

# Management of Opioid Side Effects

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# Management of Opioid Side Effects

- Constipation
- Somnolence, mental clouding
- Sleep disordered breathing
- Endocrine effects

# Opioid Bowel Dysfunction

- Constipation is one aspect of opioid-induced GI toxicity
  - Constipation
    - Reduced frequency of defecation
    - Abdominal discomfort/pain
    - Difficulty with evacuation
    - Abdominal distention
  - Upper GI symptoms
    - Nausea
    - Gastroesophageal reflux

# Opioid Bowel Dysfunction

- Constipation prevalence
  - Limited epidemiology data
    - Probably as many as 40% have persistent constipation among non-medically ill
- Much higher prevalence among those with advanced illness and multiple causes

Pappagallo M. Am J Surg 2001;182(5A Suppl):11S-18S

# Opioid Bowel Dysfunction

- Constipation prevalence and impact
  - International National Health and Wellness Survey (NHWS) 2004
    - Internet-based survey of 2430 individuals  $\geq 18$  years taking opioids for  $\geq 6$  months
    - 359 (15%) reported constipation
    - Those with constipation had more physician visits ( $p < 0.05$ ), but no differences in ED visits hospitalization
    - Those with constipation had more lost work time, impaired working, and activity impairment ( $p < 0.05$ )
    - Those with constipation had less physical and mental well-being on SF-8 questionnaire ( $p < 0.05$ )

# Opioid Bowel Dysfunction

- Constipation prevalence
  - PROBE 1 study:
    - Multinational, Internet-based survey of 322 patients taking oral opioids and laxatives
    - 45% of patients reported <3 bowel movements per week, 81% reported constipation and 58% reported straining
    - Most bothersome symptoms experienced by the majority of patients  $\geq 4$  times a week
    - One-third had missed, decreased or stopped using opioids due to symptom

# Opioid Bowel Dysfunction

## ■ Contributing factors

### – Drug-related influences

#### ■ No definite effects

- Transdermal fentanyl less than oral morphine

Tassinari D et al, J Palliat Care 2009;25:172-80

- No difference among fentanyl, hydromorphone, and buprenorphine

Wirz S et al, Eur J Pain 2009;13:737-43

- Uncertain if codeine is more likely than other opioids
- Early data suggest that tapentadol is less likely

#### ■ Effects probably dose-related

# Opioid Bowel Dysfunction

- Contributing factors
  - Patient-related influences
    - Primary disease type and status
    - Comorbidities affecting bowel function
    - Age, nutrition, hydration status, and other factors
    - Other drugs

# Opioid Bowel Dysfunction

- Possible serious consequences
  - Fecal impaction
  - Pseudo-obstruction
  - Potential malabsorption
  - Persistent nausea or anorexia

# Opioid Bowel Dysfunction

## ■ Pathophysiology

- Endogenous opioids play major role in regulation of GI motility
  - Both central and peripheral opioid receptors involved
  - $\mu$ ,  $\kappa$ , and  $\delta$  receptors identified in gut
  - GI effects are principally mediated through  $\mu$  receptors, which predominate in the mucosal and submucosal layers of the gut
  - Primary role of peripheral receptors suggested by preclinical data

# Opioid Bowel Dysfunction

- Pathophysiology
  - Opioids
    - Increase non-propulsive motility
    - Decrease peristalsis
    - Reduce intraluminal secretions

Kurz & Sessler. *Drugs*. 2003;63:649-671.

# Laxatives for Opioid-Induced Constipation

- Very little 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

## ■ First-line

- Bulk-forming laxatives
- Contact cathartics (e.g., senna)
- Surfactants (docusate)
- Saline cathartics (e.g., magnesium sulfate)
- Lactulose/sorbitol
- Polyethylene glycol (“colonic lavage”)

# Laxatives for Opioid-Induced Constipation

- Second-line
  - Methylnaltrexone
  - Other second-line options
    - Prokinetic agents, e.g. metaclopramide
    - Lubiprostone
    - Anticholinesterase inhibitors (e.g., donepezil)
    - Misoprostol
    - Colchicine
    - Oral naloxone
    - Lubricants

# Opioid Antagonists Opioid-Induced Constipation

- Systematic review: Efficacy and safety of mu-opioid antagonists in the treatment of opioid-induced bowel dysfunction: systematic review and meta-analysis of randomized controlled trials

McNicol E et al, Pain Med 2008;9:634-59

- Review of randomized controlled trials
- 22 articles provided data on 2,352 patients treated with alvimopan (8 studies), methylnaltrexone (6x), naloxone (7), and nalbuphine (1)
- Meta-analysis: methylnaltrexone and alvimopan were efficacious in opioid-induced constipation and alvimopan is safe and efficacious in treating postoperative ileus
- Incidence of adverse events similar to placebo

# Opioid Antagonists Opioid-Induced Constipation

- In a 12 month trial, alvimopan was associated with increased cardiac risk
  - Approved for postoperative ileus only
- Methylnaltrexone approved for opioid-induced constipation
  - About 50-60% of patients have results, most within an hour
  - Several doses needed to determine full effects
  - Anecdotal reports of bowel perforation represent major side effect

Chamberlain BH et al, J Pain Symptom Manage 2009;38:683-90

# Management of Opioid-Induced Constipation

- Usual strategy
  - Hydration, fiber and activity, as appropriate to the medical context
  - Elimination of non-essential constipating drugs if possible
  - Add a first-line drug

# Laxatives for Opioid-Induced Constipation

## ■ First-line

- Bulk-forming laxatives
- Contact cathartics (e.g., senna, bisacodyl)
- Surfactants (docusate)
- Saline cathartics (e.g., magnesium sulfate)
- Lubricants
- Lactulose/sorbitol
- Polyethylene glycol (“colonic lavage”)

# Laxatives for Opioid-Induced Constipation

- Usual strategy
  - Add a bulk-forming laxative if risk is acceptable
  - Add docusate or a contact cathartic or propylene glycol or lactulose, or docusate plus a contact cathartic
  - Dose escalation to 1) side effects, 2) conventional limit, 3) feasibility or convenience, 4) patient preference, 5) cost
  - Add a second first-line agent, or switch if side effects
  - Repeat strategy

# Management of Opioid-Induced Constipation

- Usual strategy
  - If ineffective, consider methylnaltrexone or a second-line drug

# Laxatives for Opioid-Induced Constipation

- Second-line
  - Methylnaltrexone
  - Other second-line options
    - Prokinetic agents, e.g. metaclopramide
    - Lubiprostone
    - Anticholinesterase inhibitors (e.g., donepezil)
    - Misoprostol
    - Colchicine
    - Oral naloxone
  - Future: Other nonabsorbable opioid antagonists, and combinations of opioids and naloxone

# Opioid-Induced Somnolence/ Mental Clouding

- One aspect of side effect spectrum that includes
  - Somnolence
  - Cognitive impairment
  - Mood changes
  - Changes in perception
  - Nightmares/vivid dreams
  - Any combination of the above or a frank delirium

# Opioid-Induced Somnolence/Mental Clouding

- Very few data on prevalence during long-term therapy
- Usual strategy based on clinical experience
  - Assess
  - Treat other causes
  - Reduce or eliminate non-essential medications

# Opioid-Induced Somnolence/Mental Clouding

- Usual strategy based on clinical experience
  - Consider
    - Opioid rotation
    - Use a pharmacological approach that allows reduction of the opioid dose
      - Add a NSAID or adjuvant analgesic
      - Consider neuraxial infusion
    - Use a nonpharmacological approach that allows reduction of the opioid dose
    - Treat the side effect

# Opioid-Induced Somnolence/Mental Clouding

- Drug therapy
  - No controlled trials
  - First-line drugs: Psychostimulants
    - Methylphenidate and modafinil most often used
    - Others: Dexmethylphenidate, armodafinil, atomoxetine

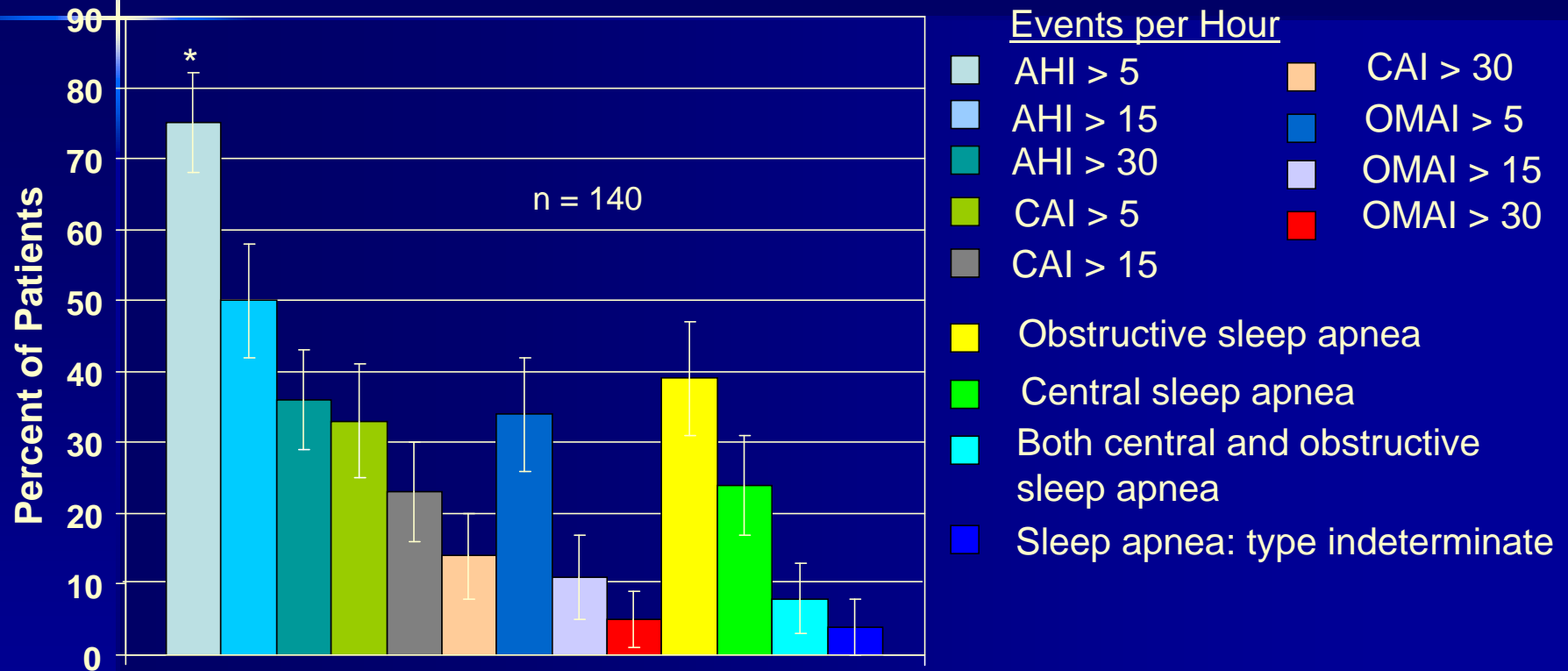
# Opioid-Induced Somnolence/Mental Clouding

- Other drugs tried empirically
  - Cholinesterase inhibitors
    - Donepezil
  - Bupropion

# Opioid-Induced Sleep-Disordered Breathing

- Limited data but high risk potential
- Early data suggest routine consideration of strategies to mitigate risk

# Opioid-Induced Sleep Disordered Breathing



\*Bars indicate hi/lo of 95% CI; AHI = apnea-hypopnea index; CAI = central apnea index; OMAI = obstructive and mixed apnea index

Webster LR, et al. Sleep-disordered breathing and chronic opioid therapy. *Pain Med*, 2009

# Opioid-Induced Sleep Disordered Breathing

## ■ Considerations

- Assess risk
  - Sleep history
  - Risk factors include ?BMI, snoring, short neck, cardiopulmonary disease, rapid titration of opioid dose
- Order sleep studies on “at risk” patients
- Avoid methadone and benzodiazepines

# Opioid-Induced Neuro-Endocrine 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

# Opioid-Induced Neuro-Endocrine Changes

- Surveys of addicts using heroin or undergoing opioid agonist treatment with methadone demonstrate high prevalence of hypogonadism

Mendelson JH and Mello NK. Clin Pharmacol Ther 1975;17:529-33

- Surveys of pain patients receiving neuraxial analgesia show high likelihood of hypothalamic hypogonadism

Abs R et al, J Clin Endocrinol Metab 2000;85:2215-22

# Opioid-Induced Neuro-Endocrine Changes

- Hypogonadism in opioid-treated women

Daniell HW, J Pain 2008;9:28-36

- Survey of 47 women ages 30 to 75 years consuming oral or transdermal opioids for pain and 68 controls
- Results:
  - Testosterone, estradiol, and dehydroepiandrosterone sulfate were 48%-57% lower in opioid-consuming women ( $P < .01-.05$ )
  - LH and FSH averaged 30% lower in premenopausal and 70% lower in postmenopausal women ( $P < .001$ )
  - Among oophorectomized women not consuming estrogen, free testosterone levels were 39% lower in opioid consumers ( $P < .05$ ), indicating impaired adrenal androgen production
  - Amenorrhea after opioid treatment started was common

# Opioid-Induced Neuro-Endocrine Changes

## ■ Hypogonadism in opioid-treated men

Daniell HW, J Pain 2002;3:377-84

- Survey of 54 men consuming oral sustained-action opioids for pain and 27 controls
- Results
  - Free testosterone (FT), total testosterone (TT), estradiol (E(2)), dihydrotestosterone (DHT), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) averaged much lower in opioid users in a dose-related pattern ( $P < .0001$  for all comparisons)
  - FT, TT, and E(2) levels were subnormal in 56%, 74%, and 74%, respectively, of opioid consumers
  - 87% (39 of 45) of opioid-ingesting men who reported normal erectile function before opioid use reported severe erectile dysfunction or diminished libido after beginning their opioid therapy

# Opioid-Induced Neuroendocrine Changes

- Most (50-75%) opioid-treated men have hypothalamic hypogonadism
- Prevalence of hypogonadism in women uncertain
- Hypogonadism can cause
  - Decreased libido, erectile dysfunction, infertility
  - Fatigue and mood disorder
  - Loss of muscle mass
  - Osteoporosis
- Still unknown
  - Interactions with other drugs and illnesses
  - Frequency of short-term and long-term effects
  - Value of treatment or opioid rotation

# Opioid-Induced Neuroendocrine Changes

- Based on limited existing data
  - Patients should be asked about symptoms of hypogonadism
  - Symptomatic patients should have hormone levels measured
  - Role of screening should be considered
  - Patients on long-term therapy should be considered for bone density screening

# Opioid-Induced Neuroendocrine Changes

- Based on limited existing data
  - Men with low testosterone should be considered for replacement therapy
  - Role of treatment of women uncertain but should be considered in premenopausal patients