# Update on the Management of Opioid-induced Constipation

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The vast majority of patients who require analgesia with opioid medications will experience constipation. While this may be an acceptable trade-off for pain relief in many patient populations, constipation is associated with a significant negative impact on quality of life. One group of patients for whom the emergence of opioid-induced adverse effects, including constipation, is particularly troubling is the growing population of patients receiving palliative care. This article will briefly discuss the current state of palliative care in Canada, review the mechanism of opioid-induced constipation and present therapeutic options for its treatment. Among the treatment options, the review will focus on peripherally acting μ-opioid receptor antagonists, a novel class of agents that has demonstrated significant efficacy and a favourable safety profile in clinical trials.

## PALLIATIVE CARE IN CANADA

There is no one accepted definition of what constitutes palliative care. However, Health Canada defines it as care that addresses the physical and psychological aspects of end of life. This involves pain and other symptom management; social, psychological, cultural, emotional and spiritual support; caregiver support; and bereavement support.[1]

The term 'palliative' is simply applied when no more curative options are available or desired. Palliative treatments are therefore not designed with curative intent; they are intended to extend life or improve quality of life by alleviating or reducing pain or discomfort. Palliative care is planned to meet not only physical needs but also the psychological needs of each person and their family.

TABLE 1. **Possible Mechanisms of Opioid-induced Constipation[8]**

- Impairment of GI motility and transit
- Increased anal sphincter tone
- Increased electrolyte and water absorption
- Impaired defecation response

The various types of patients whom the term 'palliative' is used to describe include cancer patients, as well as those suffering from progressively debilitating non-malignant illnesses that will lead to death. With respect to the time frame of palliative care, some have suggested that it be defined as treatment for patients for whom death is expected within one year (recognizing that end of life can occur at any time, within days, weeks or months). Because palliative-care services are helpful not only when a person is approaching death but also at earlier stages in the illness, this somewhat arbitrary one-year threshold is by no means definitive. Many patients who will require palliative care may be expected to live considerably longer than one year; they can still be deemed to require palliative care if their condition is such that there is no chance of cure or remission.

Recent Canadian statistics have shown that approximately 259,000 Canadians die every year.[2] Of these, approximately 62% (more than 160,000 patients) received palliative care. Due to the aging of the Canadian population, the numbers of patients requiring palliation will dramatically increase. Projections for the year 2020 show that there will be an expected increase in annual deaths of 33% compared to 2003, with the absolute number of deaths projected to be more than 330,000 annually.[2]

## OPIOID USE IN PALLIATIVE CARE

Palliative care is provided to patients with many types of advanced chronic diseases, many of whom experience significant pain as a result of their condition(s). For malignant tumours, for example, significant pain is reported by 65-85% of patients with advanced, incurable disease.[3-6]

Pain itself is clearly an unwelcome consequence of disease, which diminishes quality of life and impairs patient ability to participate in activities of daily living.[7] Both the pain itself and the treatments used to manage it may also lead to a number of other negative outcomes, including exacerbation of other symptoms, nausea, fatigue, dyspnea, impaired cognition and constipation.[3]

Opioids are the most potent analgesic agents available for use and are considered necessary in as many as 80% of patients in palliative care.[8] Along with pain relief, however, these agents are known to cause unpleasant side effects, including nausea (15-30% of patients taking oral morphine), sedation (20-60% of patients) and constipation (up to 87%).[9,10] While the two former side effects tend to subside after continued use, constipation—the passage of small amounts of hard, dry bowel movements, usually fewer than three times per week—tends to persist. As such, prevention and treatment of constipation are important components of palliative care.

## OPIOID-INDUCED CONSTIPATION

The consequences of constipation include abdominal pain, bloating, nausea and vomiting, fecal impaction and urinary retention.[11] These can be so distressing for some patients that they would even prefer to suffer the disease-related pain than the opioid-induced constipation.[10]

***Mechanisms of opioid-induced constipation.*** Opioids exert their analgesic effect by interaction with the μ-opioid receptors in the central nervous system (CNS). They also bind to these receptors in the gastrointestinal (GI) tract, which results in an impairment of GI motility and transit.[10] Other contributing factors related to opioid use are increased anal sphincter tone; increased electrolyte and water absorption; and impaired defecation response (Table 1).[8] Importantly, opioids can cause constipation even at low dosages. The constipating

effects of opioids also seem to be common to all agents, although there are some data that indicate that transdermal agents may produce less constipation.[12]

***Contribution of other factors.*** It should be noted that while opioids are a known cause of constipation, they are typically not the only cause. There are a number of other factors that contribute to constipation in patients receiving palliative care. These include lifestyle factors, comorbidities and other medications (Table 2).[13]

TABLE 2. Risk Factors for Constipation in Palliative Care[13]

| |
|---|
| LIFESTYLE |
| • Reduced food and fluid intake |
| • Dehydration |
| • Inactivity |
| OTHER CONDITIONS |
| • Hypercalcemia |
| • Intestinal obstruction |
| • Spinal cord compression |
| • Hemorrhoids |
| • Diabetes |
| • Others |
| MEDICATIONS |
| • Opioids |
| • Diuretics, antiemetics, antidepressants |
| • Antacids (calcium and aluminum) |
| • Anticonvulsants, neuroleptics, NSAIDs |
| • Others (chemotherapy drugs, anticholinergics, etc.) |

## TRADITIONAL MANAGEMENT OF OPIOID-INDUCED CONSTIPATION

There are currently no national standard protocols for the treatment of opioid-induced constipation; most institutions have their own protocols.

***Prevention.*** When initiating opioid therapy, prophylaxis (*e.g.*, increased fibre and fluid intake, regular exercise) should be considered. However, these methods may not be possible for many patients in the palliative setting and, even if successfully implemented, may not be sufficient to protect against the emergence of constipation.[14]

***Treatment.*** There are a number of different agents that might form part of a management plan for a patient with opioid-induced constipation. Oral laxatives are considered the mainstay of first-line therapy. For those patients who do not achieve relief from these agents, there is now another option available: subcutaneous methylnaltrexone bromide, a peripherally acting μ-opioid receptor antagonist. Enemas, suppositories and manual disimpaction may also be necessary for many patients.

Oral laxatives can be divided into several categories of agents.

Bulk or fibre laxatives (*e.g.*, psyllium) should be avoided in end-of-life care as their action requires considerable fluid intake. Their use in this population may actually increase the risk of intestinal obstruction and/or fecal impaction.[8]

Stool softeners (*e.g.*, docusate), although used for opioid-induced constipation, have little utility as monotherapy. At normal dosages they solely promote lubrication of stool by the addition of moisture and fat. Only at higher doses (greater than 400 mg/day) may they also promote peristalsis.[8]

Osmotic agents (*e.g.*, sorbitol, lactulose, magnesium hydroxide, PEG powder) are effective in opioid-induced constipation in this setting.[15-20] They facilitate an influx of fluid into the bowel, which primarily softens the stool and may secondarily promote peristalsis. Sorbitol and lactulose are the safest osmotic agents in renal insufficiency.

Stimulant laxatives (*e.g.,* senna, bisacodyl) are the cornerstones of treatment of opioid-induced constipation in advanced illness, except in the setting of bowel obstruction. They work by directly stimulating the myenteric plexus,[21-24] resulting in increased longitudinal smooth-muscle contractions. Prolonged use of these agents may, however, reduce colonic tone resulting in "laxative bowel", necessitating the use of higher doses over time.

FIGURE 1. **Methylnaltrexone: Mechanism of Action**

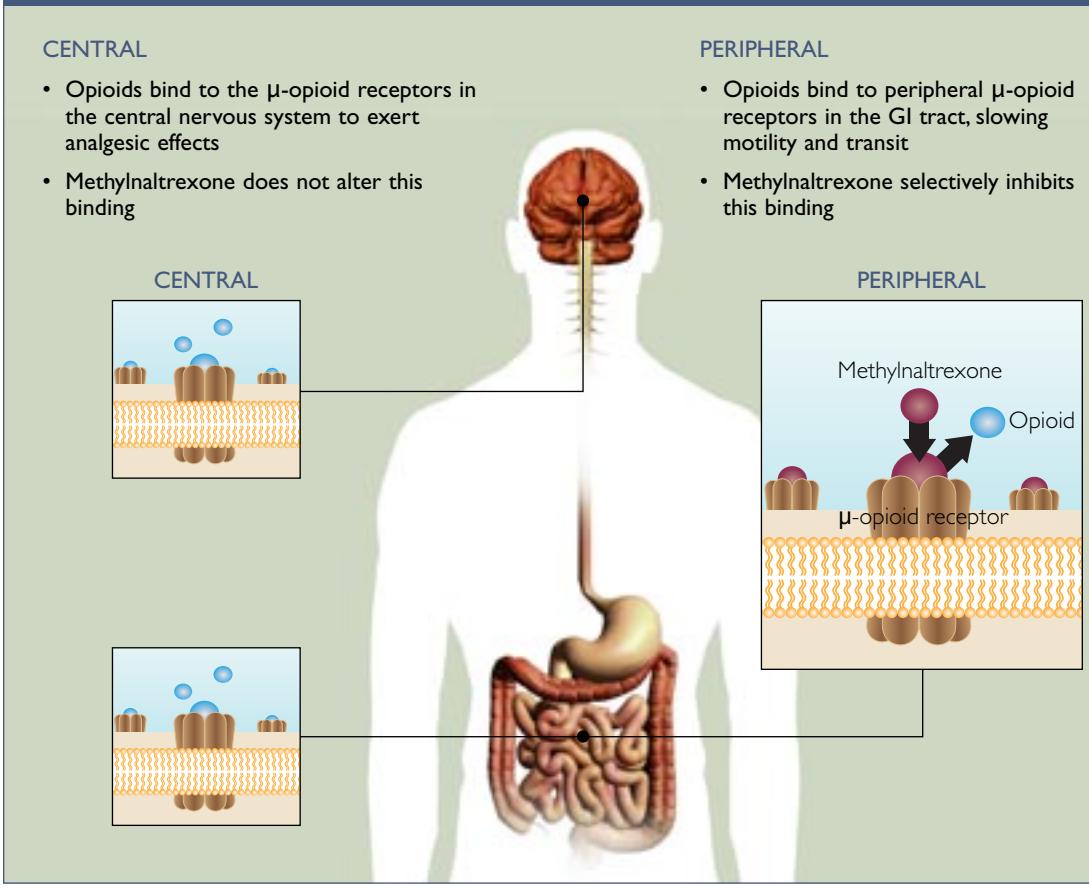



FIGURE 2. **Cumulative Proportion of Patients With a Bowel Movement Following Single-dose Administration of Methylnaltrexone or Placebo[25]**

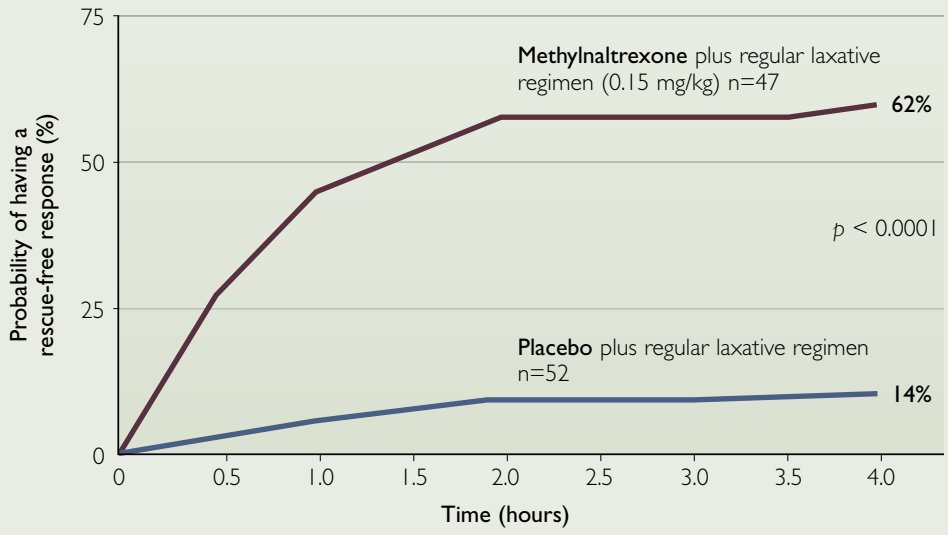
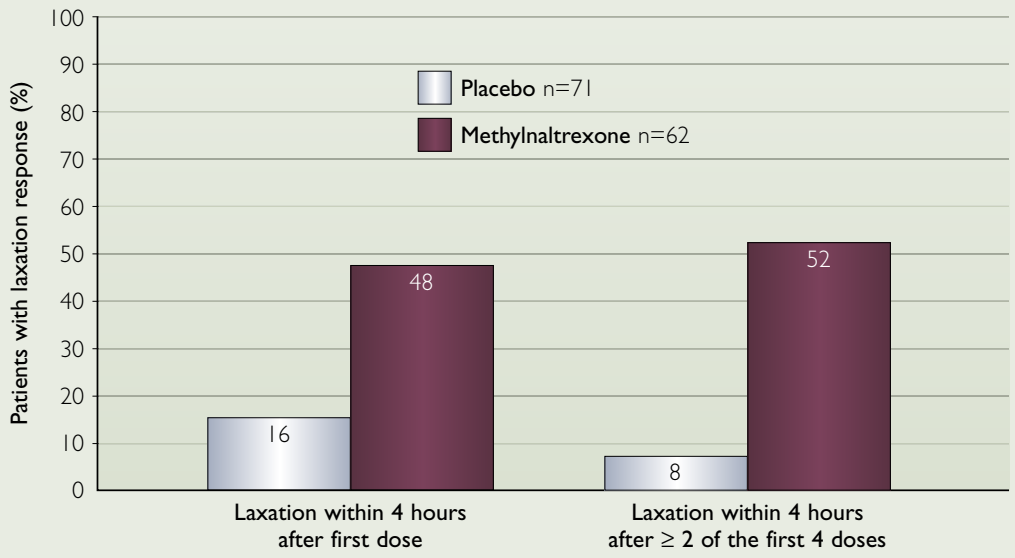


FIGURE 3. Methylnaltrexone vs. Placebo (Multiple-dose Study) Primary Outcomes[26]




## NOVEL TREATMENT OF OPIOID-INDUCED CONSTIPATION: PERIPHERALLY ACTING μ-OPIOID RECEPTOR ANTAGONISM

This novel class of agents, of which methylnaltrexone bromide is the first agent available to Canadian physicians and their patients receiving palliative care, is an important addition to the therapeutic armamentarium for opioid-induced constipation.

*Mechanism of action.* These agents selectively inhibit the binding of opioids to the μ-opioid receptors in the GI tract (but because they do not cross the blood-brain barrier, they do not inhibit the primary analgesic activity of opioids in the CNS; Figure 1). The theoretical pro-motility benefit of inhibiting opioid binding in the GI tract has been validated by the results of two pivotal Phase III studies evaluating the efficacy and safety of methylnaltrexone in palliative patients taking opioids.

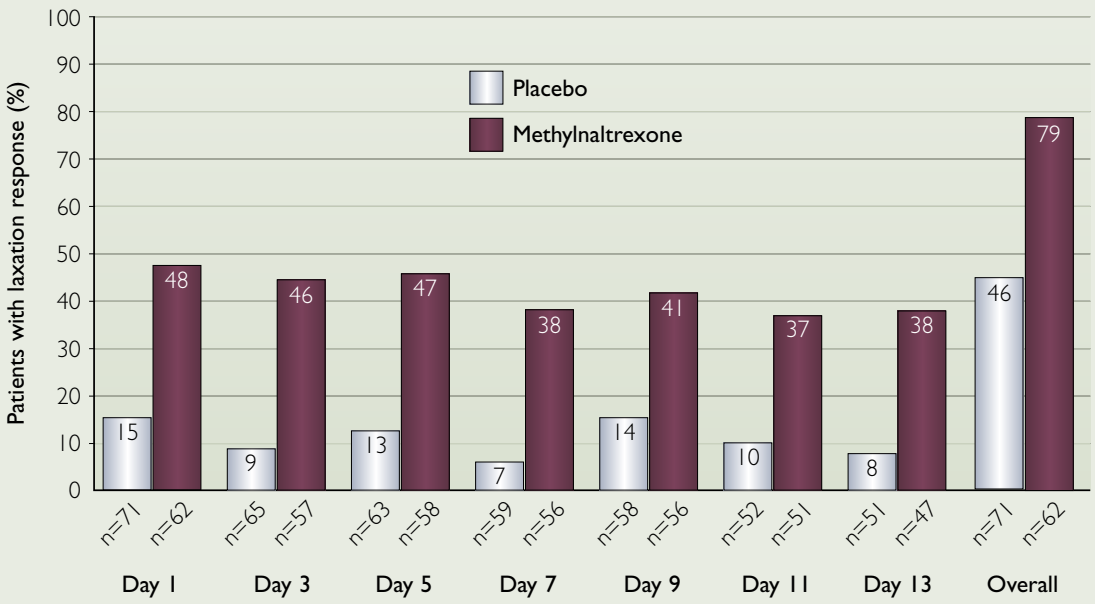
*Efficacy data.* The first study was a single-dose, double-blind study, in which 154 patients on stable opioid therapy received either methylnaltrexone 0.15 mg/kg, methylnaltrexone 0.30 mg/kg or placebo. Patients who were 18 years of age or older and had advanced illness, which was defined as a terminal disease (incurable cancer or other end-stage disease) with a life expectancy of one month or more, were eligible.

Throughout the study, all patients continued on their regular laxative and opioid regimens. Following the administration of the single, blinded dose, the treating physicians could use methylnaltrexone on an as needed basis (maximum of once every 24 hours) for any patient, regardless of the initial group. Rescue laxatives were prohibited during the period spanning four hours before administration of study medication to four hours after.

The investigators of this study reported that 62% of the patients receiving methylnaltrexone 0.15 mg/kg had a bowel movement within four hours, compared to 14% of patients receiving placebo ($p < 0.0001$; Figure 2).[25]

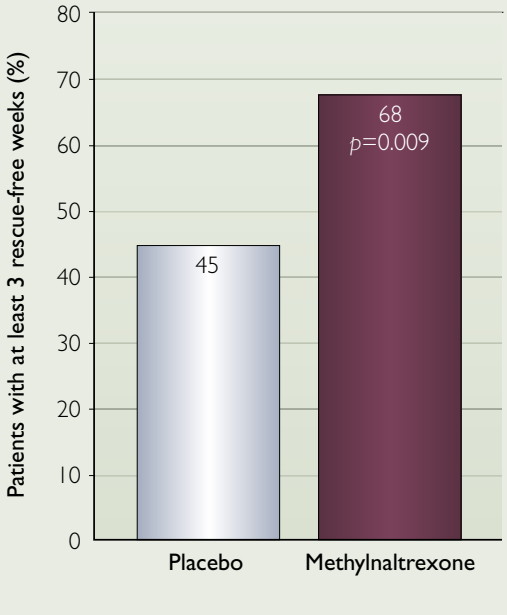
Subsequent to the single-dose trial, methylnaltrexone was also investigated in a multiple-dose study, the results of which were published in the *New England Journal of Medicine* in May 2008.[26] A total of 133 patients were enrolled in the study; all had

FIGURE 4. **Methylnaltrexone vs. Placebo: Rescue-free Laxation Within 4 hours After Each Dose[26]**




received opioid medication within two weeks of study entry and were on stable doses. The patients were randomized to receive methylnaltrexone at a dose of 0.15 mg/kg or placebo every other day for two weeks (seven doses). The methylnaltrexone dose could be increased to 0.30 mg/kg if the patient had two or fewer rescue-free laxations up to Day 8. The dose could also be reduced at any time if tolerability was a concern. All patients in the study maintained their pre-trial laxative regimen for at least three days before study entry and throughout the study. The use of rescue laxatives was prohibited during the same eight-hour window as in the single-dose study. There were two coprimary outcomes in this study: laxation (defecation) within four hours after the first dose of the study drug and laxation within four hours after two or more of the first four doses.

FIGURE 5. **Methylnaltrexone vs. Placebo: Proportion with ≥ 3 Rescue-free Laxations per Week[26]**




The investigators of this study reported that 48% of patients had laxation within four hours after the first study dose, compared to 16% of those in the placebo group ($p < 0.001$; Figure 3).[26] Also, 52% of the methylnaltrexone-treated patients experienced laxation without the use of a rescue laxative within four hours after two or more of the first four doses,

compared to 8% of the placebo group ($p < 0.001$; Figure 3).

The trial report also included several secondary analyses. The laxation response within four hours of each dose, for example, was shown to be consistently higher for methylnaltrexone compared to placebo, ranging from 37% to 48% in the treatment group and from 7% to 15% in the placebo group ($p < 0.005$ for the comparison after each dose; Figure 4).[26] Over the course of the study, 79% of methylnaltrexone-treated patients and 46% of patients receiving placebo had a laxation response within four hours after one or more doses.

The proportion of patients with three or more rescue-free laxations per week was also significantly higher in the methylnaltrexone group than in the placebo group (68% vs. 45%, $p = 0.009$; Figure 5).

Patients who completed the randomized phase of this study were also eligible to enter a three-month, open-label extension trial. This extension trial (n=89) has demonstrated that laxation response rates observed during the double-blind treatment with methylnaltrexone were sustained over the course of three months.[26]

***Safety & tolerability.*** In addition to the excellent efficacy results in the above-mentioned trials, methylnaltrexone has also been associated with a favourable safety and tolerability profile. In the multiple-dose study, the most common adverse events were abdominal pain (17% of methylnaltrexone patients and 13% of placebo patients), flatulence (13% and 7%, respectively), vomiting (13% and 13%), malignant neoplasm progression (11% and 13%) and nausea (11% vs. 7%). Most adverse events were rated as mild or moderate. Severe (grade 3) adverse events occurred in 8% of patients in the methylnaltrexone group and 13% of those in the placebo group, while grade 4 (life-threatening) adverse events occurred in 16% and 15%, respectively. All of the grade 4 events were deemed to be related to the primary illness (*e.g.*, progression of an underlying cancer). The discontinuation rate associated with adverse events was 6% for methylnaltrexone and 7% for placebo.[26]

TABLE 3. **Methylnaltrexone Dosing Recommendations**[26]

| Patient Weight | Injection Volume | Total Dose |
|---|---|---|
| 38 to < 62 kg (84 to < 136 lbs) | 0.4 mL | 8 mg |
| 62 to 114 kg (136 to 251 lbs) | 0.6 mL | 12 mg |

Patients whose weight falls outside of the ranges in the table should be dosed at 0.15 mg/kg.

No dose adjustment is needed for mild or moderate renal or hepatic insufficiency. No dosage adjustments required in geriatric patients.

In patients with severe renal impairment (creatinine clearance < 30 mL/min), reduce the dose by half. It should be injected subcutaneously into the upper arm, abdomen or thigh.

Patients should be seated or recumbent during dosing and care should be taken when the patient stands following dosing.

Patients who respond to methylnaltrexone may have a bowel movement as soon as 30 minutes. Therefore, patients should be within close proximity to toilet facilities after an injection.

***Use of methylnaltrexone.*** As a result of its favourable efficacy, tolerability and safety profile in clinical trials, methylnaltrexone was approved for use in Canada for the following indication: "For the treatment of opioid-induced constipation in patients with advanced illness, receiving palliative care. When response to laxatives has been insufficient, methylnaltrexone should be used as an adjunct therapy to induce a prompt bowel movement." It is administered as a subcutaneous injection every other day, as needed, with a minimum of four doses recommended before considering discontinuation. The recommended doses are shown in Table 3.

Notably, the use of methylnaltrexone is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction or acute surgical abdomen.

## CONCLUSIONS

Patients in palliative care who receive opioid therapy are likely to experience constipation. Given the distressing effects of constipation on quality of life, opioid-treated patients should receive prophylactic laxative therapy. Prophylaxis may not, however, be sufficient to overcome constipation in many patients. In the event that an opioid-treated patient continues to experience constipation despite laxative treatment, methylnaltrexone should be administered as an adjunctive agent to induce a prompt bowel movement (within 4 hours, median time 24 minutes[26]). This agent has proven to be effective in promoting bowel regularity in clinical trials, with a favourable tolerability and safety profile.

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