PAIN MANAGEMENT: CLINICAL PEARLS & HOSPITAL-SPECIFIC PROTOCOLS

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LEARNING OBJECTIVES

- Examine literature addressing the use of a multimodal analgesic strategy for acute inpatient pain management
- Apply clinical pearls surrounding selection of specific non-opioids to be used as part of a multimodal strategy (i.e. adverse reactions, cautions, or contraindications)
- Discuss strategies to promote safe use of opioids in hospitalized patients and avoidance of opioid-related adverse drug effects
- Explore options for managing pain in patients using methadone or Suboxone

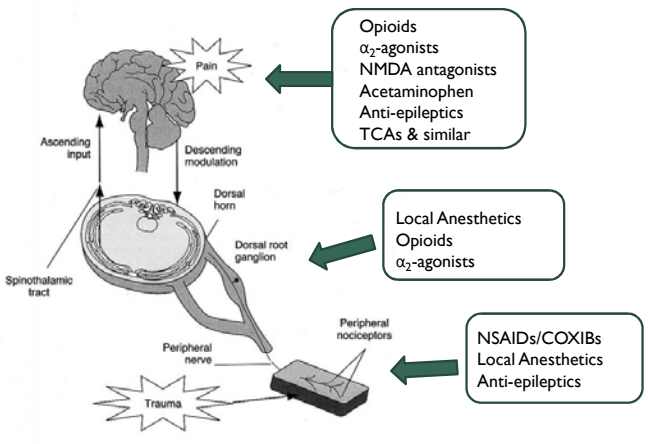
DEFINITION/RATIONALE

Multimodal Analgesia involves the concurrent administration of two or more analgesic agents with different mechanisms of action.

The combination therapy often produces a synergistic effect, and allow for better analgesia using lower doses of a given medication if it were to be used alone.

Many studies have demonstrated an opioid-sparing effect from concurrent use of NSAIDs. More recently, adjuvant medications such as anticonvulsants have demonstrated similar results.

Kehlet H and Dahl JB. Anesth Analg 1993;77:1048-56.



NON-OPIOIDS TO CONSIDER:

BASE MMA REGIMEN ON:

- Efficacy
  - Consider neuropathic component
- Patient-specific factors
  - Age
  - Organ function
    - Renal, GI
  - Tolerability & Ease of Use
  - Cost

CONSIDER THE USE OF:

- Acetaminophen
- NSAIDs
  - Ketorolac, ibuprofen, celecoxib, etodolac
- NMDA receptor antagonists
  - Ketamine
- Alpha2 agonists
  - Clonidine, dexmedetomidine
- Gabapentinoids
  - Gabapentin, pregabalin
- Local anesthetics
  - Bupivacaine, lidocaine, liposomoal bupivacaine

EXAMPLES OF MMA IN SURGICAL PATIENTS

Pre-Operative	Acetaminophen Gabapentin or Pregabalin NSAID Opioid
Intra-Operative	Regional analgesia with local anesthetic or opioid Epidural or intrathecal opioid
Post-Operative	Opioid (i.e. PCA or other) Acetaminophen NSAID Gabapentin or Pregabalin

ASA Practice Guidelines for Acute Pain Management in the Perioperative Setting. Anesthesiology 2012;116(2):248-273.

RECOMMENDATIONS FROM PROFESSIONAL SOCIETIES & ACCREDITING AGENCIES

- The multimodal concept is supported by numerous professional and regulatory organizations
  - **AAEM** (American Academy of Emergency Medicine)[1]
  - **AAOS** (American Academy of Orthopaedic Surgeons)[2]
  - **ACS** (American College of Surgeons)[3]
  - **AGS** (The American Geriatrics Society)[4]
  - **AHA** (American Heart Association)[5]
  - **AHRQ** (Agency for Healthcare Research and Quality)[6]
  - **ASA** (American Society of Anesthesiologists)[7]
  - **ASPAN** (American Society of PeriAnesthesia Nurses)[8]
  - **ASPMN** (American Society for Pain Management Nursing)[9]
  - **ERAS** Society (Enhanced Recovery After Surgery Society)[10]
  - **SCCM** (Society of Critical Care Medicine)[11]
  - **TJC** (The Joint Commission)[12]

References: 1. Cheng D et al. http://www.aaem.org/UserFiles/file/Emergency-Department-Opoid-Prescribing-Guidelines.pdf. Accessed April 1, 2016. **2.** American Academy of Orthopaedic Surgeons. http://www.aaos.org/cc_files/aaosorg/research/guidelines/hipfxguideline.pdf. Published September 5, 2014. Accessed February 29, 2016. **3.** Mohanty S et al. American College of Surgeons website. https://www.facs.org/~/media/files/quality%20programs/geriatric/acs%20nsqip%20geriatric%202016%20guidelines.ashx. Accessed February 29, 2016. **4.** Shah S et al. The American Geriatrics Society. http://www.americangeriatrics.org/gsr/anesthesiology/pain_management.pdf. Accessed February 22, 2016. **5.** Antman EM et al. *Circulation.* 2007;115(12):1634-1642. **6.** Wells N et al. Improving the quality of care through pain assessment and management. In: Hughes RG, ed. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses.* Rockville, MD: Agency for Healthcare Research and Quality; 2008:chap 17. **7.** American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248-273. **8.** Krenzischek DA and Wilson L. *J Perianesth Nurs.* 2003;18(4):232-236. **9.** Jarzyna D et al. *Pain Manag Nurs.* 2011;12(3):118-145. **10.** Gustafsson UO et al. *World J Surg.* 2013;37:259-284. **11.** Barr J et al. *Crit Care Med.* 2013;41(1):263-306. **12.** The Joint Commission. *Sentinel Event Alert.* 2012;49:1-5. http://www.jointcommission.org/assets/1/18/SEA_49_opioids_8_2_12_final.pdf. Accessed December 28, 2015.

BENEFITS OF MULTIMODAL ANALGESIA

EFFICACY

- Improved functional outcomes
- Reduced adverse events (including drug-related, and post-op related – ie..fever, PONV,…)
- Decreased need for use of naloxone

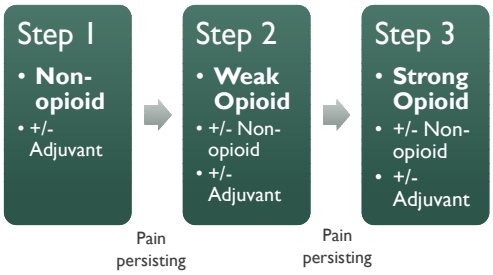
SAFETY

- Reduced doses of analgesics in the treatment plan, especially opioids
  - Federal focus on limiting opioid use
- Superior pain relief, secondary to synergistic or additive effects of the various agents in the treatment plan
- Reduce LOS
- Improved patient satisfaction[1]

1. Kehlet H, Dahl JB. *Anesth Analg.* 1993;77(5):1048-1056. 2. White PF. *Curr Opin Investig Drugs.* 2008; 9(1): 76-82. 3. Jo CH, Shin JS, Hoh J. *Eur J Orthop Surg Traumatol.* 2014; 24(3):315-322. 4. Mathiesen O, Dahl B, Thomsen BA, et al. *Eur Spine J.* 2013; 22(9):2089-2096. 5. Saraghi M, Hersh EV. *Anesth Prog.* 2013; 60(4):178-187. 6. Fu PL, Xiao J, Zhu YL, et al. *J Int Med Res.* 2010; 38(4): 1404-1412. 7. Sivrikoz N, Koltka K, Guresti E, et al. *Agri.* 2014; 26(1): 23-28. 8. Larson DW, Lovely JK, Cima RR, et al. *Br J Surg.* 2014; 101(8):1023-1030. 9. Michelson JD, Addante RA, Charlson MD. *Foot Ankle Int.* 2013; 34 (11): 1526-1534. 10. Skinner HB. *Am J Orthop.* 2004; 33(5): 5-9. 11. Titzworth et al. *J Neurosurg.* 2016;1-10. 12. Rafla W et al. J Cardiothoracic Surg 2014;9:52. 13. Karam JA. Clin Orthop Relat Res 2014;472(5):1489-95. 14. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm 15. http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

INCORPORATE MULTIMODAL ANALGESIA INTO TREATMENT

- Utilize a stepwise approach
- Recommend continuation of non-opioids for an opioid-sparing effect



Adapted from the World Health Organization (WHO) Pain Relief Ladder.

SUMMARY OF GENERAL APPROACHES

- Use an individualized, *multimodal* treatment plan to manage pain, which includes:
  - Nonpharmacologic approaches
  - Non-opioid medications
- The best approach may be to start with a *non-narcotic*
- Take extra precautions with *opioid-naïve* patients
  - Short-term trial with sufficient time to assess response before increasing the dosage
- Recognize that opioid-tolerant patients often have more complex needs

EXAMPLE OF MMA IMPLEMENTATION

KENT HOSPITAL

IMPLEMENTATION OF MMA PROTOCOLS AT KENT HOSPITAL: DRIVERS FOR CHANGE

- Joint Commission
  - Sentinel Event Alert
  - Prevention of errors
  - Prevention of duplicate orders
- Encourage use of Multimodal Approach (MMA)
- Limit occurrence of opioid-related ADEs (ORADEs)
- Our hospital specifics/background
  - Sometimes poor opioid conversions during TOC
  - Provide consistent analgesia
  - Wish list: improve patient satisfaction (HCAHPS scores)

BACKGROUND INFORMATION ON THE PROTOCOLS

- Created from analysis of inpatient opioid usage/requirements in non-surgical patients
  - Total amount of opioid used by patients [morphine equivalent doses (MED)], in a variety of medical states on first day of admission, then followed for 10 days or until discharge.
  - Sample patients did not require naloxone at any point during hospitalization

⇒ Sample deemed to have safe and effective use of opioids

SURVEILLANCE DATA

Daily Opioid Requirement (in morphine PO equivalents)	<50	51-100	101-200	201-300	>300
	"Low Dose/ Opioid Naïve"	"Medium Dose"		"High Dose/Custom"	
Surveillance Data from Kent Hospital Patients (% of patients in each category)					
Prescribed within first 24 hours	37	19	21	9	14
Actually used within first 24 hours	69	13	10	4	4
Prescribed at follow-up	33	24	21	7	15
Actually used at follow-up	66	14	9	6	5

=> High Dose

Overall Opioid Usage fo			
Average initial opioid prescribed	169.9 mg	129.5 mg	331.5 mg
Average opioid prescribed at follow-up			
Change in dose (%)	+ 12.7%	+ 7.7%	+22.2%
Opioid given in first 24 hours	63.8 mg	39.7 mg	160.0 mg
Opioid given at follow-up	77.5 mg	53.8 mg	178.5 mg
Change in dose	+ 21/5%	+ 35.5%	+ 11.5%

THE 6 ACUTE PAIN PROTOCOLS

- Breakpoints were set to distinguish 3 groups of patients:
  - Low dose (0-50 MED per day or opioid naïve)
  - Medium dose (51 – 100 MED per day)
    - Patient continues on home med of long-acting analgesic and uses this protocol to manage breakthrough pain
  - High dose (>100 MED per day)
    - Patient continues on home med of long-acting analgesic and uses this protocol to manage breakthrough pain

For each of these dose ranges, there is a regular/normal PowerPlan, and one for NPO patients

- Each protocol contains 3 steps of analgesia (and medications):
  - mild (1-3 or 'any pain >0' for purpose of medication administration)
  - moderate (pain 4-7)
  - severe (pain 8-10)

EXAMPLE OF MMA ORDER SETS: KENT HOSPITAL

- Development of 6 "Sliding Scale" Acute Pain Protocols
- Intended for use in medical patients
- For opioid-tolerant patients: Medium (50-100 MED/d) and High level (>100 MED/d)protocols

	Low Dose (<50MED/d or Opioid Naïve)	Los Dose NPO (<50MED/d or Opioid Naïve)
Level 1: Mild Pain (1-3)	Acetaminophen 650 mg PO q6h* Celecoxib 100 mg PO BID Etodolac 400 mg PO BID Ibuprofen 400 mg PO q6h	Acetaminophen 650 mg PR q6h* Acetaminophen 1000 mg IV q6h* Ketorolac 15 mg IV q6h
Level 2: Moderate Pain (4-7) Give with Level 1 drug	Tramadol 25 mg PO q6h Morphine 7.5 mg PO q4h Oxycodone 5 mg PO q4h	Morphine 4 mg IV q4h Hydromorphone 0.5 mg IV q4h
Level 3: Severe Pain (8-10) Give with Level 1 drug	Oxycodone 10 mg POq4h Morphine 4 mg IV q4h Hydromorphone 0.5 mg IV q4h	Morphine 6 mg IV q4h Hydromorphone 0.5 mg IV q3h

*Prescriber may select acetaminophen + NSAID for Mild Pain; May select only one option for Moderate and Severe Pain

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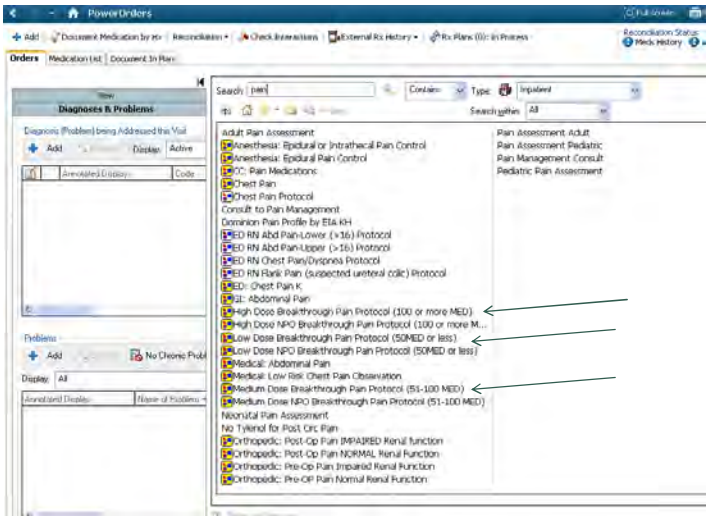
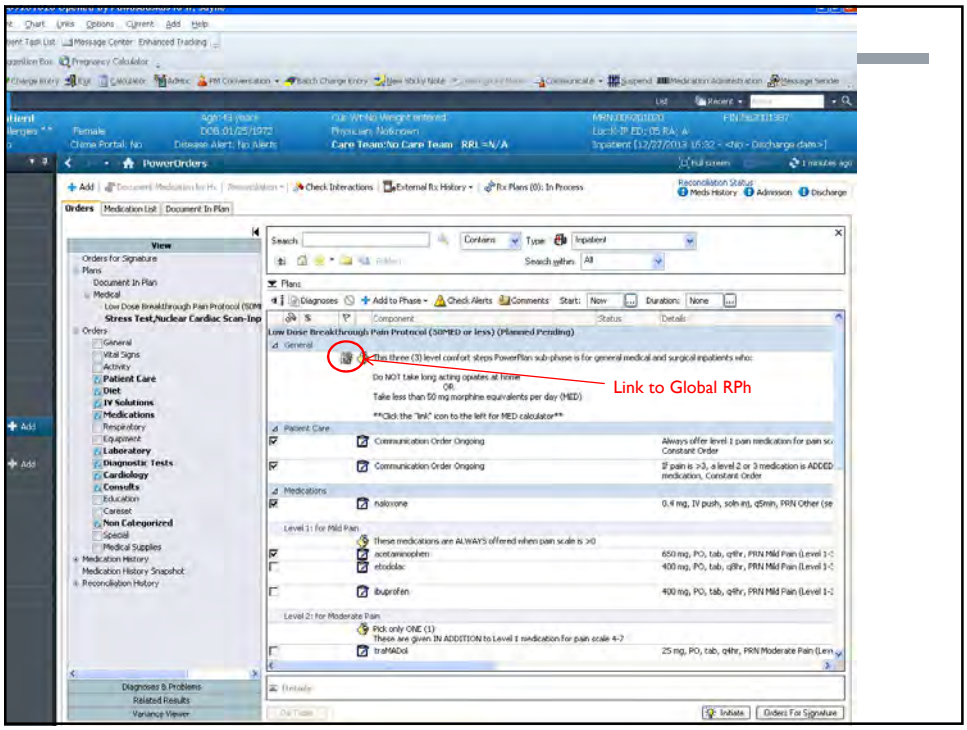
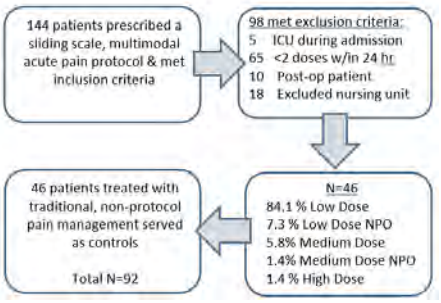

PowerOrders
Orders
Medication List
Document In Plan
Diagnoses & Problems
Adult Pain Assessment
Anesthesia: Epidural or Intrathecal Pain Control
Anesthesia: Epidural Pain Control
CC: Pain Medications
Chest Pain
Chest Pain Protocol
Consult to Pain Management
Dominion Pain Profile by ETA KH
ED RN Abd Pain-Lower (>16) Protocol
ED RN Abd Pain-Upper (>16) Protocol
ED RN Chest Pain/Dyspnea Protocol
ED RN Flank Pain (suspected ureteral colic) Protocol
ED: Chest Pain K
GI: Abdominal Pain
High Dose Breakthrough Pain Protocol (100 or more MED)
High Dose NPO Breakthrough Pain Protocol (100 or more M...
Low Dose Breakthrough Pain Protocol (50MED or less)
Low Dose NPO Breakthrough Pain Protocol (50MED or less)
Medical: Abdominal Pain
Medical: Low Risk Chest Pain Observation
Medium Dose Breakthrough Pain Protocol (51-100 MED)
Medium Dose NPO Breakthrough Pain Protocol (51-100 MED)
Neonatal Pain Assessment
No Tylenol for Post Circ Pain
Orthopedic: Post-Op Pain IMPAIRED Renal function
Orthopedic: Post-Op Pain NORMAL Renal Function
Orthopedic: Pre-Op Pain Impaired Renal Function
Orthopedic: Pre-OP Pain Normal Renal Function
Pain Assessment Adult
Pain Assessment Pediatric
Pain Management Consult
Pediatric Pain Assessment

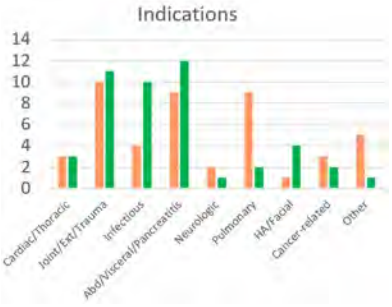

PowerOrders
Orders
Medication List
Document In Plan
Low Dose Breakthrough Pain Protocol (50MED or less) (Planned Pending)
Link to Global RPh

ANALYSIS OF MMA PROTOCOLS

6 months of data after initial implementation

Voluntary use of protocols





Results

Variable	Protocol Patients	Traditional Prescribing	p-value
Age (yrs) (±SD)	53.6(±17.86)	58(±16.11)	0.22
BMI (±SD)	30.54(±10.55)	31.88(±14.14)	0.391
Gender (% male)	37	37	1.00
Opioid Tolerant (%)	21.7	47.8	0.015
Baseline Pain Score (±SD)	7.26 (±1.89)	7.43(±2.19)	0.684
Length of Stay (days) (±SD)	3.78(±2.41)	5.20(±2.87)	0.012
Total PRN Opioid Doses (±SD)	12.7(±9.72)	24.02 (±18.28)	<0.001
Opioid MED/d (±SEM)	35.81(±5.03)	65.77(±11.40)	0.019
Total Opioid (MED) (±SEM)	122.98(±18.69)	355.11(±100.75)	0.028
Time to Analgesia (min) (±SEM)	507.52 (±85.13)	894.33 (±169.14)	0.045
Median (hr)	5.70	10	
Diarrhea (# patients)	3	2	0.353
Use of antiemetics (ave.)	1.24	3.20	0.078

CLINICAL PEARLS

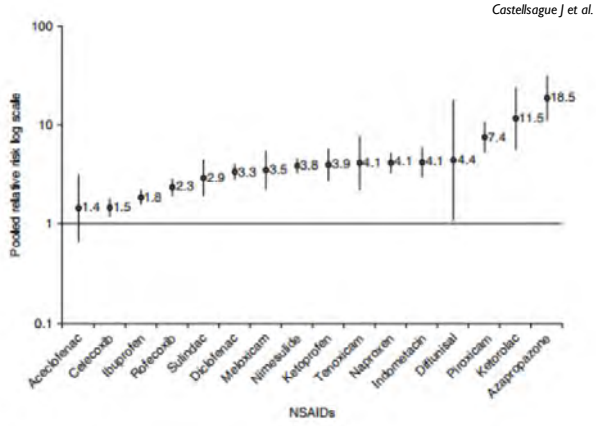
EXAMPLE OF RECOMMENDATIONS IN PUBLISHED GUIDELINES

- "Unless contraindicated, patients should receive an around-the-clock regimen of COXIBS, NSAIDS, or acetaminophen. Central regional blockade with local anesthetics should be considered."
  - *American Society of Anesthesiologists: Practice Guidelines for Acute Pain Management in the Perioperative Setting*[1]
- "The panel suggests that clinicians routinely incorporate around the clock nonopioid analgesics and nonpharmacologic therapies into multimodal analgesia regimens."
  - *American Pain Society: Guidelines on the Management of Postoperative Pain*[2]

1. *Anesthesiology 2012;116:248-73.*
2. *2. J Pain 2016;17(2):131-157.*

NSAIDS & UPPER GI COMPLICATIONS

Castellsague J et al. Drug Saf 2012;35(12):1127-1146.



NSAIDS & CARDIOVASCULAR EVENTS

McGettigan P et al. PLoS Med 2011;8(9):e1001098.

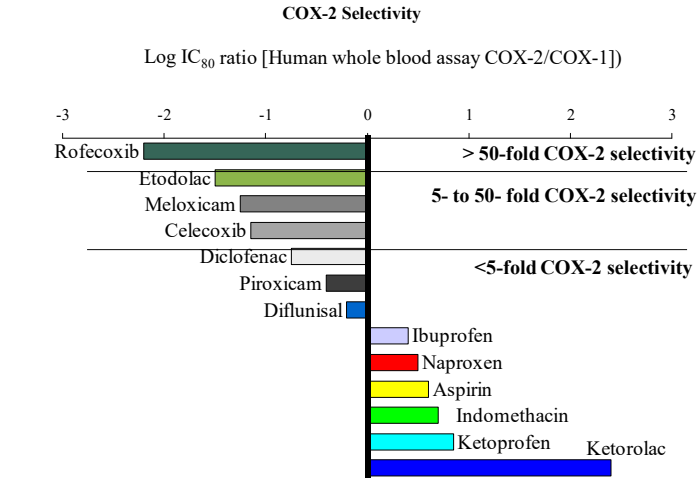
Cardiovascular Risks with Individual NSAIDs

Table 1. Summary of the numbers of studies and overall results.

Drug	Case-Control Studies		Cohort Studies		Total Number of Studies	Pooled RR (95% CI)	Heterogeneity		
	Number of Studies	Number of Exposed Cases/Controls	Number of Studies	Number of Person-Years of Exposure			Cochran *Q*	*p*-Value	I^2
Naproxen	24	3,103/24,468	17	159,824	41	1.09 (1.02, 1.16)	143.1	<0.0001	70.70%
Ibuprofen	21	5,716/52,207	17	255,621	38	1.18 (1.11, 1.25)	226.7	<0.0001	83.90%
Celecoxib	20	1,496/12,755	15	179,429	35	1.17 (1.08, 1.27)	236.9	<0.0001	84.40%
Rofecoxib	19	1,662/10,827	15	126,279	34	1.45 (1.33, 1.59)	227.8	<0.0001	84.20%
Diclofenac	16	3,181/13,523	13	50,736	29	1.40 (1.27, 1.55)	224.4	<0.0001	86.60%
Indomethacin	11	788/4,406	3	9,350	14	1.30 (1.19, 1.41)	20.8	0.1	52.60%
Piroxicam	7	288/1,216	1	0[a]	8	1.08 (0.91, 1.30)	8.6	0.3	18.90%
Meloxicam	6	240/714	1	0[a]	7	1.20 (1.07, 1.33)	2.8	0.7	0%
Etodolac	4	464/4,115	1	8,994	5	1.55 (1.28, 1.87)	18.9	0.01	52.70%
Etoricoxib	4	60/116	0	0	4	2.05 (1.45, 2.88)	0.7	0.9	0%
Valdecoxib	1	2/2	4	5,634	5	1.06 (0.81, 1.36)	13.4	0.004	77.60%

[a]Studies reporting adjusted risk estimates did not all report person-years of exposure.

doi:10.1371/journal.pmed.1001098.t001



Adapted from Warner TD et al.
Proc Natl Acad Sci USA 1999;96:7563-68.

- Focus on accidental opioid overdoses
- Database from 2004 – 2011 on opioid-related ADEs
  - 47% wrong dose
  - 29% improper patient monitoring
  - 11% others (e.g.drug interactions, excessive doses)

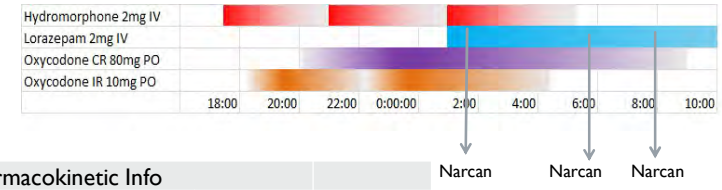
CONSIDER RISKS FOR RESPIRATORY DEPRESSION

- Sleep apnea
- Morbid obesity (BMI >30) with high risk of sleep apnea
- No recent opioid use
- Post-op; thoracic or upper abdominal
- Functional status
- Older age
- Longer length of time given anesthesia during surgery
- Receiving other sedating drugs: benzo's, antihistamines, sedative, CNS depressants
- Pre-existing cardiac or pulmonary dz; major organ failure
- Smoker

PATIENT-SPECIFIC RISK FACTORS

- 48 y.o. ♂
- Problem list: diverticulitis with multiple abdominal surgeries, recent colectomy with complications; arthritis, anxiety, pain
- BMI = 32.7
- + tobacco: 1 ppd (addressed in ID consult)
- + EtOH, h/o pancreatitis
- No documented respiratory, cardiac, renal or hepatic disease
- Combination of CNS depressant drugs

PHARMACOKINETIC EXAMPLE



Pharmacokinetic Info		
	Tmax	T 1/2
Oxycodone CR	2.5hrs	5-8hrs
Oxycodone IR	1.5hrs	4hrs
Lorazepam IV	15-20 min	12-14hrs
Hydromorphone IV	15 min	2.3hrs

RECOMMENDATIONS

- Full body skin assessment
  - E.g. look for fentanyl or buprenorphine patch; incisions from implanted pumps
- Assess respirations
  - set frequency
    - Consider when dose changes or addition of more opioids
- High-risk opioids identified
  - Methadone
  - Fentanyl
  - IV hydromorphone
- Use technology to reduce system errors
  - SmartPumps
  - CPOE
  - PCA to reduce risk of oversedation

Predictors of naloxone use for respiratory depression and oversedation in hospitalized adults

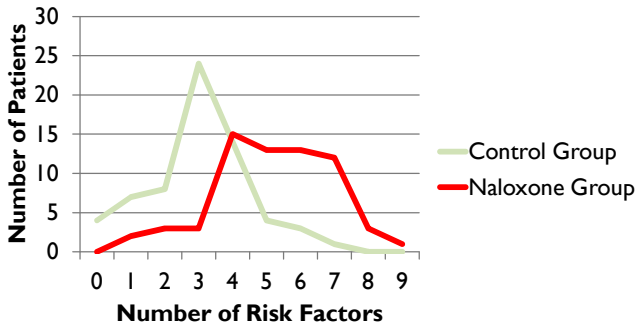
Jayne Pawasauskas, Benjamin Stevens, Rouba Youssef, and Michelle Kelley

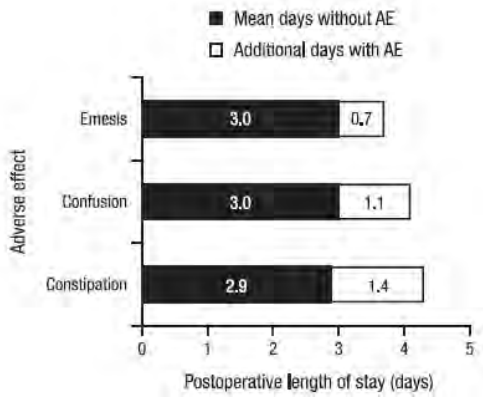
Am J Health-Syst Pharm—Vol 71 May 1, 2014

Table 2.
Association Between Risk Factors and Treatment With Naloxone for Opioid-Associated Oversedation or Respiratory Depression[a]

Risk Factor	Odds Ratio (95% Confidence Interval)
Renal disease	6.034 (2.565–14.195)
Cardiac disease	5.829 (2.687–12.642)
Concurrent sedating medication	4.750 (1.949–11.578)
Smoking history	4.421 (2.114–9.245)
Respiratory disease	3.600 (1.742–7.441)
Hepatic disease	2.444 (0.798–7.486)
Age range, yr	
61–70	1.739 (0.791–3.821)
71–80	1.876 (0.688–5.119)
>80	1.227 (0.505–2.985)
BMI of ≥30 kg/m^2	1.132 (0.568–2.257)
Opioid naive	0.317 (0.150–0.667)

RISK FACTOR GROUPING GRAPH





Pizzi et al. Pharmacotherapy 2012;32(6):502-514.

SCOPE OF OPIOID-INDUCED CONSTIPATION

- Estimated that almost half of patients who use strong opioids will report constipation
- Risk factors include older patients, women, and longer durations of opioid use
- Patients opt to decrease doses of opioids, skip doses, or stop using in order to avoid OIC.
- QOL/patient satisfaction
- Morphine commonly reported/transdermals & injectables less so

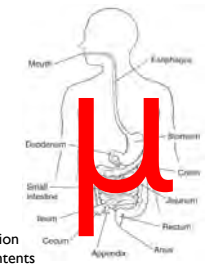
Kalsa E et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80. Bell TJ et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European patient survey (PROBE 1). Pain Med 2009;10:35-42.

PATHOPHYSIOLOGY OF OIC (AKA OBD: OPIOID BOWEL DYSFUNCTION)

μ, K, δ receptors in GI tract:

Inhibited movement through small and large intestines

Increased water absorption absorption from bowel contents



K, δ

K, δ

Esophageal contractions (non-peristaltic)

Decreased gastric motility and emptying

Increased pyloric sphincter tone

Decreased GI, biliary and pancreatic secretions

Increased anal sphincter tone

Constriction of Sphincter of Oddi

Poppagallo M. Am J Surg 2001;182:115-85. Kraichely RE et al. Aliment Pharmacol Ther 2010;31:601-6. Camilleri M, et al. Neurogastroenterol Motil 2014;26:1386-95.

CONSTIPATION DEFINITIONS

Constipation

- At least 2 of the following symptoms over 3 months:
  - <3 BMs per week
  - Straining
  - Lumpy or hard stools
  - Sensation of anorectal obstruction
  - Sensation of incomplete defecation
  - Present for at least 6 months

Opioid-Induced Constipation

- Opioid-treatment for at least one week
- <3 BMs per week
- Straining
- Sense of incomplete evacuation
- Harder stool

Camilleri M, et al. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014;26:1386-95. Webster LR. Opioid-induced constipation. Pain Medicine 2015;16:516-521.

MEASURES OF OIC

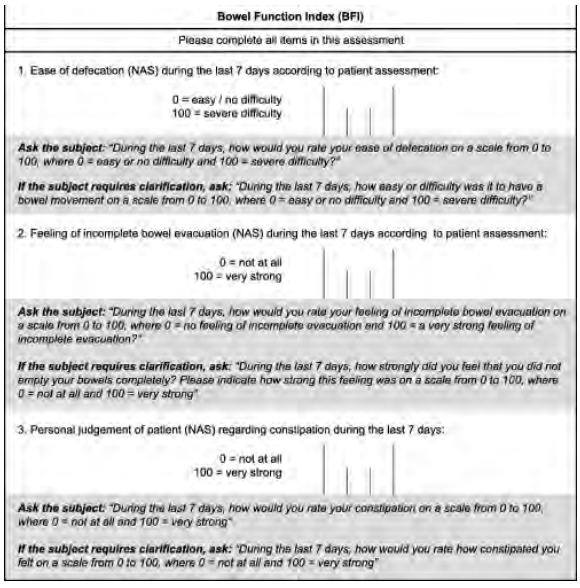
Bowel Function Diary

- Validated in a multicenter observational study of patients with chronic, non-cancer pain.
- 4 items that patients complete after each BM
- 5 items that patients complete each evening to capture symptoms within previous 24 hr
- Portion where patient indicates any tx's for constipation within previous 24 hr

Bowel Function Index (BFI)

- 3-item, clinician-administered assessment
- Data from 3 multi-center studies in patient with cancer and non-cancer pain
- Patients rate 3 areas:
  - their perception of ease of defecation
  - feeling of incomplete bowel emptying
  - personal judgment of constipation

Camilleri et al. Am J Gastroenterol 2011;106:487-506. Rentz AM, et al. J Med Econ 2009;12:371-83.



Bowel Function Index (BFI)

Please complete all items in this assessment

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:

0 = easy / no difficulty
100 = severe difficulty

Ask the subject: *"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*

If the subject requires clarification, ask: *"During the last 7 days, how easy or difficulty was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:

0 = not at all
100 = very strong

Ask the subject: *"During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"*

If the subject requires clarification, ask: *"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

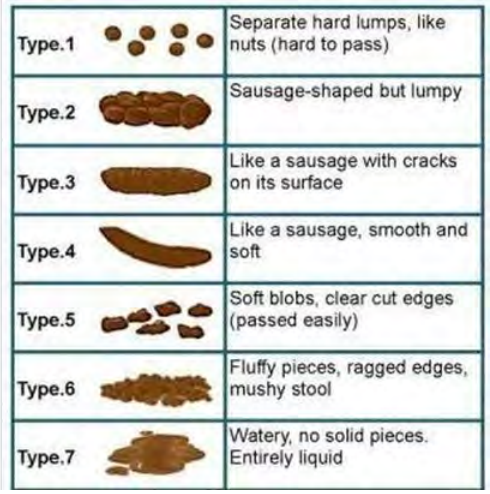
3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:

0 = not at all
100 = very strong

Ask the subject: *"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

If the subject requires clarification, ask: *"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

Rentz AM et al. J Med Econ 2009;12:371–83. Argoff et al. Pain Med 2015;16:2334-2337.



- May be useful for advanced illness, cognitive impairment or other communication barriers.

Lewis SJ et al. Scand J Gastroenterol 1997 Sep;32(9):920-4.

'OLDER' THERAPIES FOR OIC: LAXATIVES

Mechanism of Action	Drug	Typical Dose	Onset of Action
Stool Softener	Docusate sodium	100 mg PO daily	12 hr to 3 days
Osmotic agents	polyethylene glycol (Miralax) Magnesium salts Lactulose Glycerin suppository	17g pwdr in 4-8 oz of beverage MgOH 400-800mg PO daily; Mg citrate 195-300mL PO daily 10-20g PO daily 1 supp PR daily PRN	1-4 days 0.5 – 6 hr 1-2 days 15-30 min,
Stimulants	Bisacodyl Senna	10-20mg PO daily; also PR 17.2mg PO daily	6-12 hr (PO); 20 min to 3 hr (PR) 6-12 hr
Enema	Mineral oil Sodium phosphate	5-45 mL as single dose 4.5 oz as single dose	2-15 min 2-5 min

TARGETED DRUG THERAPIES

PAMORAS

"Peripherally-acting mu-opioid receptor antagonists"

Block opioid receptors in the GI tract → restore function of the enteric nervous system

PAMORAs currently available for Opioid-Induced Constipation:

- Methylnaltrexone (Relistor®)
- Naloxegol (Movantik™)
- Alvimopan (Entereg®) – only for in-hospital use

Other:

- Lubiprostone (Amitiza®)

METHYLNALTREXONE (RELISTOR®)

- Peripherally acting only (poorly crosses BBB)
- Dosing:
  - OIC with CNCP is 12 mg SC daily
  - OIC with advanced illness is weight-based, QOD PRN
    - 50% reduction for Clcr <30 ml/min.
- Ability to induce SBM ~50-60% in clinical trials of this drug
- Contraindicated if GI obstruction
- ↓ dose for patients on methadone
  - Experience increased sensitivity to ADRs of PAMORAs (abdominal pain, flatulence, nausea)

REVIEW OF METHYLNALTREXONE

- Siemens W. et al. 2016. Ther Clin Risk Manag 2016;12:401-12.
  - Meta-analysis of 7 studies (n=1860): Clinical trials with MNTX and placebo, one systematic review
  - MNTX showed more rescue-free BM within 4 hr after first dose vs placebo
  - Patient Reported Outcomes: generally more MNTX patients reported 'improvement' or satisfaction with treatment
  - Global Burden Measures: improvement in constipation-related QOL with MNTX
  - Higher incidence of abdominal pain with MNTX; nausea & diarrhea not significantly greater although trends seen

Siemens W. et al. 2016. Ther Clin Risk Manag 2016;12:401-12.

NALOXEGOL (MOVANTIK™)

- Derivative of naloxone
- Pegylated structure inhibits crossing of BBB
- Recommended dose is 25 mg PO daily; reduce to 12.5 mg if patient cannot tolerate ADRs (abdominal pain, diarrhea, nausea)
  - Start at 12.5 mg if Clcr<60 and increase if needed
- Cmax and AUC ↑ with high fat meals → recommend dosing on empty stomach
- 3A4 metabolism
  - Contraindicated with strong 3A4 inhibitors, grapefruit juice
  - Start at 12.5 mg dose if moderate 3A4 inhibitors

STUDIES OF NALOXEGOL

- **Chey et al. 2014**: 2 Phase 3 controlled studies (12.5 mg, 25 mg, or placebo); 12 wk duration (KODIAK studies)
  - Evaluated mean change from baseline of SBMs
  - Significant ↑ of SBMs in naloxegol groups
  - 25 mg dose had better responses and faster time to first SBM
  - Patients also had significant improvements in sx such as straining

- **Lawson et al. 2016**: Follow-up to KODIAK studies; 3 12-week studies of health state utility measures
  - Treatment with naloxegol improves patients' health state utility
  - Results driven mainly by relief of their constipation

- **Webster et al. 2014**: Open label study of 25 mg vs. laxatives over 52 weeks evaluated safety and tolerability.
  - Frequency of ADRs in naloxegol 82% vs. 72% in laxative group, with abdominal pain, diarrhea, nausea, headache, flatulence more common in naloxegol group

Chey WD et al. N Engl J Med 2014;370:2387-2396. Lawson R et al. Adv Ther 2016 epub ahead of print. Webster L et al. Aliment Pharmacol Ther 2014;40:771-9.

LUBIPROSTONE (AMITIZA®)

- Activator or interstitial epithelial CIC-2 chloride channels → increase transport of fluid into intestine
- Dosing for OIC is 24 mcg PO BID; take with food
- Time to first BM after initial dose of lubiprostone averages ~2
  ~6.
- Studies in trials up to 9 months.
- Diphenylheptane opioids (i.e. methadone) decrease effectiveness of lubiprostone

LUBIPROSTONE, CON'T

- Decrease dose to 16mcg ID in patients with moderate hepatic dysfunction (Child-Pugh class B), and 8 mcg BID in patients with severe dysfunction(Child-Pugh class C)
- Contraindicated if GI obstruction
- Dyspnea has been noted soon after dose; often resolves in a few hours
- Most common ADRs reported include nausea, diarrhea, and abdominal distention.

STUDIES OF LUBIPROSTONE

- **Cryer et al. 2014:**
  - Randomized, double-blind, placebo-controlled
  - n=418, CNCP with OIC
  - Lubiprostone 24mcg PO BID vs placebo for 12 wks
  - Lubiprostone significantly better at improving SBMs (3.3 vs. 2.4 per week, p=0.005)
  - More pts had first SBM within 24 hrs in lubiprostone group (p=0.018)
  - Lubiprostone group reported more improvement in symptoms of straining, discomfort, stool consistency, and constipation severity
- **Jamal et al. 2015**
  - Randomized, double-blind placebo-controlled
  - N=432; CNCP with OIC
  - Lubiprostone 24 mcg PO BID vs placebo for 12 weeks
  - Lubiprostone significantly better at improving SBMs (3.2 vs 2.4, p=0.001)
  - Time to first SBM significantly shorter with lubiprostone (23.5 hr vs. 37.7 hr, p=0.004)
  - Improvements in straining, stool consistency, constipation severity
  - No change in QOL or use of rescue meds

Cryer et al. Pain Med 2014;15:1825-1834. Jamal MM et al. Am J Gastroenterol 2015;110(5):725-732.

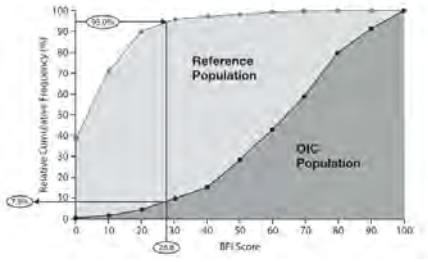
CLINICAL PEARLS

- Patients using PAMORAs often still need to use laxatives
  - Generally, stop pre-existing laxatives, resume if OIC persists 3 days after PAMORA tried
- Targeted therapies are considered second-line agents after laxatives, lifestyle changes (incr. fluid intake, dietary fiber, exercise), or opioid rotation

GUIDELINES FOR OIC MANAGEMENT

- Pain Guidelines….
- **Camilleri M et al**. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014;26:1386-1395.
  - Definition & diagnosis of OIC
  - Assessment tools
  - Treatment approaches including laxatives & targeted drug therapy
- **Argoff et al**. Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation. Pain Med 2015; 16: 2324–2337.
  - Best methods to assess OIC
    - Bowel Function Index
  - Create threshold for consideration of targeted therapy for OIC

CONSENSUS STATEMENT ON WHEN TO USE PRESCRIPTION OIC TREATMENTS



Argoff et al. Pain Med 2015;16:2334-2337.

CLINICAL PEARLS, ETC.

- Consider a prescription treatment if BFI score ≥ 30.
- Long-term effects are still under investigation
- Consider drug interactions that require dosage adjustments or avoidance of use

WHAT ABOUT THOSE PATIENTS WHO ARE ON METHADONE OR SUBOXONE???

METHADONE

- Used for pain in late 1940's
- Mainly used in opioid addiction treatment in 1960's
  - Suppresses cravings, withdrawal symptoms, and euphoric effects for 24-36 hrs
- Increasing use as analgesic since late 1990's
  - Some advantages as an analgesic
  - Cause for concern?

METHADONE, CON'T

- R-methadone = μ opioid agonist
- S-methadone = NMDA receptor antagonist; blocks reuptake of 5-HT & NE
- Long elimination $t_{1/2}$
- Toxicity seen days after dose
- Potential for QTc prolongation
  - Greatest with higher doses (ex. >100-120 mg)
  - Caution with antipsychotics & TCAs
- Metabolized by P450 3A4, 2B6, 2D6

METHADONE DRUG INTERACTIONS

↑ Methadone Levels

- Quinolones
- Macrolides
- Azole antifungals
- SSRIs
- Ritonavir

↓ Methadone Levels

- Rifampin
- CBZ
- Phenytoin
- Efavirenz, Nelfinavir, Amprenavir, Darunavir

BUPRENORPHINE

- Indications: Substance Abuse
  - SL tablets
  - Transmucosal film (buccal & sublingual)
  - Subdermal implant
  - Moderate or Severe Pain
    - Transdermal patch
    - Buccal film
    - Parenteral
- Phenanthrene derivative; Partial μ agonist; k antagonist
- High affinity and binding capacity for opioid receptors
  - Buprenorphine slowly dissociates from receptors
- Ceiling effect; high protein binding

MU OPIOID RECEPTOR SATURATION

Buprenorphine strength (SL tablets)	Receptor saturation
2 mg	~ 40-50%
16 mg	~ 80% or more
32 mg	~ 84 % or more

Still have space for receptors

SURGICAL PATIENTS

IV NSAIDS

Regional Nerve Blocks

Gabapentinoids

SNRIs

Adjuvant Medications

Sedatives

IV Acetaminophen

Muscle Relaxants

Ketamine

SURGERY: BUPRENORPHINE

Elective

- Mild (Minor Surgery) – Use Adjuvants
- Moderate to Severe – taper 2-4 weeks prior to surgery*
  - If buprenorphine was for pain, can supplement with short-acting pure opioid agonists
    - Careful for toxicity from non-opioid components; illicit use
  - Use in-patient pain protocols
    - When post-op pain resolves, restart buprenorphine; titrate if high dose

Emergent

(Tends to be moderate or severe)

1. Maximize adjuvants
2. High doses of short-acting opioids (while continuing buprenorphine)
   - Consider lipophilicity
   - If buprenorphine is discontinued, extra cautionary steps are required

* High relapse potential

ACUTE PAIN + METHADONE OR SUBOXONE:

Option 1:	Option 2:	Option 3:
Hold Suboxone/ Methadone;	Continue same dose Suboxone/ Methadone;	Continue Suboxone/ Methadone;
Use other opioids to manage acute pain	Use other opioids to manage acute pain	Use higher dosing: change once daily dosing to q 6-8 hours

WHAT YOU MAY SEE FOR PATIENTS WITH SUBSTANCE ABUSE HISTORY…

- Long-acting meds used frequently
- If short-acting used, specific times may be given
  - Ex: "1 tab at _____ PM" rather than "TID PRN"
- Different methods of dosing… refer to suboxone and methadone info
- Use of WHO Analgesic Ladder
  - Considering adjuvants and non-opioids carefully
- Multimodal drug therapy

QUESTIONS??

THANK YOU!