Disclosures

Dr. Rastrelli, MD and Lea Price, PharmD – have no relevant financial relationships to disclose

Some medications in this presentation may be used off-label

Objectives

1. Describe the trend of the use of opioids and potential barriers to pain management
2. List factors related to opioid side effects
3. Explain initial management of opioid side effects
4. Compare and contrast opioid side effects in regards to their incidence, differential diagnosis and treatment
Prevalence of Pain

2-40% Community Dwelling Patients\(^1\)

22% of Primary Care Patients\(^2\)

33-64% Cancer Patients\(^3\)

40-50% of Hospice Patients\(^4\)

\(^1\) Verhaak PF et al. Pain. 1998;77:231-236
\(^3\) van den Beuken-van Everdingen M et al Ann Oncol. 2007; 18: 1407-1409

Barriers to Pain Management

Health care system factors

Addiction related factors

Patient factors
Barriers to Pain Management

Non-cancer pain patients with side effects

- Continue 78%
- Discontinue 22%

Factors Related to Side Effects

- Patient-related factors
- Co-morbidities
- Drug interactions
- Dose of opioid
- Choice of opioid
- Length of therapy
- Routes?

Initial Treatment Strategy

- Differential diagnosis
  - Disease state vs. drug reaction
- Drug management
  - Continue therapy
  - Reduce dose
  - Systemic management of side effects
  - Opioid rotation
  - Change routes?
- Patient education
Case Presentation

LR is an 82 yof who presented 1 mo ago with ascites, 30# wt loss, and generalized abd, pain. W/U revealed metastatic (liver, peritoneal) ovarian ca, and though it was not curable, she decided to try palliative chemo.

Other co-morbidities:
- CKD Stage IV--Cr in low 2’s
- Osteoporosis
- Early dementia but functional at home with husband and oldest son
- Hypertension
- Atrial fibrillation

Case Presentation

She started oxycodone/APAP 500mg: 1-2 Q 4-6 h prn- using around 4 pills/d X 1 wk ago. Now, LR is using 8 pills/d in addition to morphine SR 15mg Q8 h X 3 days.

She was hospitalized w/ increasing abd pain, nausea, constipation, and AMS.

Case Presentation

She was noted to have massive ascites; excoriations from generalized pruritis; jaundice

Family concerned that her appetite is much lower and she appears more confused than ever. They do not like that she is sleeping “all the time.”
Case Presentation

**Relevant Labs:**
- 125
- 91
- 80
- 3.8
- 15
- 3.1
- 9.7
- 5.6
- 27.5
- ↑ LFTs, Bili: 15, Alb: 1.8
- Blood cultures- neg
- UA- neg
- Ca: 8.5

**Med List:**
- morphine SR 15mg q 8h X 3 days
- oxycodone/APAP 500mg: 1-2 Q 4-6 h prn
- rivastigmine 1.5mg BID
- losinopil 5mg daily
- HCTZ 25mg daily
- alendronate 70 q week for osteo
- calcium + D 500mg TID
- diphenhydramine 50-100mg qhs

**Allergies:** None

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Opioid Side Effects

- Sedation/Decreased Cognition
  - Reported to occur in 20-60% of patients

  **Differential diagnosis**
  - Infection, dehydration, depression, advancing cancer, other medications

  **Transient**
  - Usually resolves in 3-5 days
  - May reoccur with dosing adjustments

### Sedation/Decreased Cognition

**Treatment**
- Decrease dose of opioid

**Methylphenidate**
- Start with q am dosing and increase by 2.5-5 mg increments to BID dosing (Max 20mg/day)
- Side effects (SE): hallucinations, cardiac arrhythmias, insomnia, nervousness, agitation
- Continually assess for need

**Other medications**
- Dextroamphetamine
- Modafinil ($$$$

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### Nausea/Vomiting

**Reported in 7-50% of patients**

**Differential diagnosis**
- Constipation
- Other medications

**Transient**
- Usually resolves in 3-5 days

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### Nausea/Vomiting

**Treatment**
- Prophylactic treatment is usually NOT required
- Prochlorperazine 5-10mg po/iv q 6-8 h prn
- Metoclopramide 5mg po/iv q 6h prn
- Haloperidol 0.5-1mg po/iv/sq q 6h prn

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### Constipation

**Reported to occur in**
- 40% of patients on chronic opioid therapy
- 90% of cancer patients on opioid therapy
- 15% of chronic non-malignancy patients on opioid therapy

**Characteristics**
- Abdominal pain
- Colic
- Nausea/vomiting
- Resemble bowel obstruction


### Precipitating factors

- Dehydration
- Sedentary
- Recent surgery or barium studies
- Gastrointestinal metastases
- Other medications
- Hypercalcemia
- Lack of privacy

### Differential diagnosis

- Tumor progression, hypercalcemia
- Other medications (TCAs, diltiazem)

### Mechanism

- Delayed peristalsis, decreased secretions and increase sphincter tone
Constipation

Prevention

- The hand that writes for opioid must also write for the bowel regimen!!!!!!
- Stimulant laxative (senna, bisacodyl)
  - +
- Stool softener/Detergent (docusate)
  - +/-
- Osmotic agent (lactulose, polyethylene glycol 3350)


Constipation: Transdermal Vs. SR Oral

<table>
<thead>
<tr>
<th>Study</th>
<th>TO</th>
<th>SR OR</th>
<th>Odds ratio and 95% CI</th>
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<tr>
<td>Ahmoodi et al. 1997</td>
<td>19 / 51</td>
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<td>van Seewert et al. 2003</td>
<td>16 / 67</td>
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<td>Pace et al. 2007</td>
<td>3 / 38</td>
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Better TO Better SR OR


Constipation

Treatment

- Mobility, hydration
- Increase dose of current laxatives
- Addition of suppositories and/or enemas
Constipation

Treatment (cont)

- Oral Naloxone
  - Initiate 1mg po BID (max 5mg)
  - Studied at 20% of daily morphine dose divided q 4h
  - SE: withdrawal, yawning, diaphoresis, diarrhea
- Methylaltrexone (Relistor)
  - Inject 1 dose SubQ every other day (Max 1 dose/day)
  - Dose is weight-based
  - Avoid in intestinal obstructions
  - SE: Abdominal pain, gas, nausea, diarrhea

2. www.fda.gov/bbs/topics/NEWS/2008/NEW01826.html

Pruritus

Reported to occur in 2-10% of patients

Differential diagnosis

- Uremia, cholestasis, hyperthyroidism, xerosis

Mechanism

- Histamine release and/or CNS receptor activation


Pruritus

Treatment

- Switch to alternative agent
  - Morphine/codeine > oxycodone/hydromorphone > fentanyl
- Switch routes
- Add antihistamine, Others?

Case Presentation (cont)

- Hydrated
- Ascites/edema
- Diaphoresis
- Dyspnea
- Urinary retention-foley
- Confusion
- Pain
- Anxiety

BP: 80-100; HR: 100-120 (A Fib)

Tmax: 102, BM: neg

O2 Sat: 80%>>88% (5L O2 NC)

UA: Cloudy

Cr: 2.6, BUN: 60

CXR: B infiltrates/effusion

Abd CT: Liver mets, Bil Hydronephrosis

Case Presentation (cont)

New meds:
- Metoclopramide 5mg BID
- Sennakot-S BID
- Morphine SR 30mg BID
- Haloperidol 2.5mg iv q 6h prn
- Lorazepam 1mg iv q 6h prn

Sweating

Reported to occur in 4-12% of patients

Differential diagnosis
- Neoplasm, infection, hypoglycemia
- Room temperature

Mechanism????
- Histamine release
- Central-thermoregulatory systems
Sweating

**Treatment**
- Mostly case reports
- Opioid rotation
- Scopolamine patch 1 patch q 72 hours
- H2-blockers

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Urinary Retention

**Reported to occur mostly in elderly males**
**Differential diagnosis**
- BPH, other medications (TCAs)

**Mechanism**
- Increased sphincter tone in the bladder
- Bladder spasms

**Transient**
- Usually resolves in 3-5 days

**Treatment**
- Catheterization

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Case Presentation (cont)

- Bil Nephrostomies
- Thora/Paracentesis
- No BM→?SBO
- Increased pain

**Cr:** ↓, **BUN:** ↓
**Dyspnea:** ↓

**Meds Changes:**
- D/C morphine SR
- Dilaudid PCA started
Case Presentation (cont)

- Initial relief; sleep...then...
- Hallucinations; agitation
- Generalized pain
- Muscle jerking
- Family distressed!

Hyperalgesia

**Risk factors**
- Chronic pain therapy
- Reported in low or high dose opioid therapy

**Differential diagnosis**
- Progression of disease or new insult
- Opioid withdrawal

Mechanism

- Unknown
- Related to NMDA receptor activation
- Related to G protein coupling of opioid receptors
- May see hyperesthesia and/or allodynia

Hyperalgesia

**Treatment**
- Dose reduction +/- adjuvant therapy
- Opioid rotation
- NMDA receptor antagonist
  - Ketamine infusion


Xerostomia

**Reported to occur in 30-50% of patients**

**Differential diagnosis**
- Head and neck radiation
- Other medications (TCAs, tiotropium, antipsychotics)

**Mechanism**
- Unknown

Xerostomia

**Treatment**
- Pilocarpine 5mg TID
- Artificial saliva (Biotene®, Salivart®)
- Sugarless gum

Hallucinations/Delirium

Reported to occur in 25% of patients

Differential diagnosis
- Constipation, infections, other medications
- Cancer, dementia, electrolyte abnormalities

Possible risk factors
- Renal dysfunction
- Prior cognitive impairment
- High doses of opioid
- Medications (benzos, anticholinergic drugs, steroids)
- Untreated pain


Hallucinations/Delirium

Treatment
- Treat/remove other potential causes
- Rotate opioid and/or reduce dose by 25%
- Consider alternative agents for pain
- Haloperidol 0.5mg - 2mg iv/sq/po q 6h prn, (max 3mg/day)
- Quetiapine 25 - 50 mg q hs titrate by 25mg slowly
- SE: QTc prolongation, stroke, hypotension


Myoclonus

Reported to occur in ~3% of patients

Risk factors
- High dose opioids
- Renal/liver dysfunction

Characteristics
- Mild twitching → generalized spasms
- Exacerbate pain by involuntary movement
Myoclonus

**Differential diagnosis**
- Seizures, essential tremors, medications (meperidine)

**Mechanism**
- Unknown
- Described as sudden, brief, shock-like, involuntary movements
- May be associated with hyperalgesia

3. Ferris, DJ AJHP. 1996;56:

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**Myoclonus**

**Treatment**
- Dose reduction +/- adjuvant therapy
- Opioid rotation
- Benzodiazipine
  - Lorazepam 1-2mg po/iv q 8h
  - Midazolam continuous infusion 1-2 mg/h
- Muscle relaxant
  - Baclofen 5mg TID
  - Dantrolene 50mg daily - TID
- SE: sedation

2. Ferris, DJ AJHP. 1996;56

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**Hypotension**

**Reported to occur in < 5% of patients**

**Risk factors**
- Hypovolemia, septic shock

**Mechanism**
- Peripheral dilation due to histamine release

**Treatment**
- Slow rate of opioid infusion
- Use shorter-acting opioids

Micromedex. Morphine. 4/30/2008
Emerging concerns

Sleep disturbances
- Decrease in NREM sleep
- Risk increases with sleep apnea

Endocrine changes
Immune dysfunction


Conclusion

Trend for an increased use of opioids

Side effects are a barrier to pain management

Important to quickly recognized and treat side effects for best pain management

Questions