Pain Management After Orthopedic Surgery: *Use of Multimodal Analgesia*

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Learning Objectives

- Examine literature addressing the use of a multimodal analgesic strategy for post-operative orthopedic patients
- 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 post-operative patients and avoidance of opioid-related adverse drug effects
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.

Opioids
α₂-agonists
NMDA antagonists
Acetaminophen
Anti-epileptics
TCAs & similar

Local Anesthetics
Opioids
α₂-agonists

NSAIDs/COXIBs
Local Anesthetics
Anti-epileptics
Non-Opioids to Consider:

DEVELOPMENT OF A MMA PROTOCOL

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

Base multimodal regimen on:

- Acetaminophen
- NSAIDs
  - Ketorolac, ibuprofen, celecoxib, etodolac
- NMDA receptor antagonists
  - Ketamine
- Alpha2 agonists
  - Clonidine, dexmedetomidine
- Gabapentinoids
  - Gabapentin, pregabalin
- Local anesthetics
  - Bupivacaine, lidocaine, liposomal bupivacaine
### Examples of MMA in surgical patients

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Medication Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Operative</td>
<td>Acetaminophen, Gabapentin or Pregabalin, NSAID, Opioid</td>
</tr>
<tr>
<td>Intra-Operative</td>
<td>Regional analgesia with local anesthetic or opioid, Epidural or intrathecal opioid</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>Opioid (i.e. PCA or other), Acetaminophen, NSAID, Gabapentin or Pregabalin</td>
</tr>
</tbody>
</table>

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

- “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

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:

EFFICACY

BENEFITS OF MULTIMODAL ANALGESIA

- Improved functional outcomes\textsuperscript{1,2,8}
- Reduced adverse events (including drug-related, and post-op related – ie..fever, PONV,...)\textsuperscript{11,12,13}
- Decreased need for use of naloxone\textsuperscript{11}

SAFETY

- Reduced doses of analgesics in the treatment plan, especially opioids\textsuperscript{1,2,3,4}
  - Recent federal focus on limiting opioid use\textsuperscript{14,15}
- Superior pain relief, secondary to synergistic or additive effects of the various agents in the treatment plan\textsuperscript{1,2,5,6,7}
- Fewer “analgesic gaps”\textsuperscript{1,2}
- Reduce LOS\textsuperscript{9}
- Improved patient satisfaction\textsuperscript{10}

Recent Controlled Trials Support Multimodal Analgesia in Practice

- The value of multimodal analgesia has been demonstrated in multiple surgical patient types
  - Brooks et al. 2015
    - Osteotomy (N=230)
  - Garcia et al. 2013
    - Lumbar surgery (N=22)
  - Jo et al. 2014
    - Arthroscopic rotator cuff surgery (N=54)
  - Lamplot et al. 2014
    - Total knee arthroplasty (N=36)

Incorporate Multimodal Analgesia into treatment

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

Step 1
• Non-opioid
  • +/- Adjuvant

Step 2
• Weak Opioid
  • +/- Non-opioid
  • +/- Adjuvant

Step 3
• Strong Opioid
  • +/- Non-opioid
  • +/- Adjuvant

Pain persisting

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 order sets: Kent Hospital  
Warwick, RI

- 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

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

<table>
<thead>
<tr>
<th>Level 1: Mild Pain (1-3)</th>
<th>Low Dose (&lt;50MED/d or Opioid Naïve)</th>
<th>Los Dose NPO (&lt;50MED/d or Opioid Naïve)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acetaminophen 650 mg PO q6h*</td>
<td>Acetaminophen 650 mg PR q6h*</td>
</tr>
<tr>
<td></td>
<td>Celecoxib 100 mg PO BID</td>
<td>Acetaminophen 1000 mg IV q6h*</td>
</tr>
<tr>
<td></td>
<td>Etodolac 400 mg PO BID</td>
<td>Ketorolac 15 mg IV q6h</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen 400 mg PO q6h</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2: Moderate Pain (4-7)</th>
<th>Give with Level 1 drug</th>
<th>Tramadol 25 mg PO q6h</th>
<th>Morphine 7.5 mg PO q4h</th>
<th>Oxycodone 5 mg PO q4h</th>
<th>Morphine 4 mg IV q4h</th>
<th>Hydromorphone 0.5 mg IV q4h</th>
</tr>
</thead>
</table>

| Level 3: Severe Pain (8-10) | Give with Level 1 drug | Oxycodone 10 mg PO q4h | Morphine 4 mg IV q4h | Hydromorphone 0.5 mg IV q4h | Morphine 6 mg IV q4h | Hydromorphone 0.5 mg IV q3h |
Clinical Pearls
Acetaminophen

- Doesn’t show anti-inflammatory properties in vivo.
- Good analgesic, anti-pyretic
- Efficacy for nociceptive pain, ∅ neuropathic pain
- Prominent central activity
- Do not exceed 4 g/day
  - Hepatotoxicity
  - Ceiling effect
- Available in parenteral formulation
NSAIDs

- How do select a specific drug?
  - What do you need the drug to do?
    - Fever
    - Pain (acute injury-related, menstrual-related, etc)
    - Inflammation
    - Anti-platelet
NSAIDs – clinical uses

- Analgesic
  - Acetaminophen
  - Ketorolac

- Analgesic + anti-inflammatory
  - Aspirin
  - Non-selective NSAIDs
    - Ibuprofen, ketoprofen, naproxen, indomethacin, etodolac
  - COX-2 selective NSAIDs
    - Celebrex (celecoxib)
  - Non-acetylated NSAIDs
    - Trilisate (choline magnesium trisalicylate), salsalate
NSAIDs – selection, con’t

- Can patient take meds orally?
  - Parenteral
    - Toradol (ketorolac), acetaminophen, ibuprofen, diclofenac
  - Rectal suppositories
    - Aspirin, Acetaminophen

- Daily dosing (BID vs. TID or QID)

- Concern for organ systems
  - GI mucosa, kidneys, platelets, bone healing
  - Cardiovascular
    - Naproxen safest
Arachidonic Acid Pathway

Cell Injury → Phospholipase

Arachidonic Acid

Cyclooxygenase

Intermediate Compounds (PGG₂, PGH₂)

Lipoxygenase

5 HPETE, 15 HPETE → Leukotrienes

Thromboxane A₂

Prostaglandins: PGE₂, PGD₂, PGF₂α, PGF₂α
COX-2
Arachidonic Acid Pathway

Arachidonic Acid

Cox-1
Produces protective prostaglandins

Cox-2
Induced at inflammation site
Produces prostaglandins for inflammation and pain

NSAIDs

Stomach
Intestine
Kidney
Platelet

Site of inflammation

Cox-2 Selective Inhibitor
Special Considerations

- **Anti-platelet effects**
  - Aspirin: irreversible
  - Ibuprofen (& other NSAIDs): reversible

- **Anti-inflammatory effects**
  - Generally use higher doses than those for analgesia
    - Ex: Ibuprofen 400 mg TID – QID for inflammation
COX-2 Selectivity

- NSAIDs marketed as COX-2 selective
  - Celebrex (celecoxib)
    - 100-200 mg BID
    - Warning if sulfa allergy

- “Non-selective” NSAIDs have different degrees of COX selectivity
COX-2 Selectivity

Log IC$_{50}$ ratio [Human whole blood assay COX-2/COX-1])

-3  -2  -1  0  1  2  3

Rofecoxib
Etodolac
Meloxicam
Celecoxib
Diclofenac
Piroxicam
Diflunisal
Ibuprofen
Naproxen
Aspirin
Ketoprofen
Indomethacin
Ketorolac

> 50-fold COX-2 selectivity
5- to 50- fold COX-2 selectivity
<5-fold COX-2 selectivity

Adapted from Warner TD et al.
Proc Natl Acad Sci USA 1999;96:7563-68.
Pregabalin (Lyrica®)

- Schedule V
- For diabetic peripheral neuropathy and postherpetic neuralgia
- Gamma-aminobutyric acid analog with similar pharmacology and side effects as gabapentin
- Binds to alpha$_2$-delta protein on voltage-gated calcium channels
- Studied doses range from 150-600 mg/d in 3 divided doses. Adjust dose for renal insufficiency (Clcr <60)
- Side effects: dizziness, somnolence, dry mouth, peripheral edema, blurred vision, weight gain, difficulty concentrating
- May increase CPK – monitor for rhabdo
- Monitor for ↓ platelets or ↑PR
Gabapentin (Neurontin)

- Data support its use in diabetic neuropathy, post-stroke pain, and neuropathic cancer pain
- Many clinicians choose gabapentin as first-line agent due to side effect profile and interactions
- Dose 100-300 mg QD, ↑ to TID dosing to a max dose of 3600 mg QD
  - Dose adjust for renal impairment
- Drowsiness is most common side effect
• 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

#### Tmax and T 1/2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Tmax</th>
<th>T 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone CR</td>
<td>2.5hrs</td>
<td>5-8hrs</td>
</tr>
<tr>
<td>Oxycodone IR</td>
<td>1.5hrs</td>
<td>4hrs</td>
</tr>
<tr>
<td>Lorazepam IV</td>
<td>15-20 min</td>
<td>12-14hrs</td>
</tr>
<tr>
<td>Hydromorphone IV</td>
<td>15 min</td>
<td>2.3hrs</td>
</tr>
</tbody>
</table>

*Note: Narcan administrations are marked on the graph.*
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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>6.034 (2.565–14.195)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>5.829 (2.687–12.642)</td>
</tr>
<tr>
<td>Concurrent sedating medication</td>
<td>4.750 (1.949–11.578)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>4.421 (2.114–9.245)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>3.600 (1.742–7.441)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>2.444 (0.798–7.486)</td>
</tr>
<tr>
<td>Age range, yr</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>1.739 (0.791–3.821)</td>
</tr>
<tr>
<td>71–80</td>
<td>1.876 (0.688–5.119)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1.227 (0.505–2.985)</td>
</tr>
<tr>
<td>BMI of ≥30 kg/m²</td>
<td>1.132 (0.568–2.257)</td>
</tr>
<tr>
<td>Opioid naive</td>
<td>0.317 (0.150–0.667)</td>
</tr>
</tbody>
</table>
Risk Factor Grouping Graph

Number of Risk Factors

Number of Patients

Control Group
Naloxone Group
Adverse effect

- Emesis: Mean days without AE = 3.0, Additional days with AE = 0.7
- Confusion: Mean days without AE = 3.0, Additional days with AE = 1.1
- Constipation: Mean days without AE = 2.9, Additional days with AE = 1.4

Postoperative length of stay (days)
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

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
- 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

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

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

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

# ‘Older’ Therapies for OIC: Laxatives

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

  - 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

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

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 ~24 hrs; NNT ~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

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….

  - Definition & diagnosis of OIC
  - Assessment tools
  - Treatment approaches including laxatives & targeted drug therapy

  - 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

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
QUESTIONS??
THANK YOU!