

Methylnaltrexone for Opioid-induced Constipation in Palliative Care



THE INSTITUTE FOR
PALLIATIVE MEDICINE
at San Diego Hospice

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**Methylnaltrexone
for Opioid-induced
Constipation in
Palliative Care**

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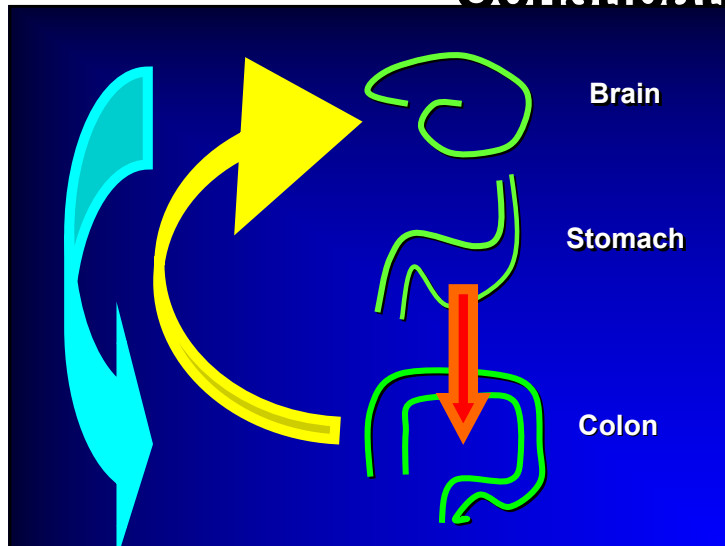
Outline

- Pathophysiology of opioid-induced constipation
- Methylnaltrexone pharmacology
- Results of phase III clinical trials
- Case example

Constipation How big an issue ?

- 50 % admitted to a hospice unit
- 50 - 63 % **not** receiving opioids require laxatives
(*Twycross and Harcourt, 1991; Sykes, 1998*)
- 87 % **taking opioids** require a laxative
(*Sykes, 1998*)
- Rivals pain as a cause of distress
(*Holmes, 1989; Dunlop, 1989*)

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Peripheral Effects of Opioids on GI Tract

Stomach

- ↓ gastric motility
- ↓ gastric emptying

Small intestine

- ↓ propulsive contractions
- ↓ fluid secretions
- ↑ oral-cecal transit time
- ↓ digestion

Large intestine

- ↑ transit time
- ↓ propulsive peristalsis
- ↑ non-propulsive contractions
- ↑ desiccation of feces
- ↓ reflex relaxation response
- ↑ anal sphincter tone

Traditional Rx of Opioid-induced Constipation

Stimulants ↑ activity

Senna
Bisacodyl
Metoclopramide
Glycerin

Osmotics ↑ water content

Lactulose
Sorbitol
Polyethylene glycol
Saline laxatives, eg, phosphosoda

Stool softeners

↑ water solubility
Docusate sodium

Bulk ↑ distention

Psyllium, cellulose
Large volume enemas

Enemas soften leading edge

Oil, water retention

PZ 32 yo ♀ ...

- Hispanic, 2 young children
- CA Breast x 3 years,
Mets – Pleural, pericardial, intracranial, leptomeningeal, spine, intrathecal
↓ function, assist / wheel chair
Normal cognitive function
- Adm. July 15 08, constipation x weeks
Hyperacidity / reflux, nausea
Distention, anorexia

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...PZ 32 yo ♀ CA Breast

- Hydromorphone
0.2 - 0.4 mg / hr + BT
- Methadone
2.5 mg q 12 h
- Dexamethasone
20 mg daily
- Bisacodyl
- Polyethylene glycol
- PPI, antacids
- Haloperidol
- Metoclopramide
- Ondansetron

...still distressed !



Analogy – Driving a Car

Normal: foot on accelerator

Opioids: apply the brake pedal

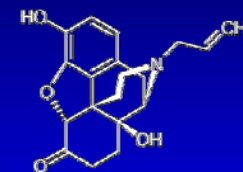
Stimulant laxatives: push down further on the accelerator

Competing effects !

Naloxone - Opioid Antagonist



Morphine
(agonist)



Naloxone
(antagonist)

- Neutral molecule
Can cross blood-brain barrier
- $K_i = 3.7$ nM at the μ receptor
- Poor oral bioavailability

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Methylnaltrexone (MNTX) a New Peripheral Opioid-receptor Antagonist

Naloxone
(antagonist)

Naltrexone
(central antagonist)

N-Methylnaltrexone
(peripheral antagonist)

J.F. Foss. *Am J Surg* 2001 (5A Suppl);182:19S–26S.

Methylnaltrexone (MNTX) a New Peripheral Opioid-receptor Antagonist

- + charged molecule
- Cannot cross the blood-brain barrier
 - Confirmed in animal studies
 - No interaction with CNS opioid receptors
- $K_i = 70 \text{ nM}$ at the μ receptor
- Poor oral bioavailability $\approx 2 \%$

J.F. Foss. *Am J Surg* 2001 (5A Suppl);182:19S–26S.

MNTX 301 & 302 Studies

- Double-blinded
- Randomized
- Placebo controlled
- Advanced illness (Px < 6 months)
- < 3 bowel movements in preceding week
- No laxation > 48 hours
- Stable opioid & laxative Rx ≥ 3 days

MNTX Trials

301	302
<ul style="list-style-type: none"> • Effect of single dose placebo, 0.15 or 0.30 mg / kg after 4 & 24 hours • N = 154 • Mean oral morphine equivalent dose / day 70 - 100 mg 	<ul style="list-style-type: none"> • Effect of repeat dosing 0.15 mg / kg every other day x 2 weeks • N = 133 • Median oral morphine equivalent dose / day Placebo group 100 mg MNTX group 150 mg

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Precedents...

First research exclusively in palliative care

Real life, advanced disease

Px < 6 months

Standard laxative trial

Stable enough to go on trial



IPM Accrued Largest # Patients Worldwide

Screened hundreds

(10 : 1 enrolled)

Enrolled 68 (2 / month)

All at home

=/= inpatients

...Precedents

News to US FDA

Expert: Charles von Gunten, MD, PhD

Translation

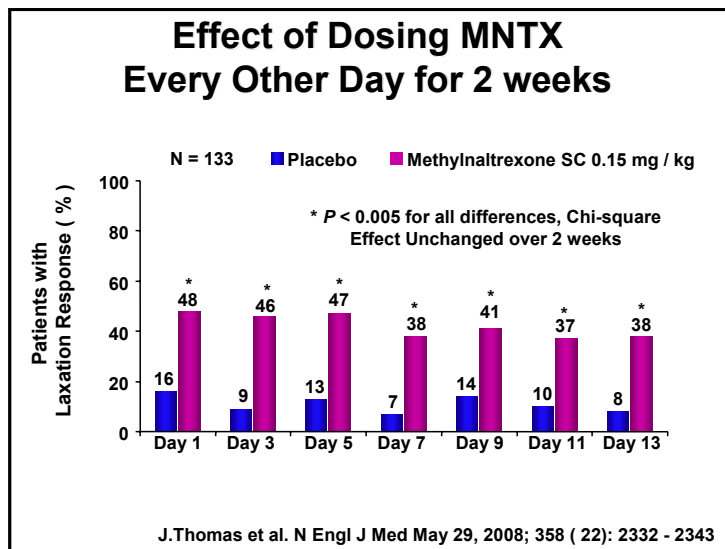
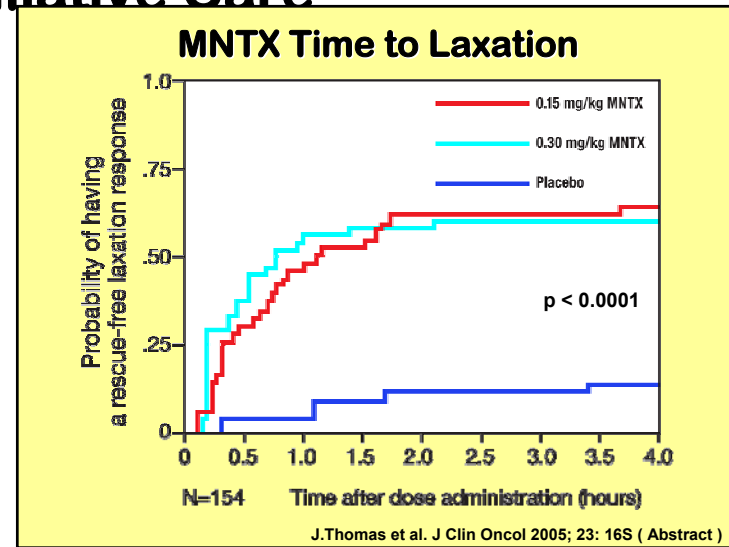
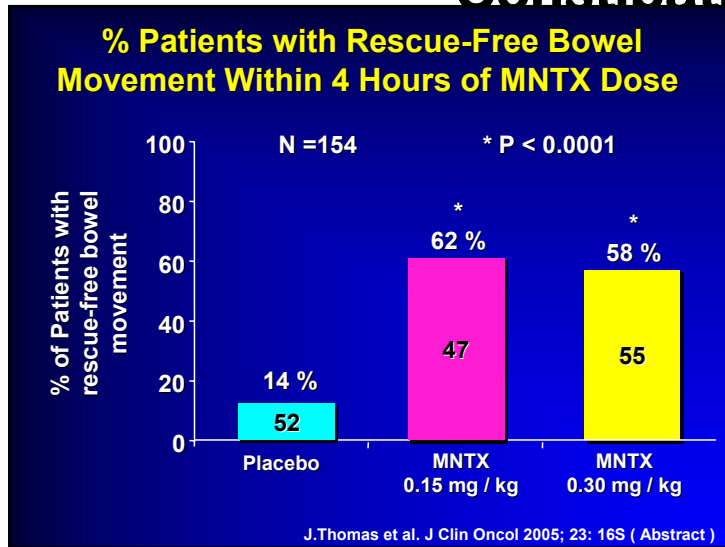
Progenics: Lab → phase II & III trials

Wyeth: Trials → clinical practice



Summary of Results

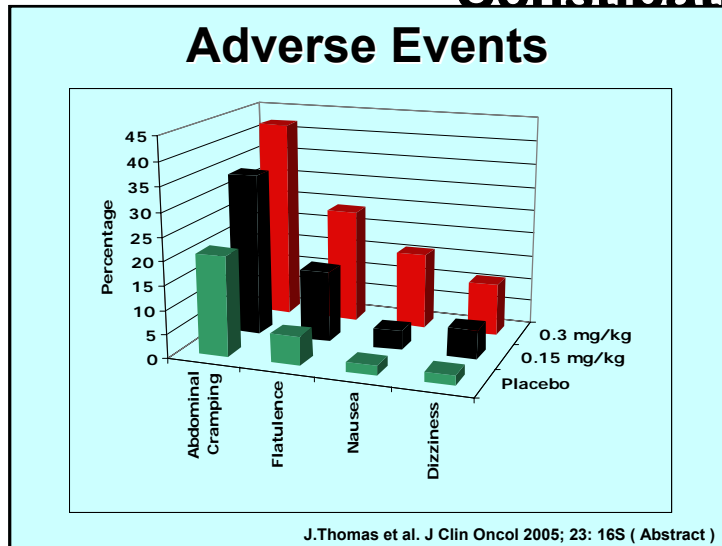
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Secondary Endpoints

- No signs of withdrawal
- No change in pain scores

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Most Common Adverse Events (≥ 5 %)

Adverse Event	No. of patients with AE (%) Placebo (n = 123)	Methylnaltrexone (n = 165)
Abdominal pain	12 (9.8)	47 (28.5)
Flatulence	7 (5.7)	22 (13.3)
Nausea	6 (4.9)	19 (11.5)
Vomiting	10 (8.1)	14 (8.5)
Pain	13 (10.6)	13 (7.9)
Malignant neoplasm progression	14 (11.4)	12 (7.3)
Dizziness	3 (2.4)	12 (7.3)
Restlessness	8 (6.5)	11 (6.7)
Hyperhidrosis	8 (6.5)	11 (6.7)
Diarrhea	3 (2.4)	9 (5.5)
Asthenia	5 (4.1)	9 (5.5)
Edema	10 (8.1)	7 (4.2)
Fall	8 (6.5)	2 (1.2)

○ On US FDA Label

MNTX 301 & 302 Combined Data

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness

Jay Thomas, M.D., Ph.D., Sloan Karver, M.D., Gail Austin Cooney, M.D.,
Bruce H. Chamberlain, M.D., Charles Kevin Watt, D.O., Neal E. Slatkin, M.D.,
Nancy Stambler, M.S., Alton B. Kremer, M.D., Ph.D., and Robert J. Israel, M.D.

ABSTRACT

BACKGROUND: Constipation is a distressing side effect of opioid treatment. As a quaternary amine, methylnaltrexone, a μ -opioid-receptor antagonist, has restricted ability to cross the blood-brain barrier. We investigated the safety and efficacy of subcutaneous methylnaltrexone for treating opioid-induced constipation in patients with advanced illness.

METHODS:

From San Diego Hospice and the Institute for Palliative Medicine, San Diego, CA (J.T.); Gulfside Regional Hospice, New Port Richey, FL (S.K.); Hospice of Palm Beach County, West Palm Beach, FL (G.A.C.); Palliative Consulting, Orem, UT (B.H.C.); Research Center of the Ozarks, Everton, MO (C.K.W.); City of Hope Na-

New Engl J Med 358 (22); 2332
May 29, 2008

PZ 32 yo ♀ CA Breast

- July 19: MNTX 8 mg SC
Some abdominal cramping
Large BM within 30 minutes
Relief of
Hyperacidity / reflux, nausea
Distention, anorexia
2 hours later - ate / enjoyed significant meal
- Repeated MNTX 8 mg SC daily
if no BM last 48 hrs – died Sept. 11 08

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Analogy – Driving a Car

Normal: foot on accelerator

Opioids: apply the brake pedal

Peripheral opioid antagonists:
remove foot from the brake pedal

Functions normally !

Methylnaltrexone (Relistor™) Dosing

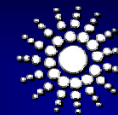
< 62 kg: 8 mg SC every other day
(0.4 ml)

62 kg - 114 kg: 12 mg SC every other day
(0.6 ml)



Conclusion

Peripheral opioid antagonists are a new way to treat opioid-induced constipation when laxatives are insufficient for patients receiving palliative care



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