

ANESTHESIOLOGY

Identifying and Treating Opioid Side Effects

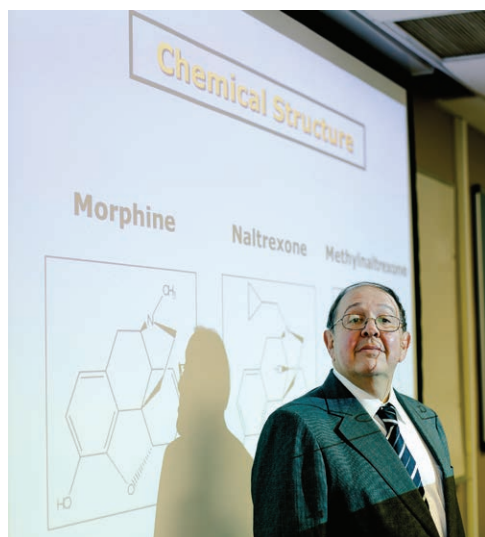
The Development of Methylnaltrexone

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In an era when big data often drives the development of new compounds, hypothesis-driven research, based on clinical observations, can still lead to important pharmacologic discoveries. Such is the case for methylnaltrexone, which was developed over a 30-yr period at the University of Chicago (Chicago, Illinois). To demonstrate this process, I have chosen to highlight the work of Yuan *et al.*¹ in this Classic Papers Revisited article.

Although methylnaltrexone was initially approved to treat μ -opioid-induced constipation in patients with advanced illness who were unresponsive to conventional laxatives, its development allowed us to distinguish between the peripheral and central effects of opioids and demonstrate



Jonathan Moss, M.D., Ph.D. Photo by Lucy Hewett.

Methylnaltrexone Reverses Chronic Opioid-induced Constipation: A Randomized, Controlled Trial. By Yuan CS, Foss JF, O'Connor M, Osinski J, Karrison T, Moss J, Roizen MF. *JAMA* 2000; 130:142–8. Reprinted with permission.

Abstract

Context: Constipation is the most common chronic adverse effect of opioid pain medications in patients who require long-term opioid administration, such as patients with advanced cancer, but conventional measures for ameliorating constipation often are insufficient.

Objective: To evaluate the efficacy of methylnaltrexone, the first peripheral opioid receptor antagonist, in treating chronic methadone-induced constipation.

Design: Double-blind, randomized, placebo-controlled trial conducted between May 1997 and December 1998.

Setting: Clinical research center of a university hospital.

Participants: Twenty-two subjects (9 men and 13 women; mean [SD] age, 43.2 [5.5] years) enrolled in a methadone maintenance program and having methadone-induced constipation.

Main Outcome Measures: Laxation response, oral-cecal transit time, and central opioid withdrawal symptoms were compared between the 2 groups.

Results: The 11 subjects in the placebo group showed no laxation response, and all 11 subjects in the intervention group had laxation response after intravenous methylnaltrexone administration ($P < .001$). The oral-cecal transit times at baseline for subjects in the methylnaltrexone and placebo groups averaged 132.3 and 126.8 minutes, respectively. The average (SD) change in the methylnaltrexone-treated group was -77.7 (37.2) minutes, significantly greater than the average change in the placebo group (-1.4 [12.0] minutes; $P < .001$). No opioid withdrawal was observed in any subject, and no significant adverse effects were reported by the subjects during the study.

Conclusions: Our data demonstrate that intravenous methylnaltrexone can induce laxation and reverse slowing of oral cecal-transit time in subjects taking high opioid dosages. Low-dosage methylnaltrexone may have clinical utility in managing opioid-induced constipation.

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the potential use of peripheral-acting μ -opioid receptor antagonists for treatment of some of these peripheral side effects. This led to the study of interactions between opioids and cancer progression. Many of these findings have been driven by direct observation of patients.

The concept of methylnaltrexone is attributable to Professor Leon I. Goldberg, M.D., Ph.D., Chair of Clinical Pharmacology at the University of Chicago. Dr. Goldberg, the developer of dopamine for clinical use and

one of the pioneers of modern clinical pharmacology, was driven to develop the peripheral opioid antagonist methylnaltrexone to treat a faculty member with advanced prostate cancer who was receiving opioids but whose constipation was so debilitating he could not receive enough opioids for pain relief. Goldberg reasoned that if he could develop a form of naltrexone that was charged (and thus did not cross into the central nervous system), he might be able to treat the constipating effect of opioids without affecting central analgesia. Goldberg had several molecules synthesized in 1980. One in particular, methylnaltrexone, showed promise.² Although there is no information as to whether the faculty member actually received the drug, Goldberg pursued its development in a series of animal studies.

On arriving at the University of Chicago in 1985, Dr. Michael Roizen, M.D., and I recognized the importance of Goldberg's work for our patients and entered into a series of collaborations with him. Having spent more than 15 yr doing research on the autonomic and histaminergic side effects of anesthetic drugs,^{3,4} this line of inquiry seemed a logical progression for my work. At the time, Dr. Joseph Foss, M.D., a former resident, was doing a fellowship in clinical pharmacology and started to work on the antiemetic effect of methylnaltrexone with Goldberg.⁵ After Goldberg's death in 1989, we as a group made a decision to continue work on methylnaltrexone. To facilitate its development, I chose to do my sabbatical in London (United Kingdom) in the laboratory of Professor Geoffrey Burnstock, Ph.D., in 1991 to 1992, who was recognized as the leading pharmacologist in enteric pharmacology.⁶ His expertise in investigating gut function proved extremely important for me as we increasingly recognized that methylnaltrexone could be meaningful in treating μ -opioid-induced constipation.

On my return to the University of Chicago, we modified our laboratory to be able to measure the effects of opioids on gut contraction *in vitro*. In 1993, Dr. Chun-Su Yuan, M.D., Ph.D., had started as my fellow in clinical pharmacology. With Dr. Foss, we studied both the human and the animal gut based on the hanging gut model developed by Sir William D. Paton, M.B., B.Ch., D.M., at Oxford University (Oxford, United Kingdom). That initial study demonstrated that, although methylnaltrexone was much less potent than naltrexone as an antagonist, it was equally efficacious in reversing the effects of opioids on gut contraction.⁷ This observation encouraged us to continue our work.

We next performed studies to examine the effects of methylnaltrexone on μ -opioid-induced constipation in human volunteers. Almost all of this development was done by Foss, Yuan, Roizen, and myself over more than 12 yr, although many in our department helped in specific studies. After discussion with the U.S. Food and Drug Administration, it was determined that oral-cecal

transit time could be used as an initial surrogate for bowel motility, and the cold pressor test could be used to assess pain. In our initial randomized, double-blind study of 12 volunteers who were given intravenous placebo, placebo plus 0.5 mg of morphine, or 0.45 mg/kg methylnaltrexone plus 0.5 mg of morphine, we determined that morphine caused a significant increase in oral-cecal transit time, which was almost completely (97%) reversed by methylnaltrexone. There was no change whatsoever in the cold pressor test. This, therefore, was the first demonstration in humans that the effects of morphine on gut motility were peripheral in nature.⁸ The study was repeated with oral methylnaltrexone (at a dose approximately 40 times greater than was given intravenously) with similar results.⁹

Although we recognized that for us to go further we would have to utilize this in the patients for whom the drug was initially intended, palliative care patients with μ -opioid-induced constipation, the U.S. Food and Drug Administration required that we do a proof-of-concept trial in methadone-maintenance patients before proceeding with advanced-cancer patients. This was initially extremely discouraging to us because it required a 2-yr detour in the development of the drug, and the practical logistics of the study in methadone maintenance patients were challenging. However, we did do the study, which is the featured classic study for this article, and it proved seminal in our development.¹ Some of the issues involved were population-specific; ensuring that there were not confounding drugs, developing a reward for study participation that would not cause subjects to further their drug habit (the Institutional Review Board of the University of Chicago eventually allowed us to use pizzas as a reward), and aspects of reliability (many patients were entered but there was a much higher dropout rate than in traditional studies).

The results of the study were dramatic. Although the expected change in oral-cecal transit time occurred, all subjects receiving methylnaltrexone intravenously responded with laxation within minutes of intravenous drug administration, and none had opioid withdrawal (table 1). Further, the dose required to cause laxation was lower than we had anticipated from volunteer studies. This study was the first human study to prove that constipation in patients

Table 1. Effects of Intravenous Methylnaltrexone on Laxation in Patients Receiving Chronic Methadone Maintenance

	Number of Patients	
	Laxation	No Laxation
Placebo	0	11
Methylnaltrexone	11	0

All laxation was immediate. No evidence of opioid withdrawal was observed.

with chronic opioid use was peripheral in nature.¹ The study was repeated with oral methylnaltrexone by using reduced doses.⁹ Our publication brought us to the attention of a small drug company, Progenics Pharmaceuticals (USA), who licensed the compound from the University of Chicago for further development.

Recognizing that giving the drug intravenously would be challenging for many patients, we developed the subcutaneous route.¹⁰ We viewed this as an important practical advantage because it allowed patients time to prepare and coordinate their activities. Further, because reimbursement for home health nurses was then limited to 3 h of time with these palliative care patients, bowel function and cleanup could be accommodated. The phase 3 trials demonstrated results with subcutaneous methylnaltrexone similar to what we had seen in the methadone patients.^{11,12} The subcutaneous dosing of 0.15 mg/kg caused laxation within the period of approximately 1 h. Not all patients responded with laxation; about one third of our palliative care patients failed to show a response to methylnaltrexone. The reason for the lack of response did not appear to be related to opioid dose, and nonresponders could not be predicted. The data from the trials permitted approval by the U.S., Canadian, and the European agencies in 2008, and several hundred thousand patients have since received subcutaneous methylnaltrexone. Incidences of withdrawal proved to be clinically very rare if occurring at all. Methylnaltrexone should not be given if there is evidence of an obstruction because the increased motility could potentially precipitate gastrointestinal catastrophe.

In 2014, the U.S. Food and Drug Administration granted approval for subcutaneous methylnaltrexone for μ -opioid-induced constipation in patients with chronic pain. This meeting also led to the approval of naloxegol for clinical use. At that juncture, we had treated 800,000 patients. The U.S. Food and Drug Administration approved methylnaltrexone in oral form in 2016. A third compound in this class, naldemedine, has recently been approved.

Aside from its intended clinical use to treat μ -opioid-induced constipation, methylnaltrexone proved to be important in differentiating between central and peripheral opioid side effects. An early study by Foss *et al.*⁵ demonstrated that methylnaltrexone was an effective antiemetic. Although the vomiting center is central, this area of the brain proved to be outside the blood-brain barrier.¹³ Dr. Carl Rosow, M.D., Ph.D., at the Massachusetts General Hospital (Boston, Massachusetts) performed an important volunteer study demonstrating that much of the urinary retention associated with opioid use was in fact largely peripheral in nature.¹⁴ In that study, he measured both pupillary and bladder function. Other side effects, such as itch, have proved more challenging to study. Although we demonstrated that the itch associated with the use of systemic opioids could be relieved

by methylnaltrexone,¹⁵ another study found that itch occurring with the administration of intrathecal opioids was not relieved by methylnaltrexone.¹⁶ We were able to show both in volunteers and in some critical care patients that gastric emptying was peripheral in nature.¹⁷ At low opioid doses, we and others showed that gastric residuals were markedly increased and that this increase was almost completely attenuated by methylnaltrexone.¹⁷

A second area that proved to be interesting involved the effect of opioids on both viral and bacterial function. Working with Dr. Steven Douglas, M.D., at Children's Hospital of Philadelphia (Philadelphia, Pennsylvania), we showed that low concentrations of μ -opioids greatly influenced the entry of the human immunodeficiency virus across the CCR5 receptor and that this effect could be blocked by low-dose methylnaltrexone.¹⁸ Working with Dr. John Alverdy, M.D., in the Department of Surgery at the University of Chicago, we determined that *Pseudomonas* entry across the gut was related to opioid use and that this effect potentially could be blocked by methylnaltrexone.¹⁹ Thus, there appeared to be effects of opioids on endothelial and epithelial function that were peripheral in nature and often could be blocked by methylnaltrexone.

A third area that proved to be of great interest over the past decade involves the effect of μ -opioids on cancer progression, suggesting a potential therapeutic use for opioid antagonists in cancer.²⁰ After the publication of the *JAMA* article,¹ we received many inquiries from patients for compassionate use of this drug. Using a University of Chicago Institutional Review Board-approved compassionate use protocol, we initiated short-term use of methylnaltrexone to facilitate the treatment of debilitating μ -opioid-induced constipation, particularly in patients with advanced cancer. One such patient provided an observation that caused me to examine whether there may be some involvement between the use of these opioid antagonists and the progression of tumors. Specifically, a 46-yr-old white woman with both multiple sclerosis and breast cancer metastatic to the spine, lung, kidney, and adrenal glands presented to my clinic for treatment of μ -opioid-induced constipation. Her current medication of a fentanyl patch and methadone was barely adequate to maintain any relief. This patient, who was expected to have a very short life expectancy, was treated with methylnaltrexone twice a week. Much to my surprise, she survived approximately 6 months. This caused me to wonder if there could be an effect of opioids on tumor progression and growth that involved the μ -receptor. At that time, an important article appeared in the literature. Dr. Kalpna Gupta, Ph.D., and her colleagues at the University of Minnesota (Minneapolis, Minnesota) had shown that morphine in clinically relevant doses promoted tumor neovascularization in the human breast tumor xenograft model in mice, leading to increased tumor progression.²¹

Based on our clinical perception, Dr. Patrick Singleton, Ph.D., and I undertook a decade-long series of laboratory

studies that demonstrated the role of the peripheral μ -opioid receptor in tumor growth and progression. We uncovered three molecular targets of μ -opioids: vascular endothelial-derived growth factor, Src, and mechanistic target of rapamycin. In our first study, we demonstrated that methylnaltrexone at clinical doses could block μ -opioid-induced endothelial cell migration and proliferation, key components of angiogenesis,²² in human endothelial cells by a mechanism involving receptor transactivation of vascular endothelial-derived growth factor. μ -Opioids have 70% of the angiogenic activity of vascular endothelial-derived growth factor. Recognizing that some of the effects of methylnaltrexone on angiogenesis were beyond the μ -opioid receptor, we hypothesized the synergy with chemotherapeutic agents even without opioids. We subsequently demonstrated potentiation of bevacizumab and 5-fluorouracil (the major therapies for colon cancer) by methylnaltrexone in endothelial cells. During these studies, we noted that methylnaltrexone in clinically relevant concentrations inhibited Src in a concentration-dependent manner. This appeared to be unique to methylnaltrexone because naltrexone exhibited no such synergy.²³ Importantly, we noted that μ -opioids altered endothelial cell barrier function and integrity, causing vascular leakage.²⁴ These changes were reversed by methylnaltrexone. In a series of *in vivo* and *in vitro* studies, we were able to demonstrate a proposed mechanism for the protective effect of methylnaltrexone on barrier-induced endothelial cell dysfunction. We subsequently determined that the μ -opioid receptor promoted opioid- and growth factor-induced proliferation migration in human lung cell cancer through an effect on epithelial-mesenchymal transition, providing a relevant biologic mechanism to explain the effects of opioids on tumor progression.^{24,25} We also demonstrated that methylnaltrexone potentiated the angiogenic effects of the mammalian target of rapamycin (mTOR).²⁶

Although molecular and cellular experiments were very suggestive of an effect of μ -opioids on tumor growth and progression and the ability of methylnaltrexone to block them, we undertook a series of animal experiments using the Lewis lung carcinoma model to test this. In 2011, we

demonstrated four lines of evidence for μ -opioid receptor involvement in cancer (table 2; fig. 1).²⁷ Although this evidence strongly suggested a direct effect of opioids, we could not rule out an effect of opioids on the immune system. We therefore repeated many of these studies in nude mice that lacked T-cell immunity. We demonstrated a persistent twofold increase in tumor volume when the μ -opioid receptor was overexpressed in human non-small-cell lung cancer cells and a twentyfold incidence of metastasis in these mice.²⁸ The presence of a direct effect of opioids on tumor growth and progression could not preclude an effect of opioids on the immune system, but effects on angiogenesis could occur without it. About this time, studies involving regional and general anesthesia and their effects on cancer growth emerged in a joint paper from Mater Misericordiae University Hospital, University College (Dublin, Ireland) and the Cleveland Clinic (Cleveland, Ohio).²⁹ These studies suggested that regional anesthesia might provide some benefit in terms of preventing the spread of the tumor. An alternate explanation was a reduction in perioperative opioid doses.

Despite an abundance of laboratory data suggesting that opioids could be involved in the development and proliferation of various forms of tumors, until recently there was little clinical evidence demonstrating this effect in humans. A small study in 34 patients with non-small-cell lung cancer showed that specimens of adjacent nonmalignant tissue had lower μ -opioid receptor expression, and tumor samples from patients with metastatic disease had the highest μ -opioid receptor expression (fig. 2).³⁰ One important retrospective study demonstrated that the A118g mutation of the μ -opioid receptor, which is thought to make individuals relatively resistant to opioids and to be involved in aspects of the drug dependence, exerted an effect on breast cancer recurrence.³¹ These authors demonstrated that, in 2,039 patients with breast cancer,

Table 2. Four Lines of Evidence for μ -Opioid Receptor Involvement in Cancer

1. Increased μ -opioid receptor expression in lung cancer patients and cell lines.
2. μ -Opioid receptor knockout mouse did not develop or metastasize lung cancer in LLC model.
3. *In vitro* and *in vivo* (mouse) studies of LLC cells with a silenced μ -opioid receptor showed marked reductions in invasion and metastasis as did treatment with methylnaltrexone.
4. Methylnaltrexone infusion in mice attenuates lung cancer growth and metastasis after tumor injection.

LLC, Lewis lung cancer.

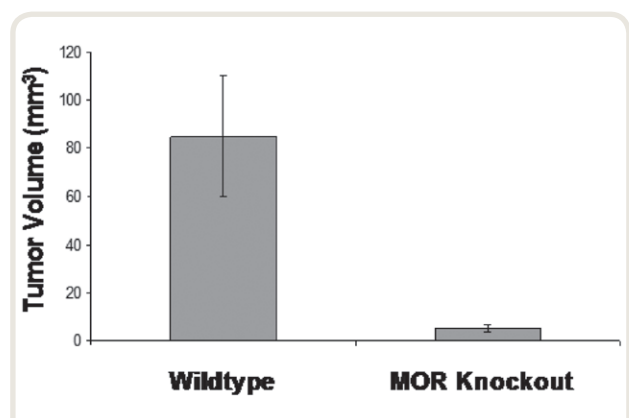


Fig. 1. Graphical analysis of Lewis lung carcinoma tumor volume in wild-type and μ -opioid receptor (MOR) knockout mice ($P < 0.001$, $n = 5$ animals per condition). Error bars indicate SD. Reprinted with permission from Mathew *et al.*²⁷

METASTASIS AS A FUNCTION OF MOR IN LUNG CANCER PATIENTS

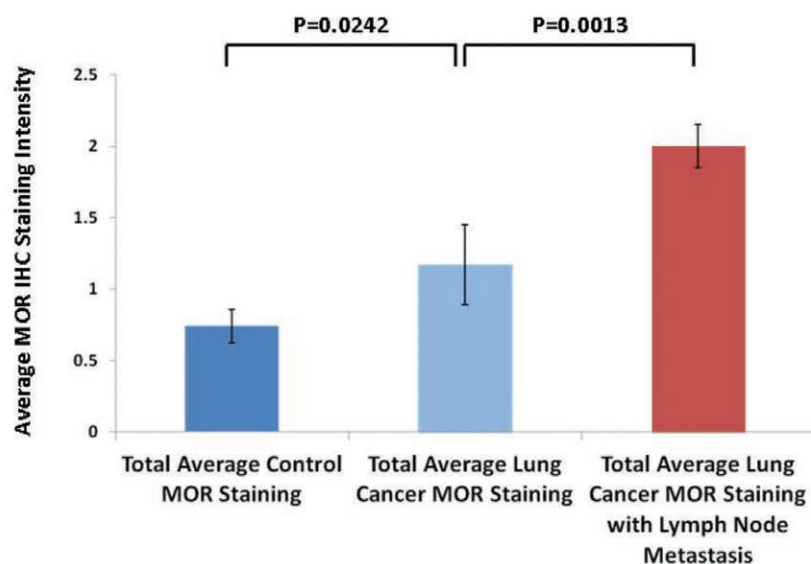


Fig. 2. Graphical representation of the average μ -opioid receptor (MOR) immunohistochemical (IHC) staining intensity of normal adjacent, total lung cancer, and a subset of lung cancer with lymph node metastasis patient samples. μ -Opioid receptor immunohistochemistry was performed on deidentified normal adjacent control and lung cancer patient samples, scored by two independent pathologists on a 4-point scale (0, 1, 2, and 3), and box plots were generated as described in the Methods.³⁰ There was a statistically significant difference between normal adjacent control and total lung cancer ($P = 0.0242$) and also total lung cancer and a subset of lung cancer with lymph node metastasis ($P = 0.0013$). Reprinted with permission from Singleton *et al.*³⁰

looking at 10-yr cancer-specific survival, heterozygotes had a twofold difference in survival, and homozygotes had a fourfold difference in survival. The relative influence of endogenous and exogenous opioids could not be evaluated in this study.³¹ The first study to show a direct effect of opioids on cancer growth and patient survival was from the University of Minnesota in patients with advanced prostate cancer.³²

More recently, we showed that methylnaltrexone was associated with improved survival in patients with advanced cancers. Collaborating with Dr. Filip Janku, M.D., Ph.D., of MD Anderson Cancer Center (Houston, Texas) and Dr. Lorin Johnson, Ph.D., of Salix Pharmaceuticals (Raleigh, North Carolina), which had licensed the drug, we analyzed survival from our randomized phase 3 and phase 4 studies of methylnaltrexone on μ -opioid-induced constipation.³³ Although these randomized trials demonstrated an effect of methylnaltrexone on μ -opioid-induced constipation, we asked whether it might improve survival in patients with advanced illness. Many of these patients ($n = 229$) had advanced cancer. We determined that cancer patients who received methylnaltrexone had a longer survival time than those who received placebo alone (76 vs. 56 days; $P = 0.033$). Further, those who responded to methylnaltrexone for μ -opioid-induced constipation lived twice as long

as nonresponders or placebo patients (118 vs. 55 days; $P \leq 0.001$). Initially, we thought this might be because of improved feeding, but 134 patients with advanced illness other than cancer demonstrated equally improved gut function but had no increase in survival. The improved survival was particularly noticeable in both advanced lung cancer and pancreatic cancer patients. Based on this, we have proposed a prospective trial in advanced pancreatic cancer examining the effect of methylnaltrexone on tumor growth and proliferation and survival. The National Cancer Institute (Rockville, Maryland) recently authorized a trial using the drug naloxegol, another peripheral acting μ -opioid receptor antagonist, in the progression of advanced lung cancer.³⁴ Thus, peripheral-acting μ -opioid receptor antagonists may eventually prove useful in treating cancer growth and metastasis.

The very arduous process of the development of methylnaltrexone highlights that hypothesis-based research and clinical insights can be important in drug development. The development of methylnaltrexone from Goldberg's original idea through worldwide approval to treat μ -opioid-induced constipation has not only helped patients with this syndrome but has also allowed us to discriminate between central and peripheral effects of μ -opioids and to identify side effects that were not widely

recognized (angiogenesis, viral entry, and epithelial and endothelial barrier function). Indeed, given the numerous cellular effects that appear to be mediated by the μ -opioid receptor, we speculate that endogenous opioids may serve as a marker for a compromised host. Finally, the potential to actually influence cancer recurrence and survival in patients with advanced malignancies is under active study. There are significant implications both perioperatively and in chronic cancer pain management.

Competing Interests

Methylnaltrexone was developed at the University of Chicago (Chicago, Illinois), licensed to Progenics Pharmaceuticals (New York, New York), and subsequently sublicensed to Salix Pharmaceuticals, which is now a division of Bausch Healthcare (Bridgewater Township, New Jersey). Dr. Moss was a paid consultant for Progenics Pharmaceuticals and for Salix Pharmaceuticals. He receives royalties through the University of Chicago.

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