Management of Opioid Induced Side Effects
Don't Throw the Baby Out With the Bathwater

Molly Feely MD
Assistant Professor of Medicine
Department of General Internal Medicine
Section of Palliative Medicine
Disclosures

I have no financial relationships

Off Label Use

Haldol
Methylnaltrexone
Ondansetron
Naloxone
Modafinil
Methylphenidate
Management of Opioid Side Effects

Common Side Effects
- Constipation
- Nausea
- Sedation
- Delirium
- Sweating
- Dry Mouth
- Pruritus

Uncommon Side Effects
- Urinary retention
- Myoclonus
- Hyperalgesia
- Seizure
- Hypogonadism
- Sleep Disordered Breathing
- Respiratory Depression
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OBJECTIVES

• Recognize which opioid side effects are typically transient and which are pervasive
• List management options for each opioid side effect discussed
• Distinguish when to rotate opioid vs. when to treat the symptom
ROAD MAP

• Case
• Principles
• Tips
• Take Home Points
Constipation

- Patient is a 37 y.o. ♀
- widely metastatic breast cancer
- no BM in the last 8 days
- Quit taking her opioids due to constipation

MEDS

- Fentanyl patch 75mcg q3days
- Hydromorphone 4mg po q4h prn pain
- Docusate 100mg po bid prn
- MOM 30mL po tid prn
- PEG 17gm in water daily prn
Constipation

• In addition to successful enema in the office, which of the following would be the next best step?
  • A. Add sorbitol 30mL po bid prn
  • B. Add scheduled fiber supplement
  • C. Add scheduled stimulant laxative
  • D. Add methylnaltrexone
Constipation

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  • A. Add sorbitol 30mL po bid prn
  • B. Add scheduled fiber supplement
  • C. Add scheduled stimulant laxative
  • D. Add methylnaltrexone
OIC --- principles of management

1. Opioid induced constipation (OIC) is virtually universal with scheduled opioids
2. Tolerance to OIC does **NOT** develop
3. Schedule stimulant laxative
## TIP --- Suggested OIC bowel regimen

<table>
<thead>
<tr>
<th>STEP</th>
<th>MEDICATION</th>
<th>REGIMEN</th>
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<tbody>
<tr>
<td>1</td>
<td>Docusate</td>
<td>1 cap po bid</td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>1 tab po bid</td>
</tr>
<tr>
<td>2</td>
<td>Increase senna</td>
<td>2 cap po bid</td>
</tr>
<tr>
<td>3</td>
<td>Increase senna</td>
<td>3 cap po bid</td>
</tr>
<tr>
<td>4</td>
<td>Increase senna AND ADD</td>
<td>4 cap po bid</td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td>30mL po bid</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td>17gm in 4-8oz liquid po daily</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bisacodyl</td>
<td>2 tab po bid</td>
</tr>
<tr>
<td>5</td>
<td>Increase sorbitol OR</td>
<td>30mL po tid</td>
</tr>
<tr>
<td></td>
<td>PEG</td>
<td>17gm in 4-8oz liquid bid</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bisacodyl</td>
<td>3 tab po tid</td>
</tr>
<tr>
<td>6</td>
<td>methylnaltrexone</td>
<td>See dosing guidelines</td>
</tr>
</tbody>
</table>

Weinstein, SM et. al. UNIPAC 3. 2012
OIC --- principles of management

1. Opioid induced constipation (OIC) is virtually universal with scheduled opioids
2. Tolerance to OIC does **NOT** develop
3. Schedule stimulant laxative
4. Fiber supplement not helpful
5. Consider methylnaltrexone if:
   1. Maxed out aggressive bowel regimen **AND**
   2. Ruled out bowel obstruction
TIP --- Methylnaltrexone

- Peripheral opioid antagonist
- Bowel obstruction absolute contraindication
- Highly effective in OIC
- Cost $50-75 per dose
- Dosing

<table>
<thead>
<tr>
<th>INJECTION VOLUME</th>
<th>SUBCUTANEOUS DOSE</th>
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<tbody>
<tr>
<td>Less than 38 kg</td>
<td>See below*</td>
</tr>
<tr>
<td>38 kg to less than 62 kg</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>62 kg to 114 kg</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>More than 114 kg</td>
<td>See below*</td>
</tr>
</tbody>
</table>

*The injection volume for these patients should be calculated using the following method: Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.
• PEGylated derivative of naloxone
• Increased laxation
• Rare episodes of opioid withdrawal
• Relatively frequent GI side effects in methadone users
• Multiple drug interactions
• 25mg and 12.5mg doses
## Methylnaltrexone vs. Naloxegol

<table>
<thead>
<tr>
<th></th>
<th>Methylnaltrexone</th>
<th>Naloxegol</th>
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<tr>
<td><strong>INDICATION</strong></td>
<td>OIC in advanced illness</td>
<td>OIC in non-cancer pain</td>
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<tr>
<td><strong>CONTRAINDICATIONS</strong></td>
<td>Bowel obstruction</td>
<td>Bowel obstruction CYP3A4 inhibitors</td>
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<tr>
<td><strong>DURATION</strong></td>
<td>Short term</td>
<td>Short term</td>
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<tr>
<td><strong>COST PER DOSE</strong></td>
<td>$119.00</td>
<td>$14.48</td>
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</table>
OIC Take Home Points

- OIC virtually universal with scheduled opioids
- No tolerance to OIC
- Start scheduled laxatives with scheduled opioids
- Fiber ---- no, no, no
- Methylnaltrexone only after maxed out bowel regimen
- Role of naloxegol evolving
Nausea Case

- 18 y.o. ♀ with severe, destructive lupus arthritis
- Severe pain limits mobility
- Multiorgan dysfunction due to lupus
- Limited life expectancy due to severe, progressive SLE

You elect to start her on hydromorphone 2mg po q4h prn pain

24 hours later the patient is miserable with nausea and vomiting and tells you she can’t take this medication

Alternative etiologies of nausea ruled out
The next best step to manage her nausea would be?

- A. Opioid rotate her to fentanyl
- B. Switch her to IV hydromorphone
- C. Add scheduled prochlorperazine
- D. Add prn ondansetron
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• D. Add prn ondansetron
Principles of Opioid Induced Nausea Management

1. Occurs occasionally --- 15-40% of patients
2. Multiple mechanisms
   - CTZ, vestibular, gut inertia
3. Tolerance develops in >90% in 3-7 days
4. Anti-dopaminergic agents first line in opioid induced N/V
5. Little evidence to support one opioid over another
OINV Take Home Points

• Address alternative sources of nausea
• Avoid opioid rotation in the first 5 days
• Anti-dopaminergic agents first line, scheduled
Sedation Case

• 50 y.o. ♂ in remission from NHL.
• On chronic opioids for chemotherapy induced peripheral neuropathy
• Failed trials of gabapentin, pregabalin, carbamazepine, topiramate, lamotrigine and tricyclics
• Failed all previous oral opioids including methadone

Long time stable dose with no aberrant behavior

Complains of sleepiness that is interfering with his employment

MEDS
  Fentanyl patch
  25mcg q2days
What is the next best step to help with his somnolence

• A. Add modafinil

• B. Tell him he can’t be on opioids anymore since he has non-cancer pain

• C. Tell him he should quit his job and go on disability.

• D. Start an SSRI
What is the next best step to help with his somnolence

- A. Add modafinil
- B. Tell him he can’t be on opioids anymore since he has non-cancer pain
- C. Tell him he should quit his job and go on disability.
- D. Start an SSRI
Principles of Opioid Related Sedation

1. Common but usually transient
2. What else is going on?
3. Really, what else is going on?
4. Are there alternative drugs?
   non-opioid
   opioid rotation
5. Consider a stimulant
**TIP --- Stimulants**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
</table>
| methylphenidate | 2.5-20mg bid  
Start low and go slow.  
Don’t give second dose after 2pm | Anxiety, tremulousness, cardiac dysrhythmia, insomnia, anorexia |
| Modafinil  | 100-200mg/day  
Start with 100mg a day.  
Can increase to 100mg bid or 200mg qday  
Don’t give second dose after 2pm | |
Opioid Sedation Take Home Points

• Usually transient. Wait several days.
• What else is going on?
• Stimulants as a last resort
Opioid Induced Pruritus

- 24 y.o. ♂ admitted with tib-fib fracture
- Reports allergy to morphine, codeine, oxycodone and hydrocodone.
- Complains of pain.
- Non-opioid medications inadequate

- You order po hydromorphone for his pain
- He almost immediately starts itching
- Exam shows no rash
How would you manage his itching

• A. Switch him to IV hydromorphone
• B. Add prn diphenhydramine
• C. Schedule loratadine
• D. Switch him to nalbuphine
How would you manage his itching

• A. Switch him to IV hydromorphone
• B. Add prn diphenhydramine
• C. Schedule loratadine
• D. Switch him to nalbuphine
Principles of Opioid Pruritus

- Pruritus ≠ Allergy
- Common
- NOT histamine mediated
- Little data outside of intrathecal administration
- Management largely based on expert opinion
## TIP --- Pruritus Management Options

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<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>NOTES</th>
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<tbody>
<tr>
<td>Hydromorphone</td>
<td>Unknown</td>
<td>These opioids seem to have less itching, unknown as to why</td>
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<tr>
<td>Fentanyl</td>
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<td></td>
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<tr>
<td>Oxymorphone</td>
<td></td>
<td></td>
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<tr>
<td>Tramadol</td>
<td></td>
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<tr>
<td>Naloxone</td>
<td>Opioid antagonism</td>
<td>Obvious downside of blocking the opioid effect</td>
</tr>
<tr>
<td>Nalbuphine (Nubain) butorphanol</td>
<td>Opioid agonist/antagonist</td>
<td>They do seem to have less itching associated with them</td>
</tr>
<tr>
<td>MethylNaltrexone??</td>
<td>Opioid antagonism</td>
<td>Few case series. One RDBPCT with 72 patients showed no benefit in pruritus</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5-HT3 antagonist</td>
<td>Systematic review in intrathecal administration show benefit</td>
</tr>
<tr>
<td>Mirtazapine*</td>
<td></td>
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</table>
Opioid Induced Pruritus Take Home Points

• NOT histamine
• Consider agonist/antagonist drug
• Consider ondansetron or mirtazepine
feely.molly@mayo.edu
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### Microsoft Table

**Subtitle for Table**

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Questions & Discussion