.²² More MNTX treated patients had a RFBM within 4 hours (primary outcome) than those receiving PBO (48% vs 15%, respectively; $p < 0.001$) as well as a RFBM in ≥ 2 or the first 4 doses of MNTX (co-primary endpoint) (52% vs 8%, respectively; $p < 0.001$). Treated patients had a higher rate of \geq RFBMs per week (68% vs 45%; $p = 0.009$). Over 50% of patients had a RFBM within 30 minutes of study drug administration. The effects persisted over 7 doses with 39% of patients receiving MNTX vs 6% of patients receiving placebo have a RFBM in ≥ 4 of seven study doses of MNTX over 13 days. Patients who responded to the first dose of MNTX demonstrated a median time to laxation after dosing for the duration of the study of 6.3 hours vs greater than 48 hours in those receiving PBO ($p < 0.001$).¹²³

Serious adverse events were more common among patients receiving MNTX (28% vs 17%) but attributed to underlying disorders or disease progression. Adverse events (abdominal pain, flatulence and vomiting) were similar between groups during the 3-month open-label extension. Patients who receiving PBO in the double-blind phase, had response rates in the open-label phase (45-58%) similar to those that received blinded MNTX. Benefits were sustained over the 3 month open-label extension of the trial with no significant changes to opioid dose requirements for analgesia or opioid withdrawal scores.^{22,123} Life-threatening adverse events occurred in 16% and 15% of MNTX and placebo patients, respectively, all of which were deemed related to primary illness. Two patients were deemed to have serious adverse events during the 3-month extension of the trial related to study drug. One patient had serious muscle spasms and the other serious abdominal and exacerbated pain. No deaths occurring during any phase of the study were attributed to MNTX.

Slatkin et al, explored the effects of a single-dose of SQ MNTX 0.15 or 0.3 mg/kg or PBO in 154 patients with advanced illness (defined as a life expectancy of 1 to 6 months) and opioid-induced constipation. A dose-response relationship for MNTX was not found. The higher dose however, 0.3mg/kg, was associated with more reports of abdominal pain. More patients receiving MNX 0.15 or 0.3 mg/kg had a RFBM within 4 hours of receiving the study drug compared to placebo (61.7% or 58.2% or 13.5%, respectively, $p < 0.001$ for 0.15 and 0.3 mg/kg MNTX vs placebo, respectively). The time following dosing, until a RFBM occurred was significantly shorter at both the MNTX doses than placebo with results at 1.1h for 0.15 mg/kg, 0.8h for 0.3 mg/kg and >24 hours for PBO in each group, respectively ($p < 0.001$ for both MNTX doses). Of patients who responded to MNTX with a RFBM, 50% responded within 30 minutes of drug administration. Adverse events were seen more commonly in the patients receiving MNTX compared to PBO (76% vs 48%) and included abdominal pain, flatulence and nausea which appeared to be dose-dependent and of mild to moderate intensity in both treatment groups. In the open-label phase of the single-dose study, three patients had serious adverse events related to MNTX therapy. One patient each had, delirium, flushing or diarrhea. The patient with diarrhea died due to metastatic breast cancer, which was exacerbated by diarrhea that resulted in dehydration and cardiovascular collapse.^{124, 126, 77}

Advanced Illness, Fixed-Dose Trial

Bull et al, 2015 evaluated the use of two fixed-doses of MNTX in 230 adults with advanced illness, stable doses and regimens of laxatives and opioids and OIC. Patients were randomized to blinded therapy with MNTX SQ QOD at 8 mg (<62kg) or 12mg (≥62kg) of PBO for 2 weeks. A RFBM within 4 hours occurred in 62.9% of patients compared with 9.6% receiving PBO (p<0.0001). Secondary endpoints favored MNTX; RFBM less than 4 hours after dosing (p<0.0001), RFBM within 4 hours for at least 4 of 7 doses (p<0.0001), Median time to first-dose laxation (p<0.005). No differences relative to the different doses was observed. Adverse events were similar to other trials with no serious adverse events attributable to MNTX.¹²⁷

Advanced-Illness Open Label Extension

Lipman et al, 2011 followed 82 advanced-illness patients with OIC who completed a two-week trial evaluating MNTX 0.15 mg/kg SQ QOD compared with PBO over a 3-month open-label extension.¹²³ Patients continued on 0.15 mg/kg MNTX SQ no more than once daily with an increase or decrease in dosage (0.3 mg/kg or 0.075 mg/kg) permitted. Laxation response over the 3 month extension did not change significantly (45.3%, range 45.5-57.7%). The median time to laxation remained ~1 hour. Patients and investigators reported improvement in symptoms. Every patient reported at least one adverse event. Most commonly abdominal pain (30.5%) malignant neoplasm progression (24.4%), nausea (20.7) and vomiting (19.7%). Approximately half of the patients had at least one adverse event likely related to MNTX. Study discontinuation was noted in 7.3% of patients. Serious adverse events occurred in 43.9% of patients, most commonly due to progression of underlying disease. Serious adverse events possibly related to therapy included one patient with muscle spasms and a second patient with abdominal pain and an exacerbation of their pain.

Methylnaltrexone for Opioid-Induced Constipation in Non-Malignant Pain Pivotal Trial in Non-Malignant Pain

Michna et al, evaluated MNTX as a treatment for OIC in patients (n=460) with chronic non-malignant pain. This double-blind, randomized, placebo-controlled trial compared MNTX 12mg SQ administered daily or QOD to PBO for 28 days. During the first 4 weeks of double-blind therapy, more patients receiving MNTX QD or QD had a RFBM within 4 hours of the first dose compared with placebo (33.3% or 35.1% vs 9.9%; p<0.001 for both MNTX groups). Treatment with both MNTX 12mg QD and QOD resulted in a greater mean percent of active injections resulting in a RFBM within 4 hours of study drug administration than PBO (MNTX QD, 28.9% vs 9.4%; and MNTX QOD; 30.2% vs 9.3%; p<0.001 for both MNTX groups). RFBMs following administration of MNTX QD or QOD was more common than with patients receiving placebo (28.9% or 30.2% vs 9.4%, P<0.001 for each MNTX vs placebo). Overall, 58.7% of MNTX QD, 45.3% QOD and 38.3% in the placebo group had at least 3 RFBMs per week during the double-blind period resulting in a NNT of 5 for daily dosing MNTX, and a NNT of 14 for QOD dosing. MNTX treated patients documented normalization of bowel texture (p<0.001) and reported sensations of complete evacuation improvement from baseline (p<0.04) compared with PBO. PAC-SYM scores were better in both MNTX groups when compared to patients receiving PBO (33 or 22 vs 18 respectively; p<0.001 for MNTX QD and p<0.014 for QOD dosing).¹²⁸

The most common adverse event was abdominal pain, reported in 19.3% and 15.0% of patients treated with MNTX QD or QOD, versus 3.7% with PBO. Other adverse events noted more frequently in the MNTX groups were diarrhea, nausea, and hyperhidrosis. One drug-related SAE occurred in a patient who developed extra-systoles on day 1 of therapy which resolved without intervention the same day. Efficacy effects seen in the double-blind phase were durable during the 8-week, open-label phase of the study.¹²⁸

Long-Term Efficacy and Safety

Long-term efficacy was demonstrated in a 48-week, open-label study of SQ MNTX in chronic, non-malignant pain patients with OIC (N=1034). Patients received MNTX at least once weekly and as often as every day. Over the 48 weeks of the study, 34.1% of MNTX injections resulted in a RFBM< within 4 hours of administration and a mean increase of 1.5 RFBM/week from baseline.¹²⁹ Adverse events of mild to moderate intensity were reported in 81.5% of patients. Overall, MNTX was well tolerated and the adverse event profile mimicked the 4-week double-blind, placebo-controlled period of the trial.¹³⁰ The most commonly reported AEs were abdominal pain (24.0%), diarrhea (16.4%), N (15.1%), hyperhidrosis (8.9%) and V (7.2%).^{129,131}

Conclusion:

A laxative bowel regimen started prophylactically is appropriate for all patients receiving opioid-therapy. Because laxatives do not counter the pharmacologic mechanism of opioid-induced constipation they are often ineffective. The peripherally acting μ -opioid receptor antagonists are a new class of agents that reverse the effects of opioids on receptors within the enteric nervous system producing laxation in ~50% of patients in clinical trials. The fact that only 50% of patients respond well to this therapy may reflect the multi-factorial cause of constipation in many patients with chronic pain.

The evidence supports the use of naloxegol and methylnaltrexone in the treatment of opioid-induced constipation in patients without risk of bowel perforation who have received an opioid for a minimum of 4-weeks with an inadequate response to laxatives (i.e. stimulant laxative and osmotic laxative/stool softener). In clinical trials, these agents increase the number of spontaneous bowel movements and reduce time to laxation. Methylnaltrexone data suggests the NNT to prevent OIC is in the range of 3-6 and this is likely also true for naloxegol. No significant loss of analgesia or symptoms consistent with opioid withdrawal have been noted. Currently, there is no evidence supporting use of these agents beyond 12 months or validating superiority over other pharmacologic therapies. Naloxegol is available orally, while methylnaltrexone is administered subcutaneously. Adverse events of mild to moderate intensity are most commonly gastrointestinal in nature, including abdominal pain, nausea, vomiting, diarrhea and flatulence. No serious adverse events have been reported. These agents are comparable in efficacy and safety and offer clinicians an additional treatment option for opioid-induced constipation.

Appendix: Evidence Tables

Naloxegol (Movantik®)

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results																														
Naloxegol Studies – Non-malignant Pain																																			
Dose- Escalation Study																																			
Webster et al, 2013 Randomized, double-blind, placebo-controlled, dose-escalation	207	Outpatients age ≥18 Stable opioid regimen (30-1000 mg MEU) Non-malignant pain for ≥2weeks OIC confirmed in 2-week run in period (≤5 SBMs, <3 SBMs/week & ≥ 1 additional sign or symptom (hard/lumpy stools, straining, sensation of incomplete evacuation or anorectal obstruction)	Sequential dose cohorts Randomized to opioid use <ul style="list-style-type: none"> 30-100 MEU/day or >100 MEU/day Once daily naloxegol oral solution <ul style="list-style-type: none"> 5 mg 25 mg 50 mg 100 mg 	<u>Primary Endpoint</u> Change in SBMs/week from baseline to the end of week 1. <ul style="list-style-type: none"> NAL5 1.5 vs 1.2; p=0.7781 NAL 25 2.9 vs 1.0; p=0.0020 NAL 50 3.3 vs 0.5; p=0.0001 <u>Secondary Endpoints</u> Median time from 1 st dose of study drug to first laxation <ul style="list-style-type: none"> NAL5 6.2 vs 28.2 (NS) NAL25 6.6 hr. vs 48.6 hr. (p=0.0012) NAL50 2.9 hr. vs 44.9 hr. (p=0.0016) Percentage with SBM within 6 hours of 1 st dose <ul style="list-style-type: none"> NAL5 50% NAL25 50% NAL50 68.4% 	Adverse events at NAL5 and NAL25 were minor and transient. Dose escalation safety committee (DESC) recommended against dose escalation to 100 mg. Discontinuation due to GI AEs (diarrhea, nausea, abdominal pain) most commonly in NAL 50 mg patients (n=10; 71.4%) and 8/10 were in the high-opioid stratum cohort.																														
Pivotal Trials – Non-malignant Pain																																			
Chey et al, 2014 ¹²⁰ First of two, identical, randomized, double-blind, parallel-group, placebo-controlled KODIAC-04	652	Outpatients age 18-84 years Non-malignant pain Stable opioid ≥ 4 weeks OIC defined as: <3 SBMs/week with ≥1 of; hard/lumpy stools, straining, sensation of incomplete evacuation or anorectal obstruction in ≥25% of BMs over prior 4 weeks and confirmed with 2-week electronic diary Exclusions: history of cancer, diarrhea or constipation, GI obstruction, risk bowel perforation and interacting meds.	1:1:1 Allocation Stratified by laxative response status during 2-week assessment Administered daily for 12 weeks <ul style="list-style-type: none"> NAL 25 mg NAL 12.5 mg PBO No laxatives Rescue Laxative for no BM over ≥ 3 days <ul style="list-style-type: none"> Bisacodyl 10-15 mg If necessary a single enema 	<u>Primary End-Point</u> Response Rate: ≥ 3 or more SBMs over baseline, 9 of 12 weeks, and at least 3 or final 4 weeks (p value vs. placebo) <ul style="list-style-type: none"> NAL25 44.4% (p=0.001) NAL12.5 40.8% (p=0.02) PBO 29.4% <u>Secondary End-Points</u> Response rate in laxative inadequate response (LIR) <ul style="list-style-type: none"> NAL25 48.7% (p=0.002) NAL12.5 42.6% (p=0.03) PBO 28.8% Median Time to First SBM <ul style="list-style-type: none"> NAL25 5.9 hours PBO 35.8 hours NAL25 and NAL12.5 vs. PBO; p<0.001 Stool consistency and straining, no difference vs. PBO Mean daily opioid-doses remained stable	Any Adverse Event <table border="0"> <tr> <td>PBO</td> <td>46.9%</td> </tr> <tr> <td>NAL12.5</td> <td>49.3%</td> </tr> <tr> <td>NAL25</td> <td>61.2%</td> </tr> </table> Discontinuation from AE (Diarrhea, abdominal pain, upper abdominal pain) NAL25 > PBO > NAL12.5 Reason: <table border="0"> <tr> <td>Abdominal Pain</td> <td>Diarrhea</td> </tr> <tr> <td>PBO 3.3</td> <td>PBO 4.2</td> </tr> <tr> <td>NAL12.5 8.5</td> <td>NAL12.5 3.3</td> </tr> <tr> <td>NAL25 12.6</td> <td>NAL 25 9.3</td> </tr> <tr> <td>Nausea</td> <td>Flatulence</td> </tr> <tr> <td>PBO 4.7</td> <td>PBO 1.9</td> </tr> <tr> <td>NAL12.5 7.1</td> <td>NAL12.5 1.4</td> </tr> <tr> <td>NAL25 7.5</td> <td>NAL25 5.1</td> </tr> <tr> <td>Upper Abd. Pain</td> <td>Vomiting</td> </tr> <tr> <td>PBO 1.9</td> <td>PBO 3.3</td> </tr> <tr> <td>NAL12.5 1.4</td> <td>NAL12.5 1.4</td> </tr> <tr> <td>NAL25 5.1</td> <td>NAL25 5.1</td> </tr> </table>	PBO	46.9%	NAL12.5	49.3%	NAL25	61.2%	Abdominal Pain	Diarrhea	PBO 3.3	PBO 4.2	NAL12.5 8.5	NAL12.5 3.3	NAL25 12.6	NAL 25 9.3	Nausea	Flatulence	PBO 4.7	PBO 1.9	NAL12.5 7.1	NAL12.5 1.4	NAL25 7.5	NAL25 5.1	Upper Abd. Pain	Vomiting	PBO 1.9	PBO 3.3	NAL12.5 1.4	NAL12.5 1.4	NAL25 5.1	NAL25 5.1
PBO	46.9%																																		
NAL12.5	49.3%																																		
NAL25	61.2%																																		
Abdominal Pain	Diarrhea																																		
PBO 3.3	PBO 4.2																																		
NAL12.5 8.5	NAL12.5 3.3																																		
NAL25 12.6	NAL 25 9.3																																		
Nausea	Flatulence																																		
PBO 4.7	PBO 1.9																																		
NAL12.5 7.1	NAL12.5 1.4																																		
NAL25 7.5	NAL25 5.1																																		
Upper Abd. Pain	Vomiting																																		
PBO 1.9	PBO 3.3																																		
NAL12.5 1.4	NAL12.5 1.4																																		
NAL25 5.1	NAL25 5.1																																		

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results																																																								
<p>Chey et al, 2014²³⁰</p> <p>Second of two, identical, randomized, double-blind, parallel-group, placebo-controlled KODIAC-05</p>	700	See Above (KODIAC-04)	See above (KODIAC-04)	<p><u>Primary End-Point</u> Response Rate: ≥ 3 or more SBMs over baseline, 9 of 12 weeks, and at least 3 of final 4 weeks (p value vs. placebo)</p> <ul style="list-style-type: none"> NAL25 39.7% (p=0.02) NAL12.5 34.9% (p=NS) PBO 29.3% <p><u>Secondary End-Points</u> Response rate in laxative inadequate response (LIR)</p> <ul style="list-style-type: none"> NAL25 46.8% (p=0.01) NAL12.5 42.4% (p=NS) PBO 31.4% <p>Median Time to First SBM</p> <ul style="list-style-type: none"> NAL25 12 hours PBO 37.2 hours NAL25 vs. PBO; p<0.001 <p>Mean number of days/week with > 1 SBM over 12 weeks</p> <ul style="list-style-type: none"> NAL25 vs. PBO; p>0.01 <p>Number of SBMs per week compared to PBO</p> <ul style="list-style-type: none"> NAL25 p<0.001 NAL12.5 p<0.05 <p>Stool consistency and straining vs. PBO</p> <ul style="list-style-type: none"> NAL25 and NAL12.5 significantly improved <p>Mean daily opioid doses remained stable</p>	<p>Any Adverse Event</p> <table> <tr> <td>PBO</td> <td>58.9%</td> </tr> <tr> <td>NAL12.5</td> <td>59.6%</td> </tr> <tr> <td>NAL25</td> <td>69.0%</td> </tr> </table> <p>Most Common AEs; percentage</p> <table> <tr> <td>Abdominal Pain</td> <td>Diarrhea</td> </tr> <tr> <td>PBO 7.8</td> <td>PBO 4.3</td> </tr> <tr> <td>NAL12.5 10.9</td> <td>NAL12.5 7.8</td> </tr> <tr> <td>NAL25 17.0</td> <td>NAL25 9.1</td> </tr> <tr> <td>Nausea</td> <td>Flatulence</td> </tr> <tr> <td>PBO 4.3</td> <td>PBO 3.0</td> </tr> <tr> <td>NAL12.5 6.1</td> <td>NAL12.5 1.7</td> </tr> <tr> <td>NAL25 8.6</td> <td>NAL25 6.0</td> </tr> <tr> <td>Upper Abd. Pain</td> <td>Vomiting</td> </tr> <tr> <td>PBO 1.3</td> <td>PBO 2.6</td> </tr> <tr> <td>NAL12.5 2.2</td> <td>NAL12.5 3.0</td> </tr> <tr> <td>NAL25 2.6</td> <td>NAL25 6.0</td> </tr> <tr> <td>Headache</td> <td>Back Pain</td> </tr> <tr> <td>PBO 3.5</td> <td>PBO 1.7</td> </tr> <tr> <td>NAL12.5 5.2</td> <td>NAL12.5 5.2</td> </tr> <tr> <td>NAL25 5.2</td> <td>NAL25 5.2</td> </tr> <tr> <td>Serious AEs</td> <td></td> </tr> <tr> <td>PBO 5.2%</td> <td></td> </tr> <tr> <td>NAL12.5 6.1%</td> <td></td> </tr> <tr> <td>NAL25 3.4%</td> <td></td> </tr> <tr> <td>Deaths Related to Study Drug (none)</td> <td></td> </tr> <tr> <td>Serious Cardiovascular Events</td> <td></td> </tr> <tr> <td>One patient unrelated to study drug</td> <td></td> </tr> <tr> <td>One patient related in PBO group</td> <td></td> </tr> <tr> <td>Opioid-Withdrawal symptoms no difference</td> <td></td> </tr> </table>	PBO	58.9%	NAL12.5	59.6%	NAL25	69.0%	Abdominal Pain	Diarrhea	PBO 7.8	PBO 4.3	NAL12.5 10.9	NAL12.5 7.8	NAL25 17.0	NAL25 9.1	Nausea	Flatulence	PBO 4.3	PBO 3.0	NAL12.5 6.1	NAL12.5 1.7	NAL25 8.6	NAL25 6.0	Upper Abd. Pain	Vomiting	PBO 1.3	PBO 2.6	NAL12.5 2.2	NAL12.5 3.0	NAL25 2.6	NAL25 6.0	Headache	Back Pain	PBO 3.5	PBO 1.7	NAL12.5 5.2	NAL12.5 5.2	NAL25 5.2	NAL25 5.2	Serious AEs		PBO 5.2%		NAL12.5 6.1%		NAL25 3.4%		Deaths Related to Study Drug (none)		Serious Cardiovascular Events		One patient unrelated to study drug		One patient related in PBO group		Opioid-Withdrawal symptoms no difference	
PBO	58.9%																																																												
NAL12.5	59.6%																																																												
NAL25	69.0%																																																												
Abdominal Pain	Diarrhea																																																												
PBO 7.8	PBO 4.3																																																												
NAL12.5 10.9	NAL12.5 7.8																																																												
NAL25 17.0	NAL25 9.1																																																												
Nausea	Flatulence																																																												
PBO 4.3	PBO 3.0																																																												
NAL12.5 6.1	NAL12.5 1.7																																																												
NAL25 8.6	NAL25 6.0																																																												
Upper Abd. Pain	Vomiting																																																												
PBO 1.3	PBO 2.6																																																												
NAL12.5 2.2	NAL12.5 3.0																																																												
NAL25 2.6	NAL25 6.0																																																												
Headache	Back Pain																																																												
PBO 3.5	PBO 1.7																																																												
NAL12.5 5.2	NAL12.5 5.2																																																												
NAL25 5.2	NAL25 5.2																																																												
Serious AEs																																																													
PBO 5.2%																																																													
NAL12.5 6.1%																																																													
NAL25 3.4%																																																													
Deaths Related to Study Drug (none)																																																													
Serious Cardiovascular Events																																																													
One patient unrelated to study drug																																																													
One patient related in PBO group																																																													
Opioid-Withdrawal symptoms no difference																																																													

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results																																													
Long-Term Safety																																																		
Webster et al, 2014 ¹²⁰ 52-week, open-label, randomized, parallel-group KODIAC-08	804	<p>New patients or rollover patients from Study-04 or Study-05</p> <p>Inclusion criteria: See Chey et al, 2014</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Diarrhea, constipation • Impaired GI integrity • Recent GI surgery • Inadequate laxative response during OIC confirmation • Opioid use for cancer-related pain • 5-year history of cancer • Increased permeability of BBB • Increased risk ventricular arrhythmia • Use of opioid antagonists • Use of strong CYP3A4 or P-gp inhibitors 	<p>2:1 Randomization</p> <p><u>Open Label:</u></p> <ul style="list-style-type: none"> • NAL - naloxone 25 mg daily Or • Usual Care – Laxative regimen by investigator, modification allowed, rescue axative allowed 	<p>Randomized: 844 patients; 760 new patients, 84 rollover</p> <p>Completion rates at 52-weeks</p> <ul style="list-style-type: none"> • NAL (n=327) 58.1% • UC (n=189) 67.3% <p>Use of breakthrough opioid similar between groups</p> <p>Laxative Use: in Usual Care Group Laxative use at study entry 79% No regimen change at completion 73%</p> <p>Pain scores remained constant Mean daily opioid doses remained constant</p>	<p>Any AE</p> <ul style="list-style-type: none"> • NAL 437 (81.8%) • UC 195 (72.2%) <p>AEs causing discontinuation</p> <ul style="list-style-type: none"> • NAL 56 (10.5%) • diarrhea, abdominal pain or vomiting <p>Death:</p> <p>One in each arm, unrelated to study drug</p> <p>Most Common AEs ($\geq 5\%$ any group); N (%)</p> <table border="1"> <thead> <tr> <th></th> <th>NAL25</th> <th>PBO</th> </tr> </thead> <tbody> <tr> <td>Abdominal Pain</td> <td>95 (17.8)</td> <td>9 (3.3)</td> </tr> <tr> <td>Diarrhea</td> <td>69 (12.9)</td> <td>16 (5.9)</td> </tr> <tr> <td>Nausea</td> <td>50 (9.4)</td> <td>11 (4.1)</td> </tr> <tr> <td>Back Pain</td> <td>48 (9.0)</td> <td>24 (8.9)</td> </tr> <tr> <td>Headache</td> <td>48 (9.0)</td> <td>13 (4.8)</td> </tr> <tr> <td>Flatulence</td> <td>37 (6.9)</td> <td>3 (1.1)</td> </tr> <tr> <td>Arthralgia</td> <td>33 (6.2)</td> <td>15 (5.6)</td> </tr> <tr> <td>Nasopharyngitis</td> <td>33 (6.2)</td> <td>15 (5.6)</td> </tr> <tr> <td>URI</td> <td>31 (5.8)</td> <td>23 (8.5)</td> </tr> <tr> <td>Bronchitis</td> <td>30 (5.6)</td> <td>12 (4.4)</td> </tr> <tr> <td>Vomiting</td> <td>27 (5.1)</td> <td>15 (5.6)</td> </tr> <tr> <td>Upper abd. Pain</td> <td>27 (5.1)</td> <td>3 (1.1)</td> </tr> <tr> <td>Sinusitis</td> <td>23 (4.3)</td> <td>19 (7.0)</td> </tr> <tr> <td>UTI</td> <td>22 (4.1)</td> <td>22 (8.1)</td> </tr> </tbody> </table> <p>GI AEs with NAL were typically mild or moderate (2.2% severe) occurred in the first 12-weeks of treatment and resolved with continued treatment (≤ 14 days) or after discontinuing</p> <p>MACE Events: (2 in each group including 2 deaths, all unrelated to study drug)</p> <p>Hypotension and hypertension: Unrelated</p> <p>GI perforation: None</p> <p>Opioid withdrawal AEs noted in 2 patients in NAL group attributed to a change in the opioid dose (1 patient tapered to lower dose, one as patient ran out of opioid medication)</p>		NAL25	PBO	Abdominal Pain	95 (17.8)	9 (3.3)	Diarrhea	69 (12.9)	16 (5.9)	Nausea	50 (9.4)	11 (4.1)	Back Pain	48 (9.0)	24 (8.9)	Headache	48 (9.0)	13 (4.8)	Flatulence	37 (6.9)	3 (1.1)	Arthralgia	33 (6.2)	15 (5.6)	Nasopharyngitis	33 (6.2)	15 (5.6)	URI	31 (5.8)	23 (8.5)	Bronchitis	30 (5.6)	12 (4.4)	Vomiting	27 (5.1)	15 (5.6)	Upper abd. Pain	27 (5.1)	3 (1.1)	Sinusitis	23 (4.3)	19 (7.0)	UTI	22 (4.1)	22 (8.1)
	NAL25	PBO																																																
Abdominal Pain	95 (17.8)	9 (3.3)																																																
Diarrhea	69 (12.9)	16 (5.9)																																																
Nausea	50 (9.4)	11 (4.1)																																																
Back Pain	48 (9.0)	24 (8.9)																																																
Headache	48 (9.0)	13 (4.8)																																																
Flatulence	37 (6.9)	3 (1.1)																																																
Arthralgia	33 (6.2)	15 (5.6)																																																
Nasopharyngitis	33 (6.2)	15 (5.6)																																																
URI	31 (5.8)	23 (8.5)																																																
Bronchitis	30 (5.6)	12 (4.4)																																																
Vomiting	27 (5.1)	15 (5.6)																																																
Upper abd. Pain	27 (5.1)	3 (1.1)																																																
Sinusitis	23 (4.3)	19 (7.0)																																																
UTI	22 (4.1)	22 (8.1)																																																

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results
Methylalntrexone Trials					
Advanced Illness – Pivotal Trials					
Thomas et al, 2008 ²⁵ MNTX 302 Initial Study: Randomized, double-blind, placebo-controlled trial with 3 month open label extension	133	Age > 18 years with advanced illness (defined as incurable cancer or other end-stage disease) with a life expectancy of ≥ 1 month Stable opioid use ≥ 2 wks. Stable laxative ≥ 3 days OIC: Less than 3 laxations during the previous week (no meaningful laxation within 24 – 48 hours of the first study dose).	Design: 1:1 <u>Initial Study:</u> MNTX 0.15mg/kg SQ every other day for 2 weeks or an equal volume of SQ placebo. <u>Day 8:</u> If fewer than 3 RFL, the dose could be doubled (0.3mg/kg) Duration: 2 weeks with 3 month open label extension: <u>Open Label Extension:</u> MNTX 0.15 mg/kg as needed, up to once every 24 hours. Subsequent dosing: Increased to 0.3mg/kg if no laxation occurred at 4 hours. Decreased to 0.075mg/kg if drug-related AE's occurred.	<u>Primary Endpoint:</u> Rescue free laxation within 4 hours of initial study dose <ul style="list-style-type: none"> MNTX 48% Placebo 15% p<0.001 Rescue free laxation within 4 hours of first 2 of first 4 doses <ul style="list-style-type: none"> MNTX 52% Placebo 8% p<0.001 <u>Secondary Endpoint:</u> Rescue free laxation within 4 hours after each dose for 13 days p<0.005 Rescue free laxation within 24 hours after study drug, p<0.05 Percentage of patients with 3 or more laxations per week <ul style="list-style-type: none"> MNTX 68% Placebo 45% p=0.009 Watery rescue free laxation within 4 hours <ul style="list-style-type: none"> MNTX 16% Placebo 17% Change in laxation with dose increases <ul style="list-style-type: none"> MNTX n=20 15% → 24% Placebo n=21 8% → 7% Global Clinical Impression of Change scale on days 7 and 14 <ul style="list-style-type: none"> MNTX Majority of status improved Placebo Majority status unchanged Pain Scores - Stable throughout in each group Himmelsbach Withdrawal Scale - Stable throughout in each group	Incidence of AE similar between groups MNTX AE ≥ 5% and 3 percentage points higher than in the placebo group: Abdominal pain (17% vs 13%) Flatulence (13% vs 7%) Nausea (11% vs 7%) Increased body temperature (8% vs 3%) Dizziness (8% vs 3%) MNTX AE - 0.15mg/kg = 0.3mg/kg doses SAE: MNTX 28% vs PBO 17% <u>Open-label extension</u> Most adverse events mild to moderate in intensity <ul style="list-style-type: none"> Abdominal pain (30%) Malignant neoplasm progression (24%) Nausea (21%) Vomiting (20%). AE related to study drug: <ul style="list-style-type: none"> Muscle spasm (n=1) Abdominal pain (n=1) Exacerbated pain (n=1)

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results																																																														
<p>Slatkin et al, 2009²⁴</p> <p>MNTX 301</p> <p>Double-blind, randomized, placebo-controlled trial with optional 4 week open label phase, and 3-month, open-label extension study.</p> <p>Excerpted from abstract</p>	154	<p>Age ≥ 18 years with advanced illness and life expectancy of 1 to 6 months.</p> <p>Stable opioid and laxative regimens ≥3 days</p> <p>No clinically significant laxation within 48 hours of first study drug dose</p>	<p>1:1:1 Randomization</p> <p><u>Initial Single Dose Trial:</u></p> <p>Single SQ dose of MNTX</p> <ul style="list-style-type: none"> • 0.15mg/kg • 0.3mg/kg or placebo <p><u>Open-Label (28 day):</u></p> <p>MNTX 0.15mg/kg SQ as needed as often as every 24hours</p> <p>Subsequent dosing 2° clinical response:</p> <ul style="list-style-type: none"> • Increased to 0.3 mg/kg • Decreased to 0.075 mg/kg <p><u>Open-Label Extension (3 months):</u></p> <p>MNTX 0.15mg/kg SQ as needed as often as every 24hours</p> <p>Subsequent dosing 2° clinical response:</p> <ul style="list-style-type: none"> • Increased to 0.3 mg/kg • Decreased to 0.075 mg/kg 	<table border="0"> <tr> <td></td> <td>MNTX 0.15mg/kg N=47</td> <td>MNTX 0.3mg/kg N=55</td> <td>Placebo N=52</td> </tr> <tr> <td><u>Primary Endpoint</u> Laxation within 4 hours (p<0.0001 each MNTX group vs placebo)</td> <td>62%</td> <td>58%</td> <td>14%</td> </tr> <tr> <td><u>Secondary Endpoints</u> Laxation within 30 minutes</td> <td colspan="3" style="text-align: center;">~50%</td> </tr> <tr> <td>Percentage responders with at least one watery diarrhea</td> <td>27.6%</td> <td>37.5%</td> <td>0%</td> </tr> <tr> <td>Laxation within 24 hours</td> <td colspan="3" style="text-align: center;">p<0.0001 each MNTX group vs placebo</td> </tr> <tr> <td>Median time to RFL</td> <td>1.10 hour</td> <td>0.8 hour</td> <td>>24 hour</td> </tr> <tr> <td></td> <td colspan="3" style="text-align: center;">(p<0.0001 each MNTX group vs placebo)</td> </tr> <tr> <td>Median change in pain score = 0</td> <td colspan="3"></td> </tr> <tr> <td>Median change in opioid withdrawal scale = 0</td> <td colspan="3"></td> </tr> <tr> <td>Changes in constipation distress</td> <td colspan="3" style="text-align: center;">paralleled laxation result</td> </tr> <tr> <td>Changes in GCIC scale</td> <td colspan="3" style="text-align: center;">paralleled laxation result</td> </tr> <tr> <td><u>Open-label phase (n=147)</u> Laxation within 4 hours (1st dose)</td> <td>61.9%</td> <td>52.2%</td> <td>54.2%</td> </tr> <tr> <td><u>Open-label and extension phase</u> (1,160 doses administered; n=27 completed trial) Median of 5 doses of MNTX over median duration of 28.5 days</td> <td colspan="3"></td> </tr> <tr> <td>Median interval of 3 days between doses</td> <td colspan="3"></td> </tr> </table>		MNTX 0.15mg/kg N=47	MNTX 0.3mg/kg N=55	Placebo N=52	<u>Primary Endpoint</u> Laxation within 4 hours (p<0.0001 each MNTX group vs placebo)	62%	58%	14%	<u>Secondary Endpoints</u> Laxation within 30 minutes	~50%			Percentage responders with at least one watery diarrhea	27.6%	37.5%	0%	Laxation within 24 hours	p<0.0001 each MNTX group vs placebo			Median time to RFL	1.10 hour	0.8 hour	>24 hour		(p<0.0001 each MNTX group vs placebo)			Median change in pain score = 0				Median change in opioid withdrawal scale = 0				Changes in constipation distress	paralleled laxation result			Changes in GCIC scale	paralleled laxation result			<u>Open-label phase (n=147)</u> Laxation within 4 hours (1 st dose)	61.9%	52.2%	54.2%	<u>Open-label and extension phase</u> (1,160 doses administered; n=27 completed trial) Median of 5 doses of MNTX over median duration of 28.5 days				Median interval of 3 days between doses				<p>Over the duration of the study, the most common adverse event occurring at ≥5% of patients in MNTX group was abdominal pain, rated mild to moderate, which appeared dose-related. Abdominal pain, flatulence, nausea and dizziness occurred at a higher frequency in the MNTX groups.</p> <p>AEs possible related to MNTX include:</p> <ul style="list-style-type: none"> • Abdominal pain (N=15) • Increased sweating (N=3) • Increased pain (N=2) • One each of burning at the injection site, vomiting, diarrhea, asthenia, increased blood pressure, dehydration, muscular cramp, loss of consciousness, tremor, delirium, hallucination, dyspnea and flushing <p><u>Open Label Extension</u></p> <table border="0"> <tr> <td>Any AE</td> <td>MNTX 81%</td> <td>PBO80%</td> </tr> <tr> <td>Discontinue</td> <td>MNTX 6%</td> <td>PBO 7%</td> </tr> </table> <p>SAE - Three serious adverse reactions were possibly related to MNTX</p> <ul style="list-style-type: none"> • Flushing • Delirium • Severe diarrhea, dehydration, cardiovascular collapse 	Any AE	MNTX 81%	PBO80%	Discontinue	MNTX 6%	PBO 7%
	MNTX 0.15mg/kg N=47	MNTX 0.3mg/kg N=55	Placebo N=52																																																																
<u>Primary Endpoint</u> Laxation within 4 hours (p<0.0001 each MNTX group vs placebo)	62%	58%	14%																																																																
<u>Secondary Endpoints</u> Laxation within 30 minutes	~50%																																																																		
Percentage responders with at least one watery diarrhea	27.6%	37.5%	0%																																																																
Laxation within 24 hours	p<0.0001 each MNTX group vs placebo																																																																		
Median time to RFL	1.10 hour	0.8 hour	>24 hour																																																																
	(p<0.0001 each MNTX group vs placebo)																																																																		
Median change in pain score = 0																																																																			
Median change in opioid withdrawal scale = 0																																																																			
Changes in constipation distress	paralleled laxation result																																																																		
Changes in GCIC scale	paralleled laxation result																																																																		
<u>Open-label phase (n=147)</u> Laxation within 4 hours (1 st dose)	61.9%	52.2%	54.2%																																																																
<u>Open-label and extension phase</u> (1,160 doses administered; n=27 completed trial) Median of 5 doses of MNTX over median duration of 28.5 days																																																																			
Median interval of 3 days between doses																																																																			
Any AE	MNTX 81%	PBO80%																																																																	
Discontinue	MNTX 6%	PBO 7%																																																																	

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results															
Advanced Illness Fixed-dose Trial																				
Bull J et al, 2015 ¹²⁷ Double-blind, randomized, placebo-controlled trial	230	Age ≥ 18 years with advanced illness and life expectancy ≥ 1 month with OIC (< 3 bowel movements in the last week and no bowel movement in the 24 hours, or no bowel movement in 48 hours receiving stable doses of laxatives and opioids.	1:1 Randomization <u>Initial phase</u> Dose every other day x 2 weeks <ul style="list-style-type: none"> MNTX 8mg (<62kg) MNTX 12mg (≥62kg) PBO <u>Open-Label Extension</u> Patients completing the initial phase could enroll in the 10 week extension and receive MNTX as needed but not more than once per 24 hours	<u>Primary Efficacy Endpoint:</u> RFBM within 4 hours in 2 of first 4 doses (Percentage, 95% CI) <ul style="list-style-type: none"> MNTX 62.9%, (53.5 to 71.7%) (unaffected by weight) Placebo 9.6%, (4.9% to 16.6%) p<0.0001 <u>Secondary Endpoints:</u> <ul style="list-style-type: none"> RFBM ≤ 4 hours after first dose p<0.0001 RFBM <4 hours after at least 4 (max 7 doses) (p<0.0001) Median time to first RFBM after each MNTX dose (p<0.005) Mean # BMs ≤24 hours after dosing at 2 weeks (p=0.0083) Mean # RFBMs ≤ 24 hours after doing at 2 weeks (p=0.0024) Patients using rescue laxatives (p=0.0020) <u>Open-Label Extension</u> <ul style="list-style-type: none"> Efficacy was consistent with the two-week RCT Mean pain scores and opioid use remained unchanged 	MNTX group AEs: Abdominal pain, nausea Discontinuation rate MNTX 10.3% Placebo 6.1% Serious AEs MNTX 12.1% Placebo 21.1% <u>Open-Label Extension</u> Most commonly reported AEs were abdominal pain (15.4%), diarrhea (7.4%), and flatulence (3.4%) No study drug significant AEs															
Advanced-Illness Open-Label Extension																				
Lipman AG et al, 2011 ¹³² Results of the 3-month, open-label, extension of the 2-week, double-blind study (Thomas et al, 2008)	82	See Thomas et al, 2008 Patients completed the 2-week, double-blind, clinical trial, had stable vital signs, and if of child-bearing potential were not pregnant and on adequate birth-control.	Open Label Extension: NMTX SQ 0.15mg/kg (max. Q24hr) Subsequent Dosing: Increased to 0.3 mg/kg for laxation Decreased to 0.075mg/kg for AEs	Underlying Diagnosis: Cancer 54.9%, Cardiovascular disease 10% Laxation response* <table border="1"> <thead> <tr> <th></th> <th>MNTX group</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Results from 2-week study</td> <td>45.3%</td> <td>10.8%</td> </tr> <tr> <td>Month 1</td> <td>45.5%</td> <td>48.3%</td> </tr> <tr> <td>Month 2</td> <td>57.7%</td> <td>47.6%</td> </tr> <tr> <td>Month 3</td> <td>57.3%</td> <td>52.1%</td> </tr> </tbody> </table> *doses with laxation/total number of doses Time to rescue-free laxation in responders: <1 hour (range 0-4) Watery bowel movement in 4 hour responders 11% Bowel movement difficulty rated unchanged Improvement in constipation distress 55% Global clinical impression of change at 12 weeks rated as better in more than half of the patients. Pain scores did not change appreciably throughout the study Opioid Withdrawal symptom score ratings for all patients was none or mild.		MNTX group	Placebo	Results from 2-week study	45.3%	10.8%	Month 1	45.5%	48.3%	Month 2	57.7%	47.6%	Month 3	57.3%	52.1%	Incidence of AEs: 100% AEs ≥7.5% of patients <ul style="list-style-type: none"> Abdominal pain 30.5% Malignant neoplasm progression 24.4% Nausea 20.7% Vomiting 19.5% Of Patients with gastrointestinal AE (N=57) 54.4% were at least possibly related 7.3% resulted in drug discontinuation Serious AEs: 43.9% related to disease progression MNTX Related Serious AEs (n=2) <ul style="list-style-type: none"> Muscle spasms Abdominal pain and pain exacerbation
	MNTX group	Placebo																		
Results from 2-week study	45.3%	10.8%																		
Month 1	45.5%	48.3%																		
Month 2	57.7%	47.6%																		
Month 3	57.3%	52.1%																		

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results
Chronic Non-Malignant Pain – Pivotal Trial					
Michna E et al, 2011 ¹²⁸ Multi-center, double-blind, randomized, placebo-controlled	460	<ul style="list-style-type: none"> Age ≥ 18 years Chronic pain from a non-malignant condition for at least 2 months and receiving > 50mg oral morphine equivalents daily for at least 2 weeks OIC Fewer than 3 RFBMs weekly, associated with at least 1 of the following signs and symptoms; hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after a bowel movement. 	<p>Design: 1:1:1 allocation</p> <p>MNTX 12mg QD</p> <p>MNTX 12mg QOD</p> <p>Placebo</p> <p>Patients receive medication for 4 weeks and were eligible to enter and 8-week open-label, as-needed dosing phase with a 14-day follow-up period.</p> <p>Patients discontinued all laxatives prior to study. In the absence of a BM for 3 days the patient could receive a single dose of bisacodyl (1-4 tablets) once every 24 hours but not within 4 hours of a study dose.</p> <p>Statistically powered to detect a 15% difference in the proportion of patients having a RFBM within 4 hours after the first dose and the percentage of active injections/patient resulting in a RFBM within 4 hours.</p>	<p><u>Primary Endpoints:</u></p> <p>Proportion of patients with a RFBM within 4 hours of first dose</p> <ul style="list-style-type: none"> All MNTX 34.2% (NNT~4) Placebo 9.9% MNTX QD 33.3% p<0.001 MNTX QOD 35.1% p<0.001 <p>Percentage of active injections/patient resulting in a RFBM within 4 hours</p> <ul style="list-style-type: none"> MNTX QD 28.9% p<0.001 Placebo 9.4% MNTX QOD 30.2% p<0.001 Placebo 9.3% <p><u>Secondary Endpoints:</u></p> <p>Time to first RFBM after injection</p> <ul style="list-style-type: none"> All MNTX 46% p<0.001 Placebo 25.3% <p>Adjusted mean change from baseline in weekly number of RFBM</p> <ul style="list-style-type: none"> MNTX QD 3.1 p<0.001 MNTX QOD 2.1 p<0.01 Placebo 1.5 <p>Patients with ≥ 3 RFBMs per week (blinded)</p> <ul style="list-style-type: none"> MNTX QD 58.7% (NNT ~5) MNTX QOD 45.3% (NNT~14) Placebo 38.3% <p>Bristol Stool Form Scale, Straining Scale score, Sense of Complete Evacuation Scale score in both MNTX groups improved with MNTX</p> <p>Opiate withdrawal scales – MNTX = PBO</p> <p>PAC-QOL Questionnaire</p> <p>Day 28: MNTX QD improvement p<0.001</p> <p>Day 28: MNTX QOD improvement p=0.014</p> <p>Rescue Laxative Use</p> <ul style="list-style-type: none"> MNTX QD n=58 38.7% p<0.001 MNTX QOD n=73 49.3% p=0.03 Placebo n=100 61.7% 	<p>MNTX QD (70/150) 49.3%</p> <p>MNTX QOD (67/148) 45.3%</p> <p>Placebo (62/162) 38.3%</p> <p>Most AE mild to moderate in severity and similar between groups.</p> <p>GI AE: MNTX > PBO</p> <ul style="list-style-type: none"> abdominal pain, nausea, diarrhea <p>Hyperhidrosis: MNTX > PBO</p> <p>SAE: MNTX = PBO</p> <ul style="list-style-type: none"> One 50yo patient had extra systoles during the first double blind treatment day, which resolved on the same day.

Reference / Study Design	N	Patient Selection	Treatment Intervention	Results	Adverse Results
Long-Term Safety, Tolerability and Efficacy					
Webster et al, ¹³⁰ (abstract)	1034	Patients with non-malignant pain, OIC \geq 1 month after 14 day screening Stable opioid regimen	MNTX SQ 12mg <ul style="list-style-type: none"> At least once weekly (max. once daily) Duration 48 weeks Routine laxatives permitted	Doses resulting in a RFBM within 4 hours <ul style="list-style-type: none"> 34.1% (monthly mean rate 33.0% to 37.4%) Change in number of BMs per week compared to baseline <ul style="list-style-type: none"> +1.5 p<0.001 monthly compared to baseline Improvements were noted in straining and stool consistency From Salix ¹³³ : Mean number of doses per week ~5	Discontinuations 54% AEs 15%

1. Sullivan MD, Edlund MJ, Fan MY, DeVries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain*. 2008;138(2):440-449.
2. Verhaak PFM, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM. Prevalence of chronic benign pain disorder among adults: A review of the literature. *Pain*. 1998;77(3):231-239.
3. Academies IoMotN. Relieving pain in America. A blueprint for transforming prevention, care, education, and research. . Published 2013; http://books.nap.edu/openbook.php?record_id=13172. Accessed 11/23/2015, 2015.
4. Manchikanti KN, Manchikanti L, Damron KS, Pampati V, Fellows B. Increasing deaths from opioid analgesics in the United States: An evaluation in an interventional pain management practice. *Journal of Opioid Management*. 2008;4(5):271-283.
5. Scripts E. A Nation in Pain. 2014; <http://lab.express-scripts.com/publications/a-nation-in-pain>. Accessed 11/15, 2015.
6. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open Medicine*. 2012;6(2):41-47.
7. Trescot A, Glaser SE, Hansen H, Benyamin R, Patel S, Manchikanti L. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician*. 2008;11(SPEC. ISS. 2):S181-S200.
8. Tack J, Corsetti M. Naloxegol for the treatment of opioid-induced constipation. *Expert review of gastroenterology & hepatology*. 2014;8(8):855-861.
9. Informatics TIIIfH. A Review of the Use of Medicines in the U.S. in 2014 Medicines Use and Spending Shifts. 2015.
10. Mazer-Amirshahi M, Mullins PM, Rasooly I, van den Anker J, Pines JM. Rising opioid prescribing in adult U.S. emergency department visits: 2001-2010. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. 2014;21(3):236-243.
11. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: Pathophysiology, clinical consequences, and management. *Gastroenterology Research and Practice*. 2014;2014.
12. Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;72(14):1847-1865.
13. Lexi-Drugs. Wolters Kluwer; 2015. http://online.lexi.com/lco/action/index/dataset/patch_f. Accessed 11/7/15.
14. AHFS-DI. Hudson, OH: Wolters Kluwer; 2015: http://online.lexi.com/lco/action/index/dataset/complete_ashp.
15. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *American journal of surgery*. 2001;182(5A Suppl):11s-18s.
16. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*. 2007;61(7):1181-1187.
17. 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. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*. 2014;26(10):1386-1395.
18. Bell TJ, Poston SA, Kraft MD, Senagore AJ, Delaney CP, Techner L. Economic analysis of alvimopan in North American Phase III efficacy trials. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. 2009;66(15):1362-1368.
19. Kumar LB, C.: Emmanuel, A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Gastroenterol Res Pract*. 2014;2014:141737.
20. Corsetti M, Tack J. Naloxegol, a new drug for the treatment of opioid-induced constipation. *Expert Opinion on Pharmacotherapy*. 2015;16(3):399-406.
21. McNicol ED, Boyce D, Schumann R, Carr DB. Mu-opioid antagonists for opioid-induced bowel dysfunction. *Cochrane Database of Systematic Reviews*. 2008(2).
22. Gyawali B, Hayashi N, Tsukuura H, Honda K, Shimokata T, Ando Y. Opioid-induced constipation. *Scandinavian Journal of Gastroenterology*. 2015;50(11):1331-1338.
23. Diego L, Atayee R, Helmons P, Von Gunten CF. Methylnaltrexone: A novel approach for the management of opioid-induced constipation in patients with advanced illness. *Expert Review of Gastroenterology and Hepatology*. 2009;3(5):473-485.
24. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Annals of Pharmacotherapy*. 2007;41(6):984-993.
25. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*. 2008;358(22):2332-2343.
26. Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother*. 2007;21(1):15-25.
27. Rangnekar AS, Chey WD. Methylnaltrexone: A New Treatment for an Old Problem. *Gastroenterology*. 2008;135(5):1792-1794.
28. Bader S, Dürk T, Becker G. Methylnaltrexone for the treatment of opioid-induced constipation. *Expert Review of Gastroenterology and Hepatology*. 2013;7(1):13-26.
29. Choi YSB, J. A. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage*. 2002;24(1):71-90.

30. Boscan P, Van Hoogmoed LM, Pypendop BH, Farver TB, Snyder JR. Pharmacokinetics of the opioid antagonist N-methylnaltrexone and evaluation of its effects on gastrointestinal tract function in horses treated or not treated with morphine. *American journal of veterinary research*. 2006;67(6):998-1004.
31. Thomas JR, von Gunten CF. Management of constipation in patients with cancer. *Supportive cancer therapy*. 2004;2(1):47-51.
32. Camilleri M. Opioid-induced constipation: Challenges and therapeutic opportunities. *American Journal of Gastroenterology*. 2011;106(5):835-842.
33. Caterina Aurilio MCP, Vincenzo Pota and Pasquale Sansone. Opioid Induced Constipation, Constipation - Causes, Diagnosis and Treatment. In: Catto-Smith DA, ed. Croatia, European Union: InTech; 2012: <http://www.intechopen.com/books/constipation-causes-diagnosis-and-treatment/etiopathogenesis-incidence-and-diagnosis-of-opioid-induced-constipation>.
34. De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. *Pharmacol Ther*. 1996;69(2):103-115.
35. Friedman JD, Dello Buono FA. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. *The Annals of pharmacotherapy*. 2001;35(1):85-91.
36. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.
37. 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;10(1):35-42.
38. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis research & therapy*. 2005;7(5):R1046-1051.
39. Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *British Medical Journal*. 2001;322(7295):1154-1158.
40. Cook SF, Lanza L, Zhou X, et al. Gastrointestinal side effects in chronic opioid users: Results from a population-based survey. *Alimentary Pharmacology and Therapeutics*. 2008;27(12):1224-1232.
41. Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J Opioid Manag*. 2009;5(3):137-144.
42. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*. 2010;22(4):424-430, e496.
43. Brock C, Olesen SS, Olesen AE, Frøkjær JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: Pathophysiology and management. *Drugs*. 2012;72(14):1847-1865.
44. Glare P, Walsh D, Sheehan D. The adverse effects of morphine: a prospective survey of common symptoms during repeated dosing for chronic cancer pain. *Am J Hosp Palliat Care*. 2006;23(3):229-235.
45. Papaleontiou M, Henderson CR, Jr., Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *Journal of the American Geriatrics Society*. 2010;58(7):1353-1369.
46. Becker G, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. *J Pain Symptom Manage*. 2007;34(5):547-565.
47. Quigley C. The role of opioids in cancer pain. *British Medical Journal*. 2005;331(7520):825-829.
48. Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. *Palliat Med*. 1998;12(5):375-382.
49. Abramowitz L, Béziaud 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. *Journal of Medical Economics*. 2013;16(12):1423-1433.
50. Aklan NA, Al-Alimi KA, Alsirafy SA. Prevalence of symptoms among patients with cancer in Yemen. *Palliative Medicine*. 2014;28(6):773-774.
51. Fajardo NR, Cremonini F, Talley NJ. Management of constipation in patients with cancer. *American Journal of Cancer*. 2006;5(5):319-330.
52. Fallon MT. Constipation in cancer patients: Prevalence, pathogenesis, and cost-related issues. *European Journal of Pain*. 1999;3(SUPPL. A):3-7.
53. Koh S. Prevalence of opioid-related adverse events in cancer pain: Analysis of discrepancy between investigator-and patient-reported prevalence. *Palliative Medicine*. 2014;28(6):557.
54. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: A longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;93(3):247-257.
55. Thomas J. Cancer-related constipation. *Curr Oncol Rep*. 2007;9(4):278-284.
56. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *The journal of pain : official journal of the American Pain Society*. 2003;4(5):231-256.
57. Moskovitz BL, Benson CJ, Patel AA, et al. Analgesic treatment for moderate-to-severe acute pain in the United States: patients' perspectives in the Physicians Partnering Against Pain (P3) survey. *J Opioid Manag*. 2011;7(4):277-286.
58. Rauck RL. Treatment of opioid-induced constipation: focus on the peripheral mu-opioid receptor antagonist methylnaltrexone. *Drugs*. 2013;73(12):1297-1306.

59. Devulder J, Richarz U, Nataraja SH. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Curr Med Res Opin.* 2005;21(10):1555-1568.
60. Bell TJ, Poston SA, Kraft MD, Senagore AJ, Techner L. Economic analysis of alvimopan--a clarification and commentary. *Pharmacotherapy.* 2013;33(5):e81-82.
61. Iyer S, Davis KL, Candrilli S. Opioid use patterns and health care resource utilization in patients prescribed opioid therapy with and without constipation. *Managed care (Langhorne, Pa.).* 2010;19(3):44-51.
62. Kwong WJ, Diels J, Kavanagh S. Costs of gastrointestinal events after outpatient opioid treatment for non-cancer pain. *Annals of Pharmacotherapy.* 2010;44(4):630-640.
63. Larkin PJ, Sykes NP, Centeno C, et al. The management of constipation in palliative care: clinical practice recommendations. *Palliat Med.* 2008;22(7):796-807.
64. Librach SL, Bouvette M, De Angelis C, et al. Consensus recommendations for the management of constipation in patients with advanced, progressive illness. *J Pain Symptom Manage.* 2010;40(5):761-773.
65. Woolery M, Bisanz A, Lyons HF, et al. Putting evidence into practice: evidence-based interventions for the prevention and management of constipation in patients with cancer. *Clin J Oncol Nurs.* 2008;12(2):317-337.
66. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The journal of pain : official journal of the American Pain Society.* 2009;10(2):113-130.
67. Fallon MT, Hanks GW. Morphine, constipation and performance status in advanced cancer patients. *Palliat Med.* 1999;13(2):159-160.
68. Bell TJP, S. A.: Kraft, M. D.: Senagore, A. J.: Delaney, C. P.: Techner, L. Economic analysis of alvimopan in North American Phase III efficacy trials. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* 2009;66(15):1362-1368.
69. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370(25):2387-2396.
70. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet.* 1991;337(8755):1475.
71. Meissner W, Schmidt U, Hartmann M, Kath R, Reinhart K. Oral naloxone reverses opioid-associated constipation. *Pain.* 2000;84(1):105-109.
72. Cheskin LJ, Chami TN, Johnson RE, Jaffe JH. Assessment of nalmefene glucuronide as a selective gut opioid antagonist. *Drug Alcohol Depend.* 1995;39(2):151-154.
73. Handal KA, Schauben JL, Salamone FR. Naloxone. *Annals of emergency medicine.* 1983;12(7):438-445.
74. Webster LR, Fine PG. Overdose deaths demand a new paradigm for opioid rotation. *Pain Med.* 2012;13(4):571-574.
75. Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. *Pain Med.* 2012;13(4):562-570.
76. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Archives of internal medicine.* 2010;170(22):1979-1986.
77. Shook JE, Pelton JT, Hruby VJ, Burks TF. Peptide opioid antagonist separates peripheral and central opioid antitransit effects. *The Journal of pharmacology and experimental therapeutics.* 1987;243(2):492-500.
78. Caraceni A. The EPCRC project to revise the European Association for Palliative Care (EAPC) guidelines on the use of opioids for cancer pain. *Palliat Med.* 2011;25(5):389-390.
79. Diego LA, R.: Helmons, P.: Hsiao, G.: von Gunten, C. F. Novel opioid antagonists for opioid-induced bowel dysfunction. *Expert Opin Investig Drugs.* 2011;20(8):1047-1056.
80. Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. *ClinicoEconomics and outcomes research : CEOR.* 2014;6:269-281.
81. Coyne KS, Margolis MK, Yeomans K, et al. Opioid-Induced Constipation Among Patients with Chronic Noncancer Pain in the United States, Canada, Germany, and the United Kingdom: Laxative Use, Response, and Symptom Burden Over Time. *Pain Med.* 2015;16(8):1551-1565.
82. Hunold KM, Smith SA, Platts-Mills TF. Constipation Prophylaxis Is Rare for Adults Prescribed Outpatient Opioid Therapy from U.S. Emergency Departments. *Academic Emergency Medicine.* 2015;22(9):1118-1121.
83. Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Sao Paulo Medical Journal.* 2011;129(4):277.
84. Jones MP, Talley NJ, Nuyts G, Dubois D. Lack of objective evidence of efficacy of laxatives in chronic constipation. *Digestive diseases and sciences.* 2002;47(10):2222-2230.
85. The Esophagogastric Junction 420 questions. . In: Robert Giuli J-PG, Glyn G Jamieson, Carmelo Scarpignato (Eds), ed 1998 www.hon.ch/oeso/vol_5_eso_junction/500_chapters.html.
86. Locke GR, 3rd, Pemberton JH, Phillips SF. AGA technical review on constipation. American Gastroenterological Association. *Gastroenterology.* 2000;119(6):1766-1778.
87. Holzer P. Non-analgesic effects of opioids: Management of opioid-induced constipation by peripheral opioid receptor antagonists: Prevention or withdrawal? *Current Pharmaceutical Design.* 2012;18(37):6010-6020.
88. Brick N. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Clin J Oncol Nurs.* 2013;17(1):91-92.
89. Educators ASoP. Opioid-induced constipation pocket guide. Lake Mary, FL: International Guidelines Center; 2010.

90. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician*. 2012;15(3 Suppl):S67-116.
91. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13(2):e58-68.
92. Teoh PJ, Camm CF. NICE Opioids in Palliative Care (Clinical Guideline 140) - A Guideline Summary. *Annals of Medicine and Surgery*. 2012;1:44-48.
93. NICE. Naloxegol for treating opioid-induced constipation: NICE Guideline TA345. 2015. nice.org.uk/guidance/ta345/.
94. National Guideline C. Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management.
95. Garnock-Jones KP. Naloxegol: A review of its use in patients with opioid-induced constipation. *Drugs*. 2015;75(4):419-425.
96. AstraZeneca. Movantik (naloxegol) Prescribing Information. 2015; <https://www.movantik.com/>.
97. Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: A randomized controlled trial. *Journal of the American Medical Association*. 2000;283(3):367-372.
98. Amin HM, Sopchak AM, Foss JF, Esposito BF, Roizen MF, Camporesi EM. Efficacy of methylnaltrexone versus naloxone for reversal of morphine-induced depression of hypoxic ventilatory response. *Anesth Analg*. 1994;78(4):701-705.
99. Foss JF. A review of the potential role of methylnaltrexone in opioid bowel dysfunction. *American journal of surgery*. 2001;182(5A Suppl):19s-26s.
100. Brown DR, Goldberg LI. The use of quaternary narcotic antagonists in opiate research. *Neuropharmacology*. 1985;24(3):181-191.
101. Kotake ANK, S. K.: Burton, E.: McCoy, C. E.: Goldberg, L. I. Variations in demethylation of N-methylnaltrexone in mice, rats, dogs, and humans. *Xenobiotica*. 1989;19(11):1247-1254.
102. Yuan CS, Foss JF, O'Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: A double-blind randomized placebo-controlled trial. *Clinical Pharmacology and Therapeutics*. 1996;59(4):469-475.
103. Salix. Relistor (methylnaltrexone) Package Insert. 2014; <http://www.salix.com/products/relistor>.
104. Holzer P. Randomised controlled trial: Naloxegol increases frequency of bowel movements and combats inadequate response to laxatives. *Evidence-based medicine*. 2015;20(1):5. <http://onlinelibrary.wiley.com/doi/10.1111/ebm.12508> <http://ebm.bmj.com/content/20/1/5.full.pdf>.
105. McNicol E, Boyce DB, Schumann R, Carr D. Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: Systematic review and meta-analysis of randomized controlled trials. *Pain Medicine*. 2008;9(6):634-659.
106. Becker G, Galandi D, Blum HE. Peripherally Acting Opioid Antagonists in the Treatment of Opiate-Related Constipation: A Systematic Review. *Journal of Pain and Symptom Management*. 2007;34(5):547-565.
107. Sonu I, Triadafilopoulos G, Gardner JD. A questionable investment for our patients: Challenging the efficacy of new therapies for opioid-induced and chronic idiopathic constipation. *Gastroenterology*. 2015;148(4):S191.
108. Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: Systematic review and meta-analysis. *American Journal of Gastroenterology*. 2013;108(10):1566-1574.
109. Magge S, Lembo A, Cremonini F. The efficacy of peripherally acting opioid antagonists in opioid-induced constipation: Meta-analysis of controlled clinical trials. *Gastroenterology*. 2012;142(5):S812.
110. Brenner DMF, A. C.: Schoenfeld, P. S. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: Systematic review and meta-analysis. *Gastroenterology*. 2013;144(5):S215.
111. MacKey AC, Green L, Greene P, Avigan M. Methylnaltrexone and gastrointestinal perforation. *Journal of Pain and Symptom Management*. 2010;40(1):e1-e3.
112. Diego L, Atayee R, Helmons P, Hsiao G, von Gunten CF. Novel opioid antagonists for opioid-induced bowel dysfunction. *Expert Opin Investig Drugs*. 2011;20(8):1047-1056.
113. 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. *Journal of Pain*. 2011;12(2):185-193.
114. Anantharamu TS, S.: Gupta, A. K.: Dahiya, N.: Singh Brashier, D. B.: Sharma, A. K. Naloxegol: First oral peripherally acting mu opioid receptor antagonists for opioid-induced constipation. *J Pharmacol Pharmacother*. 2015;6(3):188-192.
115. Adolor. Adolor discontinues drug development program for entereg
2015; <http://www.fdanews.com/articles/113303-adolor-discontinues-drug-development-program-for-entereg> accessed 11/17/15. Accessed 11/24, 2015.
116. Gottfridsson C, Carlson G, Lappalainen J, Sostek M. Evaluation of the effect of Naloxegol on cardiac repolarization: a randomized, placebo- and positive-controlled crossover thorough QT/QTc study in healthy volunteers. *Clinical therapeutics*. 2013;35(12):1876-1883. <http://onlinelibrary.wiley.com/doi/10.1111/cts.12187> http://ac.els-cdn.com/S0149291813009703/1-s2.0-S0149291813009703-main.pdf?_tid=e1eb7886-817a-11e5-b001-00000aab0f6b&acdnat=1446480228_8cdcfdd7d8316810e7cc9b5cc3eb31b2.
117. Bui K, She F, Sostek M. The effects of mild or moderate hepatic impairment on the pharmacokinetics, safety, and tolerability of naloxegol. *J Clin Pharmacol*. 2014;54(12):1368-1374.
118. Bui K, She F, Sostek M. The effects of renal impairment on the pharmacokinetics, safety, and tolerability of naloxegol. *J Clin Pharmacol*. 2014;54(12):1375-1382.

119. Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. 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(9):1542-1550.
120. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *New England Journal of Medicine*. 2014;370(25):2387-2396.
121. Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: The long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. *Alimentary Pharmacology and Therapeutics*. 2014;40(7):771-779.
122. Tack JC, M. Naloxegol for the treatment of opioid-induced constipation. *Expert review of gastroenterology & hepatology*. 2014;8(8):855-861.
123. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *New England Journal of Medicine*. 2008;358(22):2332-2343.
124. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *Journal of Supportive Oncology*. 2009;7(1):39-46.
125. Diego LA, R.: Helmons, P.: Von Gunten, C. F. Methylnaltrexone: A novel approach for the management of opioid-induced constipation in patients with advanced illness. *Expert Review of Gastroenterology and Hepatology*. 2009;3(5):473-485.
126. Garnock-Jones KP, McKeage K. Methylnaltrexone. *Drugs*. 2010;70(7):919-928.
127. Bull JW, C. V.: Israel, R. J.: Barrett, A. C.: Paterson, C.: Forbes, W. P. Fixed-Dose Subcutaneous Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation: Results of a Randomized, Placebo-Controlled Study and Open-Label Extension. *Journal of palliative medicine*. 2015;18(7):593-600.
<http://onlineibrary.wiley.com/o/cochrane/clcentral/articles/086/CN-01083086/frame.html>:
<http://online.liebertpub.com/doi/pdfplus/10.1089/jpm.2014.0362>.
128. 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. *Journal of Pain*. 2011;12(5):554-562.
129. Webster LR, Michna E, Khan A, Maller E, Tzani E, Israel R. Subcutaneous Methylnaltrexone Provides Long-Term Laxation in Patients with Chronic Non-Malignant Pain and Opioid-Induced Constipation. *Neurogastroenterology and Motility*. 2011;23:44.
130. Webster LM, E.: Khan, A.: Israel, R.: Manley, A.: Zhang, H.: Tzani E, Maller, E. The long-term safety of subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain. *Journal of Pain*. 2011;12(4):P70.
131. Webster LM, E.: Khan, A.: Israel, R.: Manley, A.: Zhang, H.: Maller, E.: Tzani E. The long-term efficacy of subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain. *Journal of Pain*. 2011;12(4):P70.
132. Lipman AG, Karver S, Austin Cooney G, Stambler N, Israel RJ. Methylnaltrexone for opioid-induced constipation in patients with advanced illness: A 3-month open-label treatment extension study. *Journal of Pain and Palliative Care Pharmacotherapy*. 2011;25(2):136-145.
133. Pharmaceuticals S. Relistor (methylnaltrexone bromide) for the treatment of opioid induced constipation. Briefing document for the anesthetic and algesic drug products advisory committee meeting of 11-12 June 2014. Version Date: May 8, 2014. 2014:28-38.