IV Naloxone Infusion: A Forgotten Gem

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Disclosure

We have no potential conflicts of interest to report.

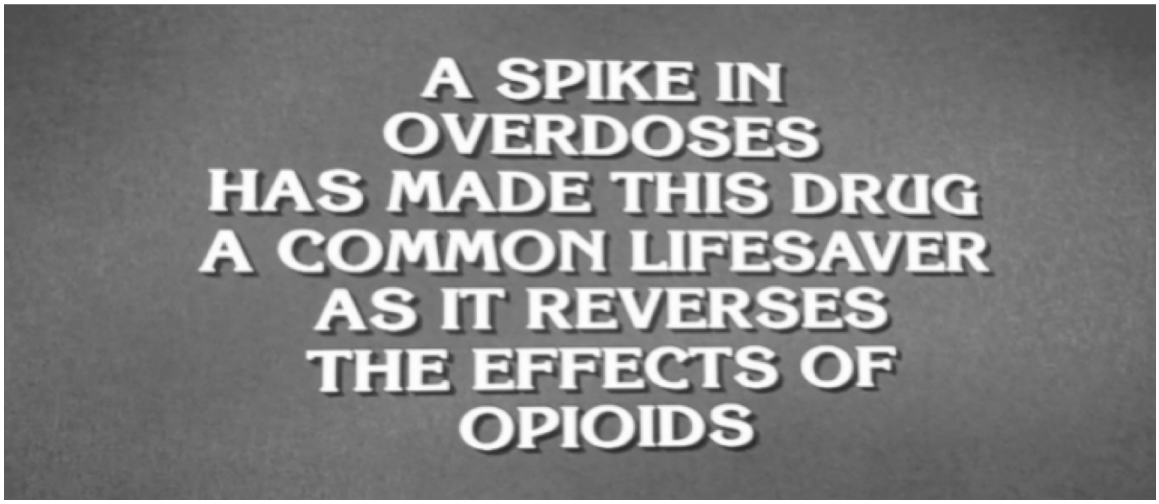
Our opinions do not necessarily reflect the opinions of Cedars-Sinai Medical Center

Learning Objectives

- Identify the benefits of low dose IV naloxone
- Discuss the evidence supporting the use of low dose IV naloxone to prevent and reverse several opioid induced side effects
- Discuss the mechanism of action of low dose IV naloxone

PAINWEEK

Debunking Myths



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Background about Naloxone

- Well known for reversal of opioid-induced respiratory depression BUT rarely used for prevention or treatment of opioid induced side effects.
- EVIDENCE
- Side effects affecting hospital LOS: opioid-induced
  - Pruritus
  - N/V
  - Ileus
  - Urinary retention
  - Hyperalgesia
- Cedars-Sinai Medical Center experience

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Naloxone Overview

- **Naloxone**
  - μ-opioid receptor antagonist
  - Low doses of naloxone can selectively eliminate adverse effects of opioids WITHOUT compromising analgesia (Cepeda et al., 2002).
- **FDA approved indications**
  - Approved to reverse opioid overdose
- **Clinical pharmacology**
  - Suggested doses of 0.1 to 2 mg intravenously repeated every 2 to 3 min as needed. **WARNING**
  - Elimination half-life for adults: 30 to 81 min with renal excretion.

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Warning against large doses of IV naloxone

- Withdrawal in the presence of physical opioid dependence
- Drug interaction with clonidine (HTN)
- Pulmonary edema, hepatotoxicity, cardiac dysrhythmia, hypertension, hypotension, and ventricular fibrillation (*NALOXONE CAN KILL*!)

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Naloxone - Titration protocol

- 0.04 mg IV q 1 minute prn RR <15 if 6-8 years old **or** RR<12 if >8 years old
- May repeat up to maximum dose of 0.8mg
- O_2 by facemask

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Low dose IV Naloxone Mechanism of action

- G-Proteins between opioid and mu receptor
- Gi-Proteins induce analgesia and respiratory depression
- Gs-Proteins induce opioid tolerance and hyperalgesia

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Literature Review: Earliest evidence

Gan TJ, et al: Anesthesiology. 1997 Nov; 87 (5): 1075-81.

- First published data on continuous infusion of naloxone + morphine PCA
- 60 pts ASA1, 2, or 3 for TAH
- Naloxone at 0.25 (low dose) vs 1 mcg/kg/hr (high dose) vs NS
- Both naloxone doses were equally effective in reducing the incidence of nausea, vomiting, and pruritus compared with placebo ($P<0.05$)
- Cumulative morphine use was the lowest in the low-dose group compared with the placebo and high-dose groups at 24 h ($P < 0.05$)

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Opioid-Induced Pruritus, Nausea

Maxwell LG, et al. Anesth Analg 2005;100:953–8

- Prospective, double-blind, RCT
- N=46 postop patients 14+/-2.5 years on MSO4 PCA
- NS vs naloxone at 0.25 mcg/Kg/hr “piggy-backed” into same IV
- Pruritus: 77% vs 20% ($p<0.05$); Nausea: 70% vs 35% ($p<0.05$)
- No differences in MSO4 consumption, pain at rest and with coughing

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Opioid-Induced Pruritus

Murphy et al, J Opioid Manag. 2011 Jul-Aug;7(4):321-7

- Meta analysis of 8 RCTs
- N=800 patients (424 in naloxone group, 376 in NS grp)
- Outcomes: incidence of pruritus, opioid consumption, VAS pain scores, nausea, vomiting, sedation
- Decrease in pruritus and nausea. NO increase in pain scores

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Opioid-Induced Pruritus, Nausea/V (2)

Monitto CL, et al., Anesth Analg. 2011 Oct. 113(4): 834-42

- Dose escalation study in 59 pediatric patients
- Min naloxone dose at which pts successfully Rx'd (<10% side effect rate) was 1mcg/kg/hr
- More effective in preventing pruritus than N/V
- "Piggy-Backed" IV naloxone infusion

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Opioid-Induced Pruritus (Prophylaxis)

West et al, Can J Anaesth. 2015 Aug;62(8):891-900

- Double blind RCT. N=92 pediatric patient who received infusion of naloxone, opioid, and saline ADMIXTURE.
- No decrease the incidence or severity of opioid induced pruritus (OIP)
- HOWEVER pruritus was only 4% among pts w/ COI vs. 40% among pts with a PCA (naloxone mixed with opioid) ($P < 0.001$)
- SEPARATE administration of naloxone may be the more effective strategy for prevention of OIP.

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PONV Prophylaxis

Barrons & Woods, Pharmacotherapy. 2017 May;37(5):546-554

- Meta-analysis of 9 RCTs
- N=946 adult and pediatric patients
- Naloxone gtt and PCA opioid/nalox ADMIXTURE (x6)
- Decreased PON but NOT for vomiting. Decreased PONV in naloxone gtt trials (x 3) at 0.05-1 mcg/kg/hr.

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Postop morphine consumption

Movafegh et al, Acta Anaesthes Scand. 2012 Nov;56(10):1241-9

- Prospective, randomized, double-blind, controlled study
- N=90 pts (35-55 yrs) for TAH
- Naloxone 1 ng/kg (?) (loading)+infusion at **0.25 mcg/kg/hr**
- ↓ MSO4 during 1st 24 hrs (P<0.001), ↓ severity of N/V 1st 20 hrs (P<0.001), ↓ # pts received ondansetron
- No diff in pain at rest and coughing between groups

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Opioid-Induced Urinary Retention

Gallo S, DuRand, Pshon N., Orthop Nurs. 2008 Mar-Apr;27(2):111-5.

- Prospective randomized but not blind
- N=97 ortho surg pts with MSO4 PCA
- **0.1 mg** IV naloxone **q4h** vs none
- # voids/hr: 0.34+/-0.13 vs 0.26+/-0.11, (P=0.001)
- Bladder scan vol/hr: 12+/-9.2 vs 20+/-22, (P=0.008)
- % pts catheterized: 11.5% vs 24.4%, (P=0.048)
- No diff. in pain scores ā v p naloxone: 4.34 v 4.28 (P=0.509)

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Opioid-Induced Urinary Retention (2)

Rosow CE et al, Clin Pharmacol Ther. 2007 Jul;82(1):48-53.

- Double-blind RCT
- N=13 healthy male volunteers received IV infusion of remifentanil, then a single i.v. dose of study medication: methylnaltrexone 0.3mg/kg, naloxone 0.01mg/kg, or NS
- 7/7 voiding in naloxone grp VS 0/6 in NS grp
- Naloxone produced a >50% decrease in bladder volume at first urge to void in 5/7 sessions, compared with methylnaltrexone (2/12), Placebo (0/6) (*P*=0.008)

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Opioid-Induced Ileus

Xiao et al, Acta Anaesthesiol Scand. 2015 Oct;59(9):1194-203

- Prospective, RCT, double-blind, single-center study
- N=72 patients undergoing open colorectal surgery
- Remifentanil: 1) Low dose
  2) Large dose
  3) Large dose+naloxone (0.25 mcg/kg/hr)
- Faster return of bowel function w naloxone ($P < 0.05$), LOS 8 vs 12 days ($P < 0.001$)

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Opioid-Induced Hyperalgesia

Koo, CH et al, Br J Anaesth. 2017 Dec 1;119(6):1161-1168

- Prospective, double-blind, single center, RCT
- N=91 pts for thyroid surgery; 3 groups
  1) High remifentanil
  2) High remifentanil with naloxone (0.05 mcg/kg/hr)
  3) Low remifentanil
- Significantly reduced peri-incisional hyperalgesia in grp 2. No effect on postoperative pain

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Summary

- 0.25 – 1 mcg/kg/hr for pruritus, nausea, vomiting, ileus
- Reversal of analgesia begins at 1 mcg/kg/hr
- Opioid-naloxone admixtures are ineffective
- Separate IV lines or “Piggy-Back”
- For urinary retention: 100 mcg IVP +/- infusion
- Analgesic effect of IV naloxone infusion?
- Reversal of hyperalgesia at 0.05 mcg/kg/hr?

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Naloxone Use at Cedars-Sinai Med Ctr

Prophylactic or Treatment for Opioid Induced Side Effects

1. Pruritus
2. Nausea / Vomiting
3. Urinary Retention
4. Ileus

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CSMC Continuous Naloxone gtt orders

Indication	Dosing
Opioid induced **PRURITIS, NAUSEA, VOMITING**	Starting dose at **0.25 mcg/kg/hr up to 0.5 mcg/kg/hr**
Opioid induced **ILEUS**	Starting dose at **0.25 mcg/kg/hr up to 0.5 mcg/kg/hr** (For use in **high risk patients** --colorectal, spine, hepatobiliary patients or **high dose opioid patients >100 MEDD)**
Opioid induced **URINARY RETENTION**	Starting dose at **0.35 mcg/kg/hr up to 0.5 mcg/kg/hr.** (For use in patients receiving high dose opioid patients >100 MEDD)

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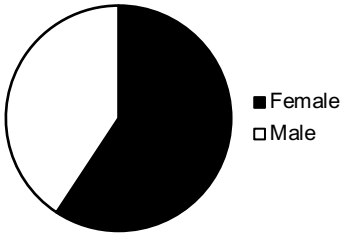
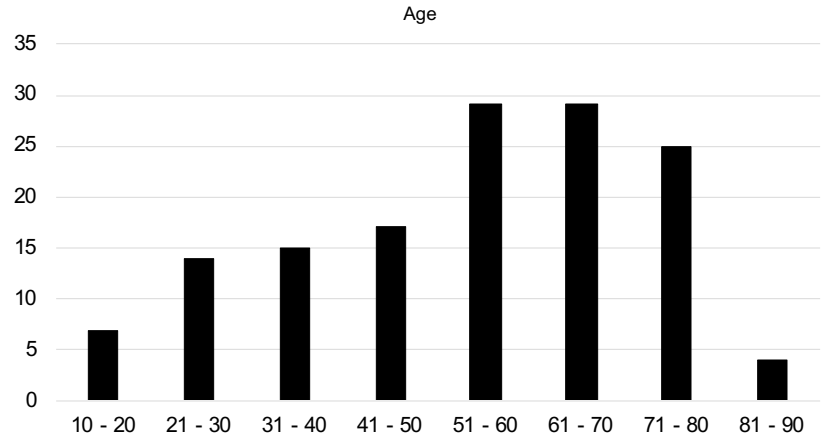
January to June 2018 Naloxone gtt

140 patients

41 % Male
59% Female





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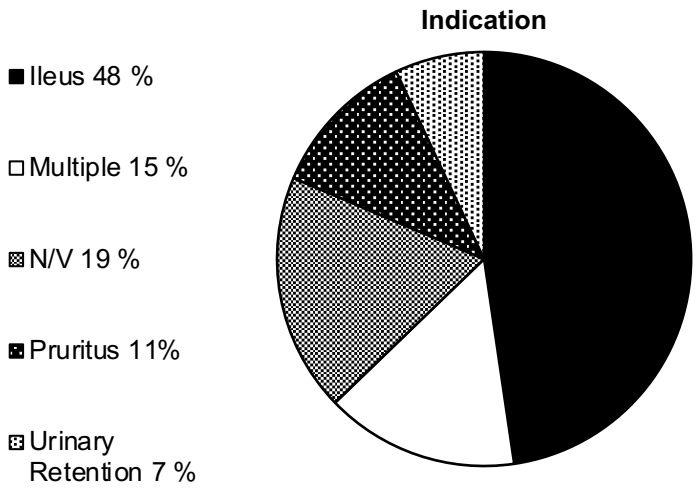
January to June 2018 Naloxone gtt



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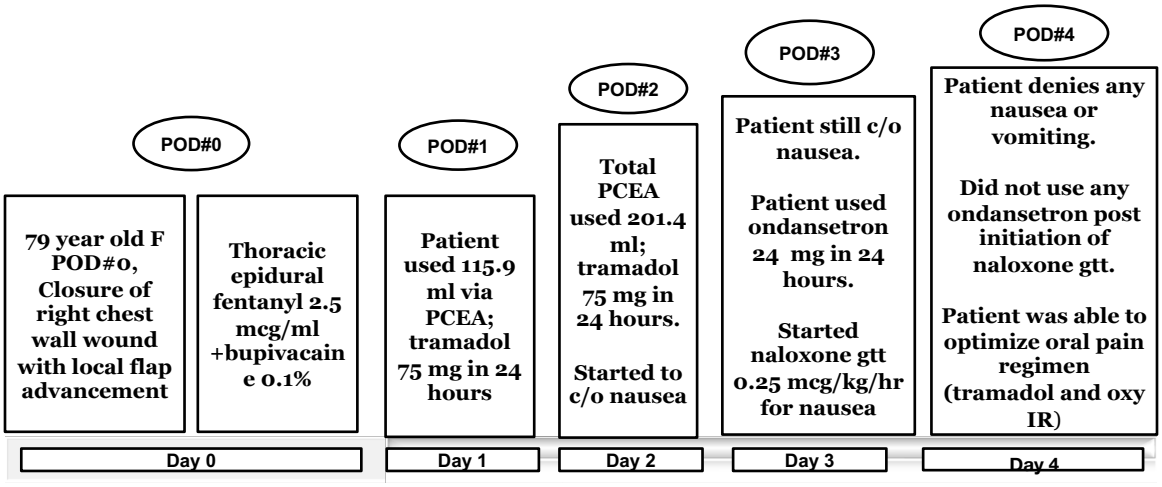
A Closer Look: Patient with nausea



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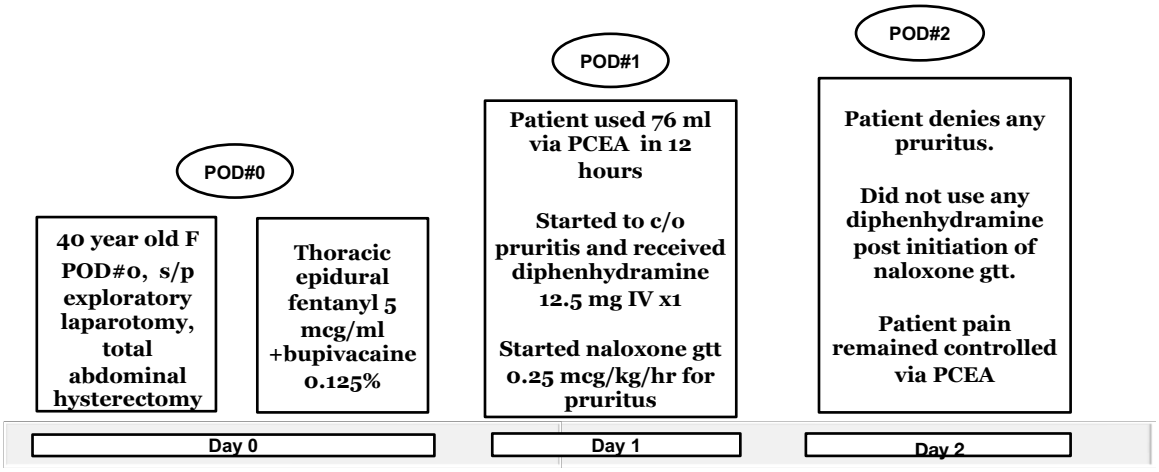
A Closer Look: Patient with pruritus



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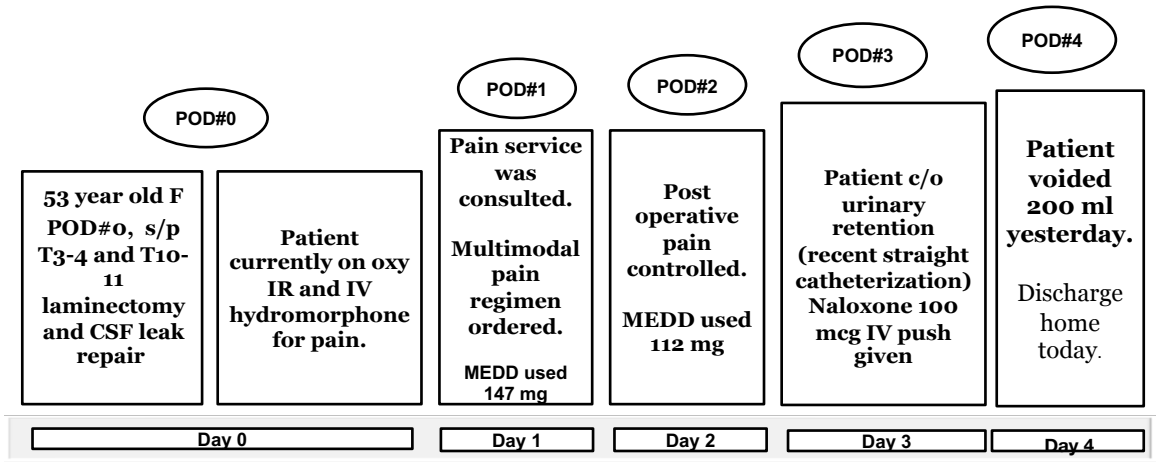
A Closer Look: Patient with urinary retention



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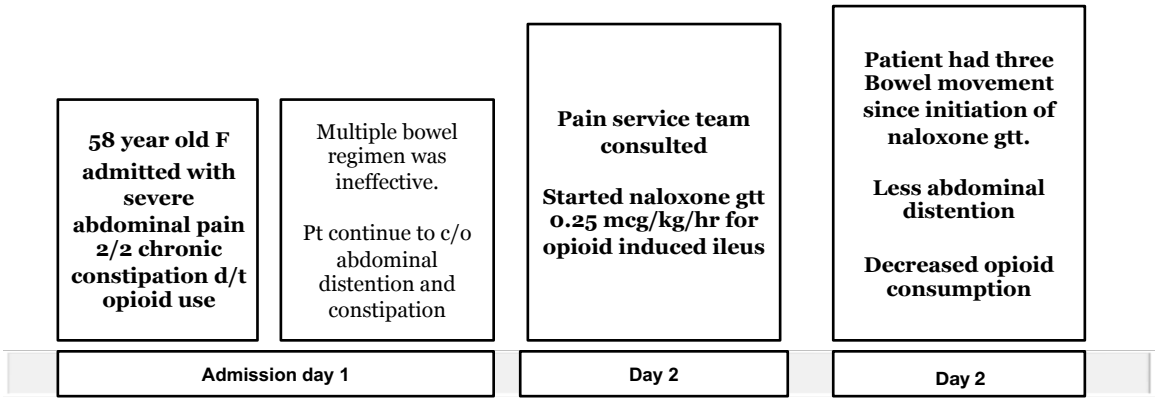
A Closer Look: Patient with ileus



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Future Directions

- Ongoing retrospective chart review for naloxone treatment outcomes.
- More proactive use of naloxone for prophylaxis
- Consider adding prevention or treatment of opioid induced hyperalgesia as an additional indication.

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