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Methylnaltrexone Bromide

Prop INN; USAN

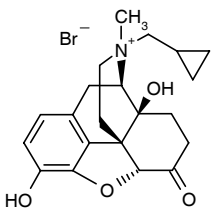
Opioid Receptor Antagonist
Treatment of Constipation
Treatment of Postoperative Ileus

MNTX
MNTX-302
MOA-728
MRZ-2663BR

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide

N-Methylnaltrexone bromide

InChI=1/C21H25NO4.BrH/c1-22(11-12-2-3-12)9-8-20-17-13-4-5-14(23)18(17)26-19(20)15(24)6-7-21(20,25)16(22)10-13;/h4-5,12,16,19,25H,2-3,6-11H2,1H3;1H/t16-,19+,20+,21-,22+;/m1./s1



$C_{21}H_{26}BrNO_4$
Mol wt: 436.3395

CAS: 073232-52-7

EN: 284766

Abstract

Opioids are widely used in patients with moderate to severe acute and chronic pain, but gastrointestinal side effects such as nausea and constipation can often be debilitating. Opioid-induced bowel dysfunction (OBD) is mediated by mu opioid receptors in both the central nervous system and bowel wall, but the "peripheral" bowel effects may be more important. Methylnaltrexone (MNTX) is a derivative of naltrexone that does not cross the blood-brain barrier. It acts as a selective antagonist at peripheral opioid receptors without reversing central effects like analgesia. In preclinical and human volunteer studies, parenteral and oral MNTX consistently reversed OBD at doses that produced minimal side effects. Intravenous MNTX also reversed opioid inhibition of bladder function, suggesting a possible role in the treatment of opioid-induced urinary retention. Two phase III studies showed that s.c. administration of 0.15-0.3 mg/kg MNTX induced laxation in patients with advanced medical illness given chronic opioids. Additional studies of MNTX targeting postoperative ileus also show promise. An NDA submission is anticipated in early 2008.

Synthesis+

The title ammonium salt is prepared by quaternization of naltrexone (I) with bromomethane in solvents such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methyl-2-pyrrolidinone (1, 2).

Background

Opioid analgesics are still the most widely accepted drugs for moderate to severe acute and chronic pain, but their use is accompanied by numerous unpleasant side effects. Dangerous opioid toxicity, such as respiratory depression, occurs infrequently, but large numbers of patients suffer from debilitating effects, such as constipation, urinary retention, or nausea and vomiting. Constipation is one symptom of a more general syndrome called opioid-induced bowel dysfunction (OBD) that includes inhibition of gastric emptying, decreased peristalsis, increased tone of intestinal sphincters, decreased secretions and increased fluid absorption (3). Slowed gastrointestinal (GI) transit and dessication of stools lead to constipation. Unlike opioid analgesia, little tolerance develops to OBD, and therefore it is a clinical problem in as many as 40-50% of patients receiving chronic opioids for metastatic malignancy (4, 5) or noncancer pain (6).

The GI effects of opioids are due to both central and peripheral mechanisms, although peripheral actions at mu opioid receptors in the gut wall appear to play the most important role (7-9). There have been numerous

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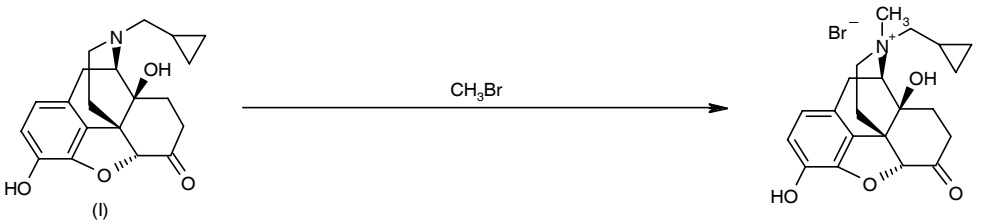
Scheme 1: Synthesis of Methylnaltrexone Bromide



attempts to decrease peripheral opioid side effects by co-administering low doses of typical mu antagonists such as naloxone or naltrexone. Unfortunately, all clinically available opioid antagonists cross the blood-brain barrier and therefore carry the risk of reversing analgesia or precipitating withdrawal (10-12). There is thus a clinical need for an opioid antagonist that selectively inhibits peripheral opioid effects while sparing those mediated by the central nervous system.

Methylnaltrexone bromide (MNTX) is a quaternary derivative of naltrexone. It is a white, odorless, water-soluble powder that has been formulated as a sterile solution for injection and as tablets for oral administration. The addition of a methyl group on the piperidine nitrogen creates a permanently charged, polar compound that does not cross the blood-brain barrier (13, 14).

Preclinical Pharmacology

MNTX is a competitive mu opioid antagonist with no intrinsic opioid-agonist properties (15). In the guinea pig ileum and rat brain, it is 25-42 times less potent than naltrexone. The IC_{50} to displace etorphine from rat brain mu opioid receptors is 305 nM *versus* 7.2 nM for naltrexone (16). MNTX has about 18 times greater affinity for mu than for kappa opioid receptors, and it does not bind appreciably to delta opioid or other receptor populations. In an isolated gastric-brainstem preparation from neonatal rats, MNTX competitively antagonized the GI-inhibitory effects of mu agonists (17). In a human small intestine preparation, administration of MNTX alone increased smooth muscle contraction by 30%, suggesting the reversal of endogenous opioid activity (18). Some forms of GI hypomotility, such as postoperative ileus, are thought to be partially mediated by endogenous opioids, suggesting a therapeutic role for MNTX in these conditions.

In vivo, MNTX antagonizes the GI but not the central effects of morphine. Morphine prolonged the intestinal transit time of a charcoal meal in rats and this effect was completely prevented by s.c. administration of MNTX. Morphine-induced analgesia can be antagonized by MNTX following intracerebroventricular but not s.c. injection (15). MNTX doses as high as 50 mg/kg do not precipitate abstinence in morphine-dependent dogs (14).

Pharmacokinetics and Metabolism

Peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) in human subjects were proportional to dose after i.v., s.c. or oral administration. Time to peak (t_{max}) was 16-20 min after s.c. and 30 min after oral dosing. The C_{max} after 0.3 mg/kg s.c. was 287 ng/ml (750 nM), a concentration twice as high as the IC_{50} needed to prevent opioid binding *in vitro* (16). Extremely low plasma concentrations were observed after oral ingestion, and enteric coating reduced them even further. This suggests that a small amount may be absorbed in the upper GI tract. No correlation exists between drug effects and plasma concentrations after 3.2 or 6.4 mg/kg of enteric-coated MNTX (19).

MNTX undergoes rapid distribution ($t_{1/2}$ = 6-9 min) followed by slower elimination ($t_{1/2}$ = 2 h in volunteers) (20). Elimination half-lives of 7 h or longer have been reported in some cancer patients (21). Administration of 0.3 mg/kg every 6 h for 12 doses showed no evidence of accumulation or toxicity in healthy subjects (22). Clearance is primarily by renal excretion of the unchanged drug. About 50% of an MNTX dose appears in the urine within 6 h after injection, while < 0.1% appears after oral dosing (19, 20). Unlike rats and mice, humans do not demethylate MNTX to the centrally active compound naltrexone (23).

Clinical Studies

A volunteer study demonstrated that MNTX prevents the effect of morphine on gastric emptying. Eleven healthy volunteers were given placebo, 0.09 mg/kg morphine or 0.09 mg/kg morphine plus 0.3 mg/kg MNTX, and the rate of gastric emptying was measured by bioimpedance and acetaminophen absorption. The times for 50% emptying were 5.5, 21 and 7.4 min, respectively, after placebo, morphine and morphine/MNTX. Morphine induced a delay in acetaminophen transfer from stomach to proximal jejunum which decreased the acetaminophen C_{max}, and this effect was also prevented by MNTX (24).

The effects on oral-cecal transit time and analgesia were assessed in 12 subjects given i.v. placebo, morphine 0.5 mg/kg or MNTX 0.45 mg/kg plus morphine 0.5 mg/kg. Transit times (measured by the lactulose-hydrogen breath test) were 105, 163 and 106 min, respective-

ly, for placebo, morphine and morphine/MNTX. Experimental pain (cold pressor test) was reduced by morphine and this effect was unchanged by the addition of MNTX. This confirms that MNTX reverses only the peripheral effects and spares the central effects such as analgesia (25). A separate volunteer study showed that MNTX does not reverse opioid-induced ventilatory depression (26).

Patients who have advanced medical illness (AMI) such as cancer or AIDS often receive large doses of opioids in a home or hospice setting. For this reason, there has been a particular effort to develop convenient s.c. and oral dosage forms of MNTX. A volunteer trial showed that s.c. administration of 0.1 or 0.3 mg/kg MNTX completely reversed the delay in intestinal transit induced by 0.05 mg/kg morphine (27). Oral MNTX was also effective, but doses as high as 19.2 mg/kg were required to produce complete reversal (28). An enteric-coated oral preparation was subsequently developed that reduces gastric absorption and releases MNTX only in the small and large intestine. Complete reversal occurred after only 3.2 mg/kg, suggesting that enteric-coated drug is about 6-fold more potent than uncoated MNTX. Greater potency was associated with lower bioavailability, suggesting that more of the enteric-coated preparation reaches opioid receptors in the colonic lumen (19).

Opioid abusers receiving chronic methadone maintenance treatment are also prone to severe OBD, and MNTX has been investigated in three relevant protocols. A pilot trial showed that i.v. MNTX produces immediate and marked laxation in these individuals, and the data suggested that lower doses might be needed. The results of a second study in 22 subjects receiving 30-100 mg/day of methadone are shown in Figure 1. Placebo was ineffective, but 0.1 mg/kg MNTX administered i.v. produced immediate laxation, decreased the intestinal transit time and caused mild to moderate cramping. Other than signs of increased GI motility, there was no indication of opioid withdrawal (29). A third trial of oral MNTX showed a dose-dependent laxation response 18, 12 and 5 h after doses of 0.3, 1.0 and 3.0 mg/kg, respectively (30).

Two pivotal phase III trials of s.c. MNTX have now been completed in patients with AMI and opioid-induced constipation. The first multicenter trial in 154 cancer patients evaluated single doses of s.c. MNTX (0.15 or 0.3 mg/kg) and found that it induced laxation within 4 h (31). The second trial examined the effect of 0.15 mg/kg given every other day for a week, with the option to double the dose as needed during a second week. A total of 48.4% of patients had laxation responses within 4 h of the initial dose, and 38.7% had responses after at least 4 of the 7 doses ($p < 0.0001$ *vs.* placebo). Other than abdominal cramping and flatulence, there were few adverse effects and no reports of opioid withdrawal (32).

Opioid-induced urinary retention is due to inhibition of bladder detrusor tone, suppression of the micturition reflex and decreases in awareness of bladder distension. The clinical problem has not been as well studied as OBD, but some reports suggest a significant incidence in the perioperative period. Certain patient populations are likely to be at greater risk; for example, one study reported an incidence of 18.1% in older patients who used patient-controlled analgesia with morphine after lower limb joint replacements (33). The occurrence of complete urinary retention can be painful and distressing for the patient, and the usual treatment is immediate insertion of a bladder catheter to relieve symptoms.

Opioid actions on the brain and spinal cord undoubtedly play a significant role in the bladder effect, but until recently, the involvement of peripheral opiate receptors had not been demonstrated. We recently compared MNTX, naloxone and placebo for reversal of bladder dys-

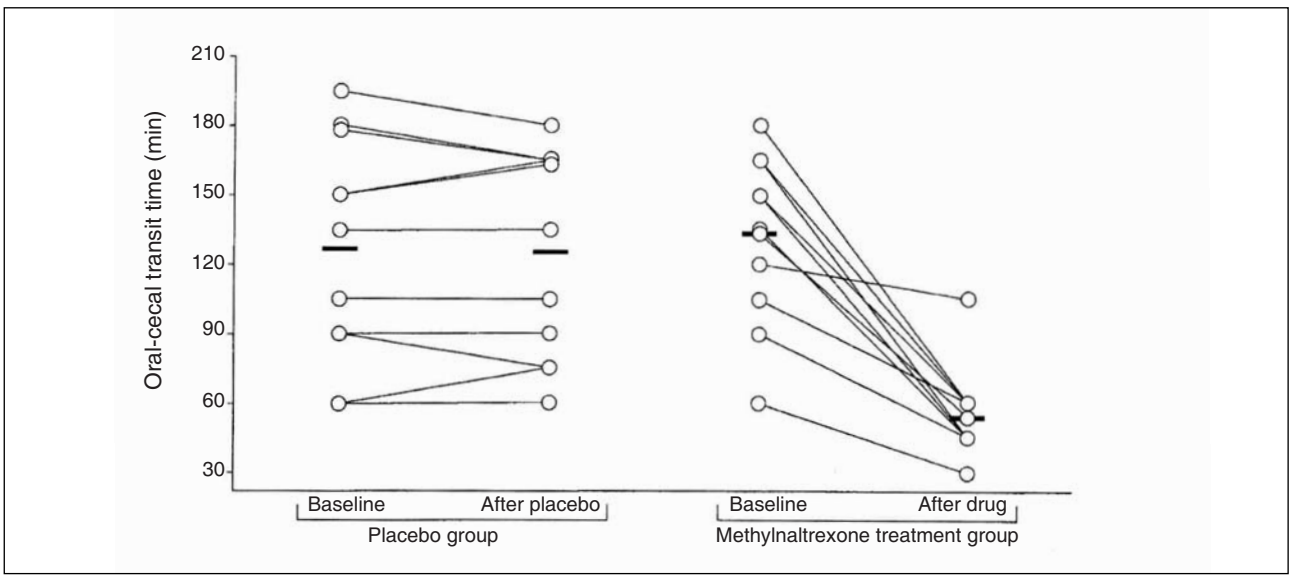


Fig. 1. Changes in individual oral-cecal transit times of subjects undergoing long-term methadone treatment. The average change in the methylnaltrexone group was significantly greater that the average change in the placebo group. Reprinted with permission from Ref. 29.

function induced by the opioid agonist remifentanil (34). Detrusor pressure was measured in 13 male volunteers using bladder and rectal catheters, and pupil constriction (a central opioid effect) was measured by infrared pupillometry. Remifentanil decreased detrusor pressure in 21 of 25 sessions and caused complete urinary retention in 18 of 25. Voiding was possible after naloxone, MNTX and placebo in 7 of 7, 5 of 12 and 0 of 6 sessions, respectively (Fig. 2). Pupil constriction was reversed only by naloxone, indicating once again that MNTX is working peripherally. To our knowledge, this is the first demonstration of a peripheral opioid effect on bladder function. It suggests that MNTX should be evaluated as a potential treatment for opioid-induced urinary retention.

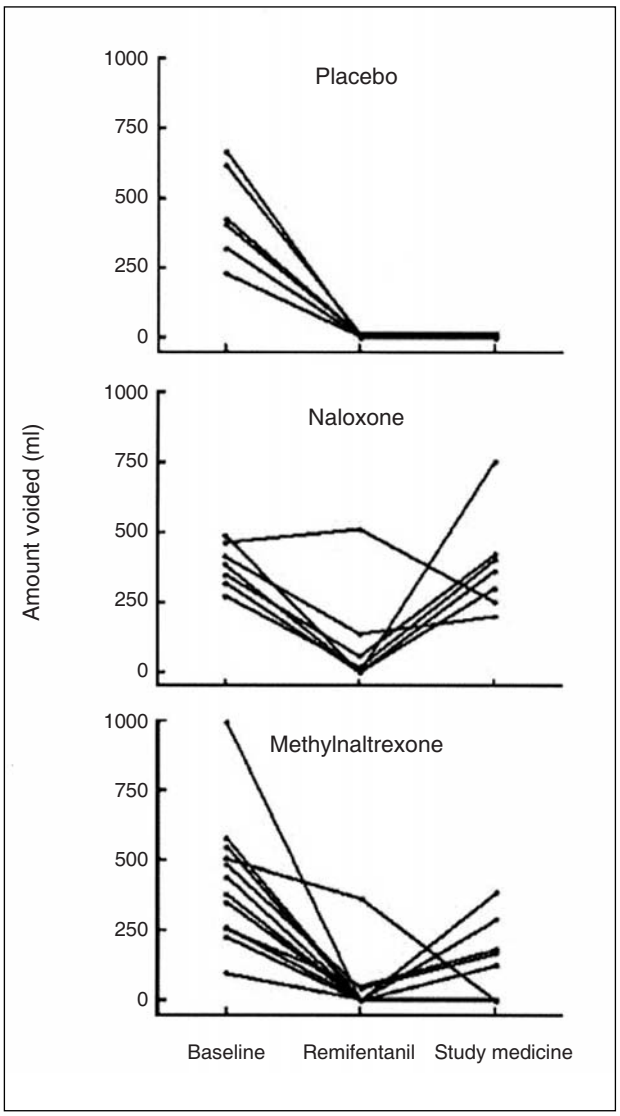


Fig. 2. Amount voided at baseline, after remifentanil and after study medicine (placebo, naloxone or methylnaltrexone). In almost every session, remifentanil prevented voiding or greatly reduced the amount voided, and this effect was fully or partially reversed by naltrexone and methylnaltrexone, but not placebo (see text). Reprinted with permission from Ref. 34.

Conclusions

MNTX is a unique peripheral opioid receptor antagonist. Animal and clinical studies demonstrate that it can reverse or prevent opioid-induced GI effects without antagonizing analgesia. Thus far, there have been remarkably few reports of adverse events, and the therapeutic dose range is likely to be quite large. The most commonly reported side effects, *i.e.*, cramping and abdominal discomfort, appear to be expected GI consequences of drug action. The drug is a hydrophilic small molecule that undergoes mainly first-order renal elimination, so more information will need to be obtained on dosing in patients with renal insufficiency. MNTX has been studied in i.v., s.c. and oral formulations, and the likely availability of all these dosage forms will afford clinicians great flexibility in its clinical application. The drug is being developed jointly by Progenics and Wyeth, and submission of an NDA with the FDA is anticipated in early 2008. A wide variety of opioid-treated patients may eventually benefit from MNTX, although the pivotal phase III studies have specifically targeted s.c. administration in cancer patients and others with AMI. Results from initial studies of postoperative ileus also appear promising (earlier laxation, earlier hospital discharge), and additional trials for this indication are being organized. The human volunteer data on bladder dysfunction are provocative, but further clinical studies will be needed to confirm them. Although not included here, there have been evaluations of MNTX action on many other opioid effects, such as cough suppression, itch and nausea (35), as well as laboratory investigations of immune modulation and endothelial barrier function. These may or may not lead to new therapeutic opportunities, but they do illustrate the value of this new drug as a tool for investigating opioid biology.

Acknowledgements

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Sources

Progenics Pharmaceuticals, Inc. (US); co-developed by Wyeth Pharmaceuticals (US).

References

1. Goldberg, L.I., Stockhaus, K., Merz, H. (Boehringer Ingelheim Pharma GmbH & Co., KG). *Quaternary derivatives of noroxymorphone which relieve intestinal immobility*. US 4176186.

2. Cantrell, G., Halvachs, R.E. (Mallinckrodt, Inc.). *Process for the preparation of quaternary N-alkyl morphinan alkaloid salts*. WO 2004043964.

3. Kurz, A., Sessler, D. *Opioid induced bowel dysfunction. Pathophysiology and potential new therapies*. Drugs 2000, 63: 649-71.

4. Walsh, T.D. *Oral morphine in chronic cancer pain*. Pain 1984, 18(1): 1-11.

5. Vanegas, G., Ripamonti, C., Sbanotto, A., De Conno, F. *Side effects of morphine administration in cancer patients*. Cancer Nurs 1998, 21(4): 289-97.

6. Pappagallo, M. *Incidence, prevalence, and management of opioid bowel dysfunction*. Am J Surg 2001, 182(5A, Suppl.): 11S-8S.

7. Manara, L., Bianchetti, A. *The central and peripheral influences of opioids on gastrointestinal propulsion*. Annu Rev Pharmacol Toxicol 1985, 25: 249-73.

8. Manara, L., Bianchi, G., Ferretti, P., Tavani, A. *Inhibition of gastrointestinal transit by morphine in rats results primarily from direct drug action on gut opioid sites*. J Pharmacol Exp Ther 1986, 237(3): 945-9.

9. Shook, J.E., Pelton, J.T., Hruby, J., Burks, T.F. *Peptide opioid antagonist separates peripheral and central opioid antitransit effects*. J Pharmacol Exp Ther 1987, 243(2): 492-500.

10. Culpepper-Morgan, J.A., Inturrisi, C.E., Portenoy, R.K., Foley, K., Houde, R.W., Marsh, F., Kreek, M.J. *Treatment of opioid-induced constipation with oral naltrexone: A pilot study*. Clin Pharmacol Ther 1992, 52(1): 90-5.

11. Sykes, N.P. *Oral naltrexone in opioid-associated constipation*. Lancet 1991, 337(8755): 1475.

12. Cheskin, L.J., Chami, T.N., Johnson, R.E., Jaffe, J.H. *Assessment of nalmefene glucuronide as a selective gut opioid antagonist*. Drug Alcohol Depend 1995, 39(2): 151-4.

13. Brown, D.R., Goldberg, L.I. *The use of quaternary narcotic antagonists in opiate research*. Neuropharmacology 1985, 24(3): 181-91.

14. Russell, J., Bass, P., Goldberg, L.I., Schuster, C.R., Merz, H. *Antagonism of gut, but not central effects of morphine with quaternary narcotic antagonists*. Eur J Pharmacol 1982, 78(3): 255-61.

15. Gmerek, D.E., Cowan, A., Woods, J.H. *Independent central and peripheral mediation of morphine-induced inhibition of gastrointestinal transit in rats*. J Pharmacol Exp Ther 1986, 236(1): 8-13.

16. Valentino, R.J., Katz, J.L., Medzihradsky, F., Woods, J.H. *Receptor binding, antagonist, and withdrawal precipitating properties of opiate antagonists*. Life Sci 1983, 32(25): 2887-96.

17. Yuan, C.S., Foss, J.F. *Gastric effects of methylnaltrexone on mu, kappa, and delta opioid agonists induced brainstem unitary responses*. Neuropharmacology 1999, 38(3): 425-32.

18. Yuan, C.S., Foss, J.F., Moss, J. *Effects of methylnaltrexone on morphine-induced inhibition of contraction in isolated guinea pig ileum and human intestine*. Eur J Pharmacol 1995, 276(1-2): 107-11.

19. Yuan, C.S., Foss, J.F., O'Connor, M., Karrison, T., Osinski, J., Roizen, M.F., Moss, J. *Effects of enteric-coated methylnaltrexone in preventing opioid-induced delay in oral-cecal transit*. Clin Pharmacol Ther 2000, 67(4): 398-404.

20. Foss, J.F., O'Connor, M.F., Yuan, C.S., Murphy, M., Moss, J., Roizen, M.F. *Safety and tolerance of methylnaltrexone in healthy humans: A randomized, placebo-controlled, intravenous, ascending-dose, pharmacokinetic study*. J Clin Pharmacol 1997, 37(1): 25-30.

21. Yuan, C.S., Foss, J.F. *Methylnaltrexone: Investigation of clinical applications*. Drug Develop Res 2000, 50(2): 133-41.

22. Yuan, C.S., Doshan, H., Charney, M.R. et al. *Tolerability, gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans*. J Clin Pharmacol 2005, 45(5): 538-46.

23. Kotake, A.N., Kuwahara, 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): 1247-54.

24. Murphy, D.B., Sutton, J.A., Prescott, L.F., Murphy, M.B. *Opioid-induced delay in gastric emptying: A peripheral mechanism in humans*. Anesthesiology 1997, 87(4): 765-70.

25. Yuan, C.S., Foss, J.F., O'Connor, M., Toledano, A., Roizen, M.F., Moss, J. *Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: A double-blind randomized placebo-controlled trial*. Clin Pharmacol Ther 1996, 59(4): 469-75.

26. Amin, H.M., Sopchak, A.M., Foss, J.F., Esposito, B.F., Roizen, M.F., Camporesi, E.M. *Efficacy of methylnaltrexone versus naloxone for reversal of morphine-induced depression of hypoxic ventilatory response*. Anesth Analg 1994, 78(4): 701-5.

27. Yuan, C.S., Wei, G., Foss, J.F., O'Connor, M., Karrison, T., Osinski, J. *Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: A double-blind randomized placebo-controlled trial*. J Pharmacol Exp Ther 2002, 300(1): 118-23.

28. Yuan, C.S., Foss, J.F., Osinski, J., Toledano, A., Roizen, M.F., Moss, J. *The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time*. Clin Pharmacol Ther 1997, 61(4): 467-75.

29. Yuan, C.S., Foss, J.F., O'Connor, M., Osinski, J., Karrison, T., Moss, J., Roizen, M.F. *Methylnaltrexone for reversal of constipation due to chronic methadone use*. JAMA – J Am Med Assoc 2000, 283(3): 367-72.

30. Yuan, C.S., Foss, J.F. *Oral methylnaltrexone for opioid-induced constipation [research letter]*. JAMA – J Am Med Assoc 2000, 284(11): 1383-4.

31. Thomas, J., Lipman, A., Slakin, N. et al. *A phase III double-blind placebo-controlled trial of methylnaltrexone (MNTX) for opioid-induced constipation (OIC) in advanced medical illness (AMI)*. 41st Annu Meet Am Soc Clin Oncol (ASCO) (May 13-17, Orlando) 2005, Abst LBA8003.

32. Slatkin, N., Karver, S., Thomas, J. et al. *A phase III double-blind, placebo-controlled trial of methylnaltrexone for opioid-induced constipation in advanced illness (MNTX 302)*. Digest Dis Week (May 20-25, Los Angeles) 2006, Abst 686e.

33. O'Riordan, J.A., Hopkins, P.M., Ravenscroft, A., Stevens, J.D. *Patient-controlled analgesia and urinary retention following lower limb joint replacement: Prospective audit and logistic regression analysis*. Eur J Anaesthesiol 2000, 17(7): 431-5.

34. Rosow, C.E., Gomery, P., Chen, T.Y., Stefanovich, P., Stambler, N., Israel, R. *Reversal of opioid-induced bladder dysfunction by intravenous naltrexone and methylnaltrexone*. Clin Pharmacol Ther 2007, 82(1): 48-53.

35. Yuan, C.S., Foss, J.F., Osinski, J.P., Roizen, M.F., Moss, J. *Efficacy of orally administered methylnaltrexone in decreasing subjective effects after intravenous morphine*. Drug Alcohol Depend 1998, 52(2): 161-5.