Methods to Reduce and Treat Opioid Induced Adverse Events

Raymond Sinatra, MD, PhD
Opioid Analgesics

- Improved Pain Control
- Annoying Side Effects
- Life Threatening Side Effects
Opioid Induced Adverse Events

**Acute Pain**
- Nausea
- Vomiting
- Confusion
- Excessive Sedation
- OBD- Ileus
- Pruritus

**Chronic Pain**
- Nausea
- Confusion
- Sedation
- OBD- Constipation
- Physical Dependence
- Psychological Dependence
# Opioid Side Effects May Contribute To Under-Management of Pain

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea(^1,^2,^3)</td>
<td>24%-54%</td>
</tr>
<tr>
<td>Vomiting(^2,^3)</td>
<td>15%-39%</td>
</tr>
<tr>
<td>Constipation(^3)</td>
<td>10%</td>
</tr>
</tbody>
</table>

Patients Rank Vomiting as the Most Undesirable Outcome, Even More Undesirable Than Pain

<table>
<thead>
<tr>
<th>Rank</th>
<th>Postoperative Anesthesia Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
</tr>
<tr>
<td>2</td>
<td>Gagging on endotracheal tube</td>
</tr>
<tr>
<td>3</td>
<td>Incisional pain</td>
</tr>
<tr>
<td>4</td>
<td>Nausea</td>
</tr>
<tr>
<td>5</td>
<td>Recall without pain</td>
</tr>
<tr>
<td>6</td>
<td>Residual weakness</td>
</tr>
<tr>
<td>7</td>
<td>Shivering</td>
</tr>
<tr>
<td>8</td>
<td>Sore throat</td>
</tr>
<tr>
<td>9</td>
<td>Somnolence</td>
</tr>
</tbody>
</table>

N=101; $F$-test <0.01.

Patient Concerns Over Side Effects Are Greater Than Fear of Pain

Post-Operative Recovery Period: Patient Concerns

- Nausea & Vomiting: 49%  
- Pain: 27%  
- Impaired Alertness: 13%

(N=220)

Multimodal Approach to Pain Management

Nontraditional techniques
- Accupuncture
- TENS
- Physical Therapy
- Relaxation
- Therapeutic Massage

Interventional Techniques
- Facet block
- Spinal Stimulation
- Neurolysis

Anti-inflammotary Agents
- NSAIDS, APAP
- Cox-2 Inhibitor

Anti-neuropathics
- Gabapentin
- Pregabalin
- Ketamine
- Cymbalta
- TCA's

Opioid Foundation

Neural Blockade
- Lidoderm Patch
- Exparel

Opioid Induced Nausea and Vomiting
# Prevalence of PONV

<table>
<thead>
<tr>
<th>Overall</th>
<th>Up to 30% for <em>all</em> surgeries and patient populations(^1\textsuperscript{–}^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td>About 40% of patients treated at outpatient surgery centers(^4)</td>
</tr>
<tr>
<td><strong>Breakthrough</strong></td>
<td>More than 30% of patients receiving prophylactic antiemetics(^3)</td>
</tr>
</tbody>
</table>

# Global Risk Factors for PONV

| **Patient** | **Primary Predictors:** Female sex, history of PONV or motion sickness, nonsmoker, use of postoperative opioids¹  
**Additional Risk Factors:** Younger age (in adults),²⁴ history of migraine,⁵ preoperative anxiety, coexisting medical conditions, presence of pain⁴ |
| --- | --- |
| **Surgery** | **Type of Procedure:** Plastic, orthopedic, ophthalmologic, ENT, gynecologic (non-D&C), laparoscopic⁶  
**Length of Procedure:** Longer duration² |
| **Anesthesia** | General anesthesia² Use of Opioids, Use of N2O |

1. Apfel CC et al. *Anesthesiology*. 1999;91:693–700,  
Nearly 80% of PONV occurs within 48 hours. Nearly 65% of patients did not experience PONV symptoms until after leaving the recovery room. Only 12% of patients experienced PONV symptoms solely in the recovery room.

Impact of Multiple Patient-Related Risk Factors*

Risk of PONV Increased Based on Number of Primary Risk Factors Present

Patients With PONV, %

No Risk Factors | 2 Risk Factors | 4 Risk Factors
---|---|---
10% | 21% | 79%

Primary Risk Factors:
- Female sex
- History of PONV or motion sickness
- Nonsmoking
- General anesthesia and use of postoperative opioids

*Validated in 2,722 adult patients receiving inhalational anesthesia.
Key Neurotransmitters in the Emetic Reflex Center

- Opioid receptors are also located in the chemoreceptor trigger zone (CTZ); opioids are a risk factor for PONV.

Overview: Mediators and Management of N & V

Vomiting Reflex

Chemotherapy, Opioids, Anesthetics

Vagal Motor Nucleus

Cerebellum

Brain Stem

CTZ

Vomiting Center

NTS

Hollow Viscus & Peritoneum

Stomach & Small Intestine

Nasal, Visual, and Noxious input

Somatosensory Cortex

Limbic Cortex

Benzodiazepines

Fear, Anxiety, Memory

ENT Surgery

Motion, N2O

Chemotherapy, Infection, Distention, Obstruction

Antihistamines, NSAIDS

5-HT and NK-1 Antagonists

Metoclopramide

Anti-Dopaminergics

Naloxone, NK-1 Inhibitors

Canabinoids

Antihistamines, Scopolamine

5-HT and NK-1 Antagonists

Canabinoids

Chemotherapy, Infection, Distention, Obstruction

Surgery, Chemotherapy, Infection, Distention, Obstruction
Targeting Emetic Neurotransmitters

- **Acetylcholine**: Anticholinergic agents (e.g., atropine, scopolamine) are among the oldest first-generation antiemetic agents.
  - Inhibit muscarinic and cholinergic receptors in cerebral cortex and pons
- **Histamine**: Antihistamines (e.g., dimenhydrinate, diphenhydramine, hydroxyzine) centrally block both $H_1$ receptors and acetylcholine.
  - Main site of action is the vomiting center and vestibular pathways
  - Particularly useful for PONV associated with middle ear surgery involving components of the vestibular nerve

First recognized with high-dose metoclopramide
More than 80% of 5-HT is localized in the gut.
At least 7 different subtypes of 5-HT receptors have been identified.

The 5-HT\textsubscript{3} receptor is highly specific for nausea and vomiting.

5-HT\textsubscript{3} receptors are located peripherally and centrally.
Substance P and NK₁ Receptor Pathway

- Substance P/NK₁ receptors are highly concentrated in brainstem vomiting center.
  - Area postrema
  - Nucleus tractus solitarius
  - Dorsal motor nucleus of the vagus nerve
- Primary mechanism of substance P/NK₁ receptor pathway appears to be central.

2 Clinical Trials of Aprepitant vs. Ondansetron

• 2 Multicenter, randomized, double-blind, active comparator-controlled, parallel-group clinical studies
• 1658 patients undergoing open abdominal surgery requiring at least an overnight stay.
• Patients were randomized to receive 40-mg aprepitant, 125-mg aprepitant, or 4-mg ondansetron.

Emend package insert June 2006
2 Clinical Trials of

- Ondansetron 40 mg given IV immediately prior to induction
- Aprepitant 125 mg or 40 mg given orally 1 to 3 hours prior to induction with 50 ml of water.
- A comparison between the 125-mg dose and the 40-mg dose did not demonstrate any additional clinical benefit.

Emend package insert June 2006
Aprepitant versus Ondansetron Study 1

Study Endpoints

- Complete Response 0-24 hrs (no N/V): 64% Aprepitant, 55% Ondansetron
- *No Vomiting 0-24 hrs: 84% Aprepitant, 71% Ondansetron
- *No Vomiting 0-48 hrs: 82% Aprepitant, 66% Ondansetron

*p<0.001

Emend package insert June 2006
Aprepitant versus Ondansetron Study 2

Study Endpoints

- Complete Response 0-24 hrs (no N/V)
  - Apprepitant 40 mg: 45%
  - Ondansetron 4 mg: 42%

- *No Vomiting 0-24 hrs
  - Apprepitant 40 mg: 74%
  - Ondansetron 4 mg: 67%

- *No Vomiting 0-48 hrs
  - Apprepitant 40 mg: 85%

*p<0.001

Emend package insert June 2006
Antiemetic Dosing

**Antihistamines and Anticholinergics**
- Diphenhydramine (Benadryl) 25 to 50 mg orally
- Meclizine (Antivert) 12.5 to 25 mg orally every six to eight hours
- Scopolamine Patch (apply every 2 days)

**Antipsychotics and related agents**
- Haloperidol (Haldol) 0.5 to 2 mg orally 2-4 times per day
- Prochlorperazine (Compazine) 5 to 10 mg oral or IV every 6-8 hrs or 25 mg rectally (less sedating than promethazine)
- Promethazine (Phenergan) 12.5 to 25 mg orally, IV, or rectally every 4-6 hours (Dopamine-blocking properties less than prochlorperazine)

**Prokinetic agents**
- Metoclopramide (Reglan) 5 to 10 mg orally or IV four times per day

**Serotonin antagonists**
- Ondansetron (Zofran) 4 mg orally or IV two to four times per day
- Granisetron (Kytril) 1 mg orally or IV twice per day

**NK-1 Antagonists**
Opioid Induced Bowel Dysfunction
Opioid-Induced Bowel Dysfunction (OBD)

- Severe constipation observed in patients treated acutely and chronically with opioid analgesics
- May lead to physical and functional deterioration
- May be dose dependent, but can occur with low opioid doses
- Variable onset and intensity between patients
- Unlike other opioid-induced side effects which resolve over time, tolerance to OBD is not observed with continued opioid therapy

Post Operative Ileus (POI)

A severe form of constipation that includes the following symptoms:

- Acute abdominal distention/bloating following surgery
- Visceral pain
- Nausea/vomiting
- Inability to pass stools
- Inability to tolerate a solid diet

Pathogenesis of POI

- **Neurogenic**: sympathetic hyperactivity
- **Inflammatory**: cellular and humoral factors including endogenous opioid peptides
- **Hormonal**: corticotrophin releasing factor

**Pharmacologic**: primarily, opioid analgesics

Due to surgical manipulation
### Management Approaches for POI

#### Current Treatments

- **Supportive care**
  - NG intubation
  - Fluid restriction
  - Early oral/enteral feeding

- **Pharmacologic Options**
  - Traditional laxatives
  - Opioid-sparing approaches

- **Surgical Options**
  - Laparoscopy vs. open surgery

#### Emerging Therapies

- Epidural analgesia as part of multimodal therapy
- Peripherally selective opioid antagonists

---

Inhibit intestinal ion and fluid secretion
Block propulsive peristalsis
Increase intestinal fluid absorption

- Most common and debilitating symptom of OBD
- Defined as less than 3 bowel movements per week
- Occurs in 33% of cancer patients, and 40% of non cancer patients on chronic opioid therapy
- Can be more distressing than pain in some patients

Duration of Adverse Events after Analgesic Therapy in Cancer Patients

OBD: Impact on Analgesia

- The benefit of opioid analgesia in nonmalignant and cancer pain is often limited by the development of OBD\(^1,2\)

- A survey by Palmer et al. demonstrated that patients might prefer \textit{inadequate pain relief} over \textit{adequate pain management with associated OBD}\(^3\)

- Would effective treatment of OBD lead to increased opioid consumption and improved pain relief?

\(^3\) Palmer et al., # 790 20th Annual Scientific meeting of the American Pain Society, 2001, Phoenix, AZ.
Strategies to Reduce Bowel Dysfunction with Chronic Opioid Treatment

- Limit opioid exposure – employ multimodal or balanced analgesic regimens
- Anticipate and aggressively treat OBD with stool softeners and laxatives
- Consider prophylactic bowel regimen
- Consider opioid rotation
- Selectively block opioid effects in the GI tract (IV and orally administered antagonists (in development)

Constipation: First-Line Treatments

Laxative agents

Stimulating agents

- Diphenylmethanes
  - Bisacodyl
  - Sodium picosulfate

- Anthraquinones
  - Dantron
  - Senna

Stool softeners

Surfactants

- Docusate sodium

Osmotic agents

- Magnesium sulfate, citrate, or hydroxide

Carbohydrates

- Lactulose
- Sorbitol
- Mannitol

Bulk-forming agents

- Fiber
- Methylcellulose
- Psyllium
- Polycarbophil

Case for Opioid Rotation

Incidence of constipation significantly lower in patients taking fentanyl for chronic pain than in those taking morphine

Fentanyl (n= 250)  Morphine (n = 238)

P<0.001

Naloxone: A central and peripheral Opioid-Receptor Antagonist

- May reduce some side effects associated with epidural opioids
- Readily crosses the BBB\(^1,2\)
- Can cause symptoms of systemic withdrawal\(^1,2\)
- Reversal of opioid-mediated analgesia\(^1,3,4\)

**Has been advocated but has not been approved for POI**\(^1\)

Peripheral Opioid Antagonists

Quaternary Opioid Compounds that do not enter the CNS

Methylnaltrexone

Alvimopan
Peripherally Selective Opioid-Receptor Antagonists: Implications for Management

Fewer opioid-related side effects at higher opioid doses
- No reversal of opioid analgesia
- Decreased nausea and vomiting
- Decreased time to upper/lower GI function
- Decreased rate of POI
- Decreased rate of NG tube insertion
- Decreased time to ready for discharge

But questions remain: appropriate patient selection (used prophylactically); cost-effectiveness
Alvimopan: A New Orally Administered mu-Opioid Receptor Antagonist

- Unique clinical pharmacologic profile
  - Limited oral bioavailability (6% in humans)
  - Primary site of activity is at opioid receptors in the myenteric plexus

- High binding affinity for gut, μ-opioid receptor ($K_i<1 \text{ nmol/L}$)

Alvimopan as Treatment for Opioid-Induced Bowel Dysfunction

Proportion of patients reporting a bowel movement within 8 hours of study drug administration significantly greater in alvimopan-treated patients

* *p < 0.01 vs. placebo, **p < 0.001 vs. placebo
Alvimopan as Treatment for Opioid-Induced Bowel Dysfunction

Time to first bowel movement sooner in patients on 0.5 and 1 mg alvimopan compared to those on placebo

N=148, p < 0.001
Methylnaltrexone (Relistor): A Peripherally Selective mu-Receptor Antagonist

- Addition of CH$_3$ (methyl) group to naltrexone, limits BBB penetration
- Does not reverse opioid-mediated analgesia or initiate withdrawal
- IV, SC, and oral preparations
- Recently approved for the treatment of OBD in patients treated with opioids for chronic pain

Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation

Patients randomized to MNTX experiencing laxation within 4 and 24 hours significantly greater than those randomized to placebo

*P<0.0001 vs. placebo; +P<0.0004 vs. placebo (Chi-square); ++P<0.0014 vs. placebo (Chi-square)

Methylnaltrexone in Patients with Advanced Illness and Opioid-Induced Constipation

Time to laxation significantly better for methylnaltrexone-treated group compared to placebo group within first 5 hours

Methylnaltrexone in Cancer Patients with Opioid-Induced Constipation

Subcutaneous methylnaltrexone rapidly induces laxation in cancer patients with opioid-induced constipation in 2-week study

- Placebo (n=42)
- MNTX 0.15 mg/kg (n=37)

* p = 0.0007; ** p < 0.0001

Opioid-Induced Pruritis

• Unpleasant and common adverse effect of opioid treatment
• Appearance more likely during epidural or intrathecal analgesia vs. systemic analgesia
• Caused by activation of opioid receptors in cervical and trigeminal centers
• Also caused by opioid-mediated release of histamine

Opioid-Induced Pruritis
Pharmacologic Treatment Options

**Antihistamines**
- **Diphenhydramine** (25-50 mg PO/IV q 6h)
- **Hydroxyzine (Atarax)** (25 mg PO q 6h)
- **Cetirizine (Zyrtec)** 10 mg orally 1X per day
- **Fexofenadine (Allegra)** 60 mg orally 2X per day
- **Loratadine (Claritin)** 10 mg orally 1X per day

**Sedative Hypnotics**
- **Lorazepam** (1 mg SL/PO/IV q 6h)
- **Droperidol** (15 µg-50 µg droperidol per mg of morphine)

**SSRI**
- **Paroxetine**

NALOXONE?

IV, intravenous; PO, by mouth; SL, sublingual; SSRI, selective serotonin reuptake inhibitor.
Opioid Induced Respiratory Depression
Opioid Induced Respiratory

• A serious to life threatening complication observed with acute administration of IV, Oral, and Neuraxial opioids
• Less commonly observed with chronic opioid exposure
• Related to opioid binding and depression of neurons in the brainstem respiratory center.
• Worsened by co-administration of sedative hypnotics and CNS depressants

Opioid Induced Respiratory Depression

- Clinical depression of CO2 induced hyperventilation is commonly observed, Bradypnea and respiratory arrest are observed in 1/1000 patients
- Symptoms are more common in elderly and debilitated patients and COPD patients
- Compared with patients aged between 16 and 45 years, those aged between 61 and 70 years had 2.8 times the risk of development of respiratory depression.
- Patients aged 71 to 80 years had 5.4 times the risk; and those over 80 years had 8.7 times the risk.

Respiratory Depression Treatment

• Generally symptoms can be controlled by removal of opioids, other sedative hypnotics and treatment with supplemental oxygen

• Mild symptoms may be controlled with Nalbuphine 10-20mgs or Naloxone 1/2-1 amp (200mcg)
• Severe overdose may be reversed with Naloxone 1-2 amps (400-800mcg)
• Respiratory arrest often requires intubation and mechanical ventilation to reduce pCO2 and reverse respiratory acidosis
CNS Effects
CNS Effects:

Opioid induced sedation is mediated by activation of Kappa opioid receptors

Excessive sedation is commonly observed in elderly and debilitated patients (effects are transient, although some patients remain symptomatic)

The reported incidence of sedation is between 20 and 60 percent. It commonly presents with initiation of opioid therapy or with dose increases.

Pharmacologic management of sedation through the use of psychostimulants may be considered, although data supporting their use are lacking in clinical trials. In addition, potential side effects of psychostimulants warrant judicious prescribing in this setting.

CNS Effects: Confusion/Agitation

Opioid induced confusion is mediated by activation of Kappa and Sigma (PCP) opioid receptors

Like sedation, confusion is commonly observed in elderly and debilitated patients, and often presents with initiation of opioid therapy or with dose increases.\(^7\)

Treatment of cognitive impairment involves the use of antipsychotics. A recent Cochrane review found that Haloperidol and chlorpromazine (Thorazine) were most effective in treating delirium.\(^3\)

Benzodiazepines have been used with antipsychotics when severe agitation is present.\(^3\) Although they could enhance sedative effects and perhaps worsen cognition.

Medications for Treating Opioid-Induced CNS symptoms

Delirium or reduced cognition
Haloperidol (Haldol) 0.5 to 2 mg orally twice per day (Often first choice; inexpensive; minimal sedation and cardiovascular effects)
Quetiapine (Seroquel) 25 to 50 mg orally twice per day (More sedating than haloperidol)
Risperidone (Risperdal) 0.25 to 1 mg orally twice per day (Expensive)
Donepezil (Ari-cept) limited evidence supporting its use

Sedation
Dextroamphetamine (Dexedrine) 2.5 to 5 mg orally twice per day (Judicious use advised; adverse effects include tremor, delirium, decreased appetite, and hallucinations)
Methylphenidate (Ritalin) 2.5 to 5 mg orally twice per day (Administer in the
Pain Management-Related Opioid Addiction Is Rare Despite Common Perceptions

• Concerns about addiction are a common reason for under-use of opioids\textsuperscript{1}
• Opioid addiction rarely develops after receiving opioids for analgesia without prior history of substance abuse
  – Long-term opioid use for non-cancer pain resulted in only 6 cases (2.6\%) of possible drug abuse\textsuperscript{2}
  • There were no cases of de novo addiction
• Addiction is primarily associated with pre-existing aberrant drug use behaviors\textsuperscript{3}

Opioid-Induced Urinary Retention

- Opioid effects on urinary bladder not well studied, but source of morbidity
- Overall incidence with IV opioids is 23%
- Epidural and intrathecal analgesia associated with higher incidence (42%-80% for intrathecal morphine)
- May be treated with IV naloxone
- Relieved by catheterization

Methylnaltrexone reverses remifentanil-induced bladder dysfunction without reversing central opioid effects.

R, remifentanil; MNTX, methylnaltrexone.
Evidence Based Recommendations for Managing Opioid Adverse Events

Opioid rotation and multimodal analgesia may be used for managing opioid-induced adverse effects.  

B

No antiemetic has been shown to be superior to another in this setting, cost can be used to determine the treatment for opioid-induced nausea.  

C

Monotherapy with stool softeners for constipation is not recommended.  

C

Transdermal fentanyl (Duragesic) is an option for pain control in patients with constipation from oral opioids.  

B

A = consistent, good-quality patient-oriented evidence;  
B = inconsistent or limited-quality patient-oriented evidence;  
Thank You! any Questions?