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Opioid Therapy in the Medically Ill: Side Effect Management

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Disclosure Slide

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Opioid Therapy: Side Effects

- Very common
 - persistent troubling side effects in about one-third of patients during long term therapy
- Very diverse
 - across patients, across drugs, across time
- Side effect management is fundamental to effective treatment

Opioid Therapy: Side Effects

- Common side effect
 - Constipation
 - Nausea
 - Somnolence, mental clouding
- Other concerns
 - Respiratory depression
 - Endocrine effects
 - QTc prolongation
 - Opioid-induced hyperalgesia
 - Urinary retention

Constipation in Advanced Disease

- Opioid analgesics used in ~ 50% of palliative care of patients with cancer in the United States.
- Estimates of constipation frequency vary
 - 23% to 63% of patients with cancer pain receiving opioids
 - 15% to 90% of patients receiving opioids for non-cancer pain
- Opioid Induced Constipation (OIC) may cause distress, increase cost of care, leading to discontinuation of analgesics, negatively affect HRQOL

Bell TJ, et al, Pain Med 2009;10:35-42.

Differential Diagnosis of Constipation

- Lifestyle factors:
 - Low level of physical activity
- Stress induced dysmotility
 - Physical and emotional
- Obstruction
 - Carcinomatosis
 - Postoperative ileus
 - Feeding tube
- Electrolyte imbalance
- Drug Induced
 - CCB, Opioids, anticholinergic, neurotoxic chemotherapy
- Patient-related influences
 - Many GI diseases
 - Comorbidities affecting bowel function, e.g., peripheral neuropathies
 - Age, nutrition, hydration status, and other factors

Sign and Symptoms Associated with Constipation

- Abdominal Pain
- Gastrointestinal Distress:
 - Nausea & Vomiting
 - Bloating
 - Diarrhea “overflow stooling”
- Urinary retention or incontinence
- Impaired gastrointestinal absorption
- Less common: dyspnea, confusion, depression

What Happens in Opioid-Induced Constipation?

Opioids bind to μ -opioid receptors in GI tract

GI motility, secretion, fluid absorption & blood flow affected

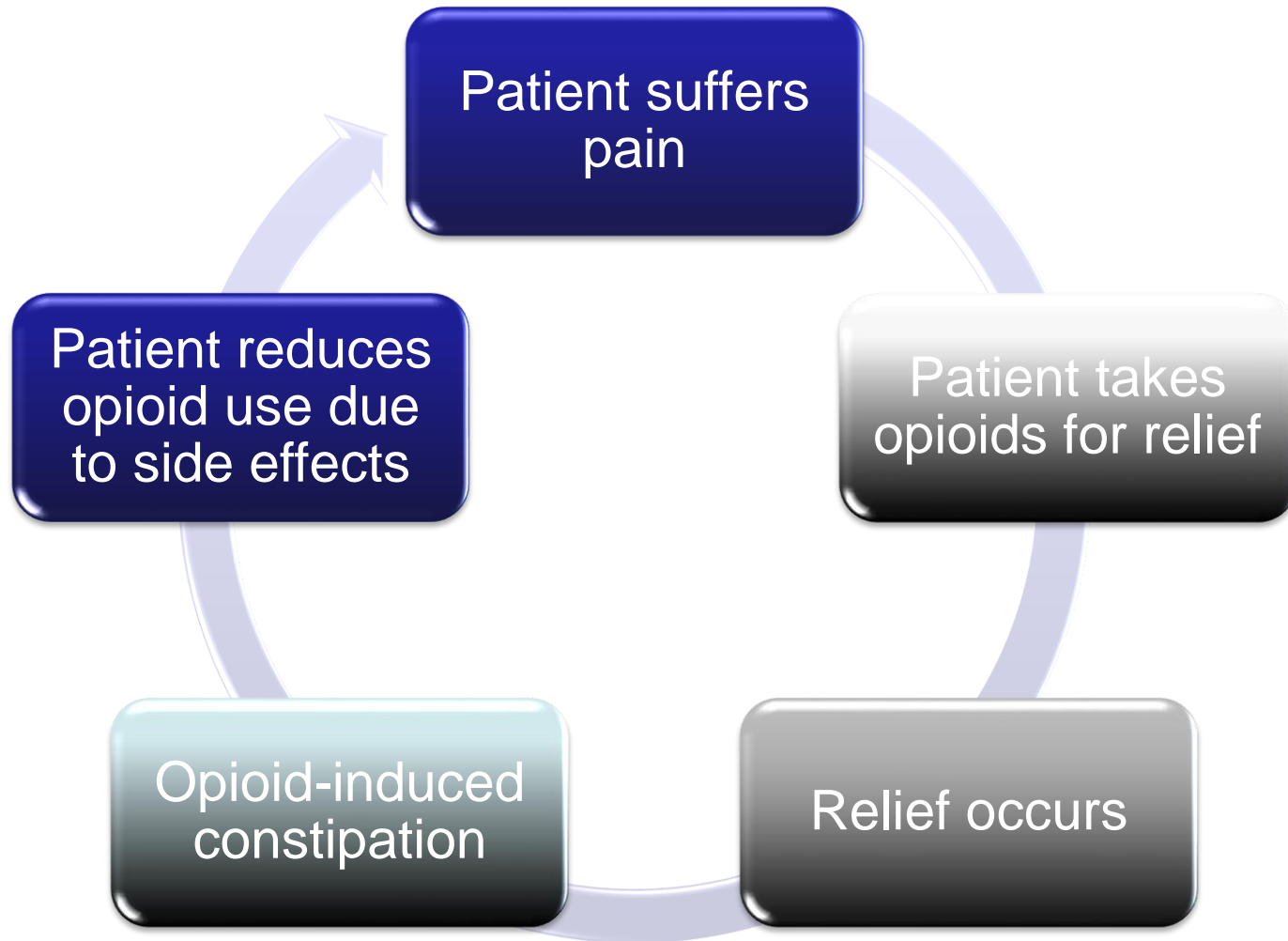
Colonic transit delayed

Sphincter tone increases

Defecation inhibited

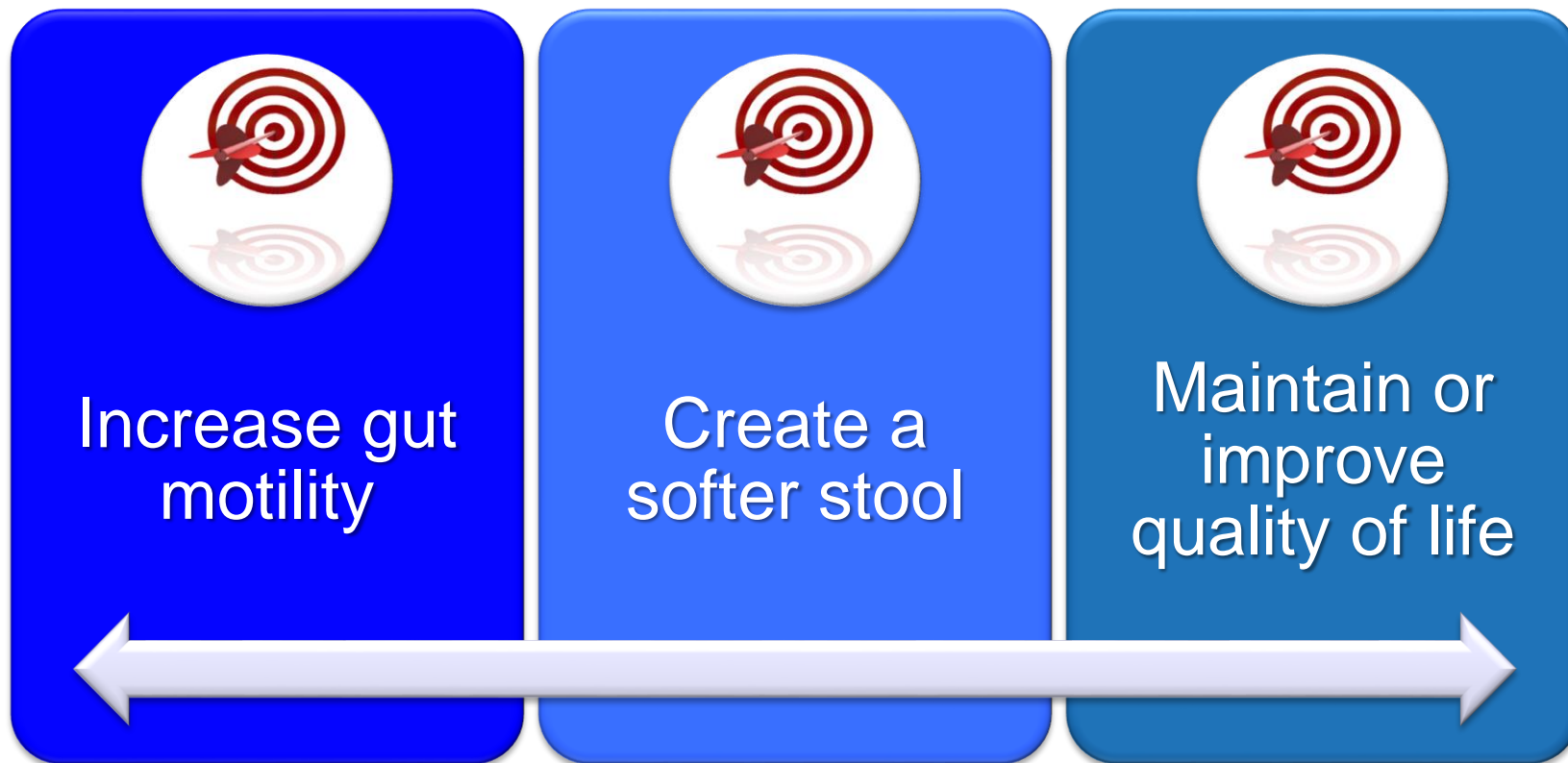
Holzer P. Regul Pept. 2009 Apr 1.; Bell TJ et al. Pain Med. 2009. 10:35-42.

The Return of Pain



Larkin PJ et al. Palliat Med. 2008;22:796-807.

Goals of Treatment



Swegle JM, Logemann. Am Fam Physician. 2006 Oct 15;74(8):1347-54.
Goodheart C, Leavitt S. Pain Treatment Topics. St. Louis MO; 2006.

Laxatives for Opioid-Induced Constipation

- Very few data to guide practice
- First-line and second-line therapy based on availability, cost and experience
- No data on dose finding, 'rotation', combinations

Laxatives for Opioid-Induced Constipation

Type	Attributes	Examples	Side Effects/Complications
<i>Bulk laxatives</i>	Dietary fiber; causes water retention in the colon and increase stool bulk	Psyllium husk, methylcellulose	Increased gas; risk of bowel obstruction in patients with strictures
<i>Osmotic laxatives</i>	Salt content retains fluid retention and increased intestinal secretion	Sorbitol, lactulose, polyethylene glycol, magnesium citrate	Electrolyte imbalances; increased gas, nausea, and dehydration
<i>Stool softeners</i>	Decrease surface tension to lubricate and soften fecal matter	Docusate	Require adequate fluid intake, useless in patients with compromised bowel motility
<i>Stimulants</i>	Increased colonic motility and electrolyte transport; stimulate fluid secretion	Senna, bisacodyl, cascara	Electrolyte imbalances; abdominal pain, nausea, and colonic dysmotility
<i>Peripheral opioid antagonist</i>	Inhibit opioid from binding to mu receptors in the GI tract	Methylnaltrexone	Abdominal pain, nausea, dizziness, flatulence

Management of Constipation in Palliative Care

First line treatment: with oral laxative: combination of stimulant (eg, senna or bisacodyl) and a softener (eg, docusate, lactulose)



Second line treatment: Rectal suppository and enema: consider use of peripherally specific opioid antagonist (eg, Methylnaltrexone)



Third line treatment: Manual evacuation; consider use of peripherally specific opioid antagonist (eg, Methylnaltrexone)



Symptom Improvement

Continue with regimen



Symptom Improvement

Continue with regimen

Larkin PJ et al. Palliat Med. 2008;22:796-807.

Opioid-Induced Nausea

- Presumed Mechanisms
 - Direct activation of chemoreceptor trigger zone
 - Sensitization of labyrinthine-vestibular system
 - Gastroparesis and slowed peristalsis
 - Reflux from lax GE sphincter
 - Risk Factors include:
 - Female > Male
 - Caucasian < African descent

Opioid-Induced Nausea

- Routine approach

- Reversal of contributing factors
- Dopamine blocking antiemetic
 - prochlorperazine
 - metoclopramide
 - haloperidol

- Other approaches

- Addition of drugs based on presumed mechanism
 - reflux symptoms → proton pump inhibitor
 - vertigo → antihistamine
 - postprandial symptoms → metoclopramide
 - Opioid rotation

Opioid-Induced Neuropsychological Effects

• Characteristics

- Can present as:
 - Somnolence
 - Cognitive impairment
 - Mood changes
 - Changes in perception
 - Any combination

• Characteristics

- Highly variable within and across individuals
- Individual variation in response to different opioids
- Often transitory

Neuropsychological Effects: Management Strategies

- Routine approach
 - Reversal of contributing factors
 - Elimination of nonessential centrally-acting drugs
 - Identify minimal effective dose
 - Consider change in dosing pattern
- Other approaches
 - Consider opioid rotation
 - Consider drug treatment of somnolence or mental clouding

Neuropsychological Effects: Management Strategies

- Psychostimulant therapy
 - Methylphenidate
 - 10 mg daily dose resulted in 35% improvement in sedation compared to 8% in placebo
 - 15 mg daily dose resulted in 61% reduction in sedation versus 21% in placebo
 - Modafinil
 - Retrospective trial data resulted in a 40% reduction in sedation scores
 - Donepezil
 - Small open label trial of 5 mg daily for 1 week resulted in improvement in sedation and fatigue in cancer patients

1. Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. Clin J Pain. 21:345-352 2005.
2. Wilwerding MB, Loprinzi CL, Mailliard JA, O'Fallon JR, Miser AW, van Haelst C, Barton DL, Foley JF, Athmann LM. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 3:135-138 1995.
3. Bruera E, Strasser F, Shen L, Palmer JL, Willey J, Driver LC, Burton AW. Journal of Pain & Symptom Management. 26;5:1049-54, 2003
4. Webster L, Andrews M, Stoddard G. Modafinil treatment of opioid-induced sedation. Pain Medicine. 4;2:135-40 2003.

Opioid-Induced Neuroendocrine Changes

- Opioids
 - Inhibit GnRH, LHRH, FSH and LH, which inhibits production of testosterone and estrogen
 - Stimulate prolactin release, which inhibits testosterone production by the testes

Neurosci 2006;140:929-937. Aloisi AM, et al. Aromatase and 5-alpha reductase gene expression: Modulation of pain and morphine treatment in male rats. Mol Pain 2010;26:69.

General Recommendations

- Opioid therapy longer than a few weeks
- Patients > 100mg morphine equivalents per day
- Patients receiving intrathecal opioids
- Symptoms to assess
 - Reduced libido, erectile dysfunction, depression, fatigue, hot flashes or night sweats & irregular menses
- May also include anemia, reduced bone mineral density
- Labs
 - TT, FT, SHBG, LH, FSH, DHEAS & estradiol
- Androgen Replacement Therapy (ART)
- Target testosterone levels
 - Males – 400-700 ng/dl
 - Females – 20-80 ng/dl
- Periodic reassessment of symptoms
- Consider rate & degree of decline
- Bone density

Smith HS, et al. Opioid-induced androgen deficiency (OPIAD). Pain Physician 2012;15:ES145-ES156.

De Maddalena C, et al. Opioid-induced hypogonadism: Why and how to treat it. Pain Physician 2012;15:ES111-ES118.

Opioid-Induced Neuroendocrine Changes

- Based on limited existing data
 - Patients should be asked about relevant symptoms
 - Sexual dysfunction, fatigue and mood disorder
 - Symptomatic patients should be tested
 - Patients on long-term therapy should be considered for bone density screening
 - Men with low testosterone should be considered for replacement therapy
 - Consider treatment in premenopausal women with adverse clinical outcomes

Smith HS, et al. Opioid-induced androgen deficiency (OPIAD). Pain Physician 2012;15:ES145-ES156. De Maddalena C, et al. Opioid-induced hypogonadism: Why and how to treat it. Pain Physician 2012;15:ES111-ES118.

Opioid-Induced Respiratory Depression

- At risk populations
 - Concurrent CNS depressants
 - Patients with COPD, obesity and recent abdominal surgery
 - Neonatal and elderly
 - Sleep apnea
 - Opioid naïve
- Prevent and monitor so you don't have to treat!
- Management
 - Low dose initiation and slow titration to effective analgesic doses
 - Accounting for incomplete cross-tolerance when converting opioids
- Pharmacologic
 - Opioid reversal

Opioid-Induced Pruritis

- Likelihood ranges from 2 to 10% of all patients that receive opioids
- Increased rate with neuraxially administered opioids; between 30-100%
- Mechanism
 - Neuraxial > Systemic
 - Histamine? Serotonin? Dopamine?
- Management
- Consider Opioid rotation
 - Antihistamines, 5HT3 antagonists, Dopamine D2 agonists

Ko MC, et al. J Pharmacol Exp Ther. 2004; 310:169-76.

Opioid-Induced Urinary Retention

- Mechanism of urinary retention with opioids is not completely understood
- Opioids have been associated with decreases in
 - Detrusor muscle tone
 - Force of detrusor contraction
 - Sensation of fullness
 - Voiding reflex
- Non-pharmacologic
 - Opioid rotation
- Pharmacologic
 - Opioid antagonists
 - Naloxone administered as a single dose or via continuous infusion showed detrusor recovery within 6-8 hours

Rawal N. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. *Anesthesia & Analgesia*. 62;7:641-7. 1983.

Opioid-Induced QTc Prolongation

- Strong evidence for a dose-dependent effect of methadone
- Methadone Risk Factors
 - Hypokalemia
 - Dose >100mg/day
 - Drugs that prolong QT interval
 - Check for history of structural heart disease, arrhythmia
 - Screen for drug interactions
 - Baseline EKG, at 30 days, and annually
 - Disclose risk to patients

Krantz M, et al. Ann Intern Med. 2009;150(6):387-395.

Opioid-Induced Hyperalgesia

- Increase in sensitivity to noxious stimulus
- Dose escalation can lead to no change in analgesia or worsening pain
- Associated with long-term utilization of opioids
- Thought to be associated with neuroexcitatory receptors
 - NMDA
 - AMPA

Opioid-Induced Hyperalgesia Management

- Non-pharmacologic
 - Opioid rotation
- Pharmacologic
 - NMDA receptor antagonist
 - Ketamine
- Clonidine
- Lidocaine

Harris JD. Management of expected and unexpected opioid-related side effects. Clinical Journal of Pain. 24 Suppl 10:S8-S13, 2008 8.

Bell RF, Eccleston C, Kalso E. Ketamine as adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage. 26:867–875 2003.

Overview of Opioid Toxicity and Risk

- Conclusion

- To optimize the outcomes of opioid therapy, the clinician must
 - Anticipate side effects
 - Counsel patient and caregiver
 - Assess and reassess
 - Treat side effects and address subtle toxicities

Case 1

A 56-year-old man with newly diagnosed prostate cancer develops left leg pain and is found to have a proximal femur bone metastasis. He has never used opioids. His oncologist tells him to take ibuprofen around-the-clock, and although his pain is improved, it remains quite bothersome. He then starts morphine 5 mg PO every 4 hours as needed for pain. His pain is well controlled with this regimen, but he becomes nauseous 30 to 60 minutes after each morphine dose. The patient is referred to the palliative care clinic, but the nausea persists after 2 weeks despite around-the-clock metoclopramide and trials of haloperidol and ondansetron. The patient has regular bowel movements. What is the best intervention?

- A. Add around-the-clock prochlorperazine.
- B. Discontinue morphine and manage pain with ibuprofen alone.
- C. Arrange for a trial of intrathecal opioids due to dose-limiting nausea.
- D. Switch the patient to another opioid using equianalgesic table.

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Case 2

A 48-year-old man with metastatic lung cancer on the palliative care service. He currently lives alone but has family visiting often. He reports that he is often unable to engage in visits with his family because of somnolence. He notes a desire and motivation to spend time with his loved ones. Although his pain is well controlled, his energy level is negatively impacting his quality of life. He has found that if he takes lower dosages of his opioid his somnolence lessens, but his pain becomes intolerable. What is the next best intervention?

- A. Methylphenidate
- B. Paroxetine
- C. Reduction of opioid dosage
- D. Modafinil

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Opioid Therapy in the Medically III: Side Effect Management

Q/A

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