Management of Cancer-Related Dyspnea: The Pros and Cons of Opioids

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Disclosure

• We will discuss off-label opioid use

• Funding sources for investigator-initiated research studies
  – National Cancer Institute
  – National Institute of Nursing Research
  – American Cancer Society
  – Andrew Sabin Family Fellowship Award
  – Sister Institution Network Fund
  – Institutional Research Grant
  – Helsinn Therapeutics
  – Insys Therapeutics
  – Teva Pharmaceutical
  – Depomed Inc
The Clinical Problem

• Dyspnea is common
  – 10-70% of cancer patients (Solano et al. JPSM 2006)
  – Increase intensity in last weeks/days of life (Hui et al. JPSM 2015)

• Dyspnea is distressing and debilitating
  – Worse than pain (Tishelman et al. J Clin Oncol 2007)

• Dyspnea has few treatment options
  – Opioids not FDA approved
  – Few other medications found to be effective
Opioids for Dyspnea: Rationale

- Dampens abnormally high inspiratory drive in the pre-Botzinger complex → decreases neuromechanical dissociation

- Modulates cortical activity

- Decreases sensitivity to hypercapnia

- Cardiovascular
  - ↑ peripheral vasodilatation
  - ↓ cardiac preload

Opioids for Dyspnea: Evidence

- Double-blind randomized crossover controlled trial in 17 COPD patients
- Naloxone 10 mg or saline 5 min before treadmill exercise

Implication: Endorphins have a role in modulating dyspnea

P=0.02  P=0.04

Mahler et al. *Eur Respir J* 2009
Opioids for Dyspnea: Evidence

Double-blind, crossover, randomized controlled trial

10 advanced cancer patients
- dyspnea at rest
- on continuous O₂

R

SC Morphine q4h x 1 day
Placebo q4h x1 day

Placebo q4h x 1 day
SC Morphine q4h x1 day

Primary Outcome: Dyspnea VAS at 45 minutes
Morphine: 30 ± 23 → 14 ± 18
Placebo: 31 ± 27 → 32 ± 27

Opioids for Dyspnea: Cochrane

- Low quality evidence that shows benefit for the use of oral or parenteral opioids to palliate breathlessness
- No evidence to support the use of nebulised opioids

Barnes et al. Cochrane Database 2016
Opioids for Dyspnea: Cochrane

- Negative studies may be affected by
  - Sample size
  - Patient selection
  - Sensitivity of outcome measure
  - Study intervention (dose, timing etc)

- Methodologic issues
  - 26 RCTs with 526 participants
  - Most studies high or unclear risk of bias
  - Many opioids: dihydrocodeine, diamorphine, morphine (PO, NEB), fentanyl (SC, NED), oxycodone, hydromorphone
  - Heterogeneous designs: 12 included exercise testing, variable outcomes (NRS, VAS, Borg, OCD)

Barnes et al. Cochrane Database 2016
Opioids for Dyspnea: Prophylaxis

- Double-blind randomized controlled trial
- Fentanyl dose 20-50% of morphine equivalent daily dose
- 22 patients enrolled (1:1 ratio)

Cancer patients with exercise induced dyspnea

Walk #1 (no medications given)

Walk #2 (study medications given)

Hui et al. J Pain Symp Manage 2017
Common Side Effects/Concerns

- Barnes et al. *Cochrane Database* 2016
  - Nausea and vomiting: RR 4.7 (95% CI 1.7, 13.0)
  - Constipation: RR 3 (95% CI 1.6, 5.5)
  - Drowsiness: RR 2.9 (95% CI 1.2, 7.0)

- Other concerns
  - Respiratory depression
  - Sleep disordered breathing
  - Addiction
Common Side Effects/Concerns

• Barnes et al. *Cochrane Database* 2016
  – Nausea and vomiting: RR 4.7 (95% CI 1.7, 13.0) >> Antiemetics
  – Constipation: RR 3 (95% CI 1.6, 5.5) >> Laxatives
  – Drowsiness: RR 2.9 (95% CI 1.2, 7.0) >> Psychostimulants

• Other concerns
  – Respiratory depression >> Appropriate use and prescribing
  – Sleep disordered breathing >> Monitoring and careful prescribing
  – Addiction >> Monitoring and careful prescribing
Respiratory Depression

- 15 opioid-naïve and 12 opioid-tolerant patients admitted to palliative care unit started on strong opioids for moderate/severe dyspnea
  - Opioid naïve: Immediate release morphine 2.5 mg q4h and q15min PRN or equivalent doses of hydromorphone; titrate as needed up to >20 mg q4h
  - Opioid tolerant: Increase MEDD by 25%

Sleep Disordered Breathing

• Prevalence (Correa et al. Anesth Analg 2015)
  – Selective populations in 8 small studies
  – Overall: 70% (42-85%)
  – Central sleep apnea: 24% (14-60%)
  – Obstructive sleep apnea: 8-39%
  – Risk factors: MEDD >200 mg/d, low BMI

• Management (Van Ryswyk & Antic Chest 2016)
  – Monitoring
  – Opioid dose reduction
  – Adaptive servo-ventilation
Addiction

  – 0-50% in chronic non-malignant pain patients
  – 0-7.7% in cancer patients
  – 0.6% in US general population (2/319 million, 2013 data)

• Management (Paice et al. *J Clin Oncol* 2016)
  – Monitoring and risk stratification
  – Risk mitigation strategies
  – Psychological interventions
  – Harm reduction
## Clinical Practice Guidelines

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<tbody>
<tr>
<td><strong>Opioids recommended</strong></td>
<td>Yes</td>
<td>Yes, first line</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Opioids mentioned</strong></td>
<td>Morphine, Fentanyl, Oxycodone</td>
<td>Morphine, Diamorphine, Dihydrocodeine, Others</td>
<td>Not specified</td>
<td>Hydrocodone, Morphine, Oxycodone, Hydromorphone, Codeine, Others</td>
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<tr>
<td><strong>Opioid naïve dosing</strong></td>
<td>Morphine 2.5-10 mg PO q2h PRN or 1-3 mg IV q2h PRN</td>
<td>Morphine 2.5-5 mg PO q4h or 1-2.5 mg SC q4h, Hydromorphone 1.3 mg PO q4h or 0.2-0.5 mg SC q4h</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td><strong>Opioid tolerant dosing</strong></td>
<td>Increase dose by 25%</td>
<td>Increase dose by up to 25%-50%</td>
<td>Not specified</td>
<td>Increase dose by 50%</td>
</tr>
<tr>
<td><strong>Nebulized</strong></td>
<td>May be considered</td>
<td>Not supported</td>
<td>No fewer side effects</td>
<td>Not supported</td>
</tr>
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Summary

• Every treatment should be personalized based on risk:benefit ratio
  – Clinical problem: significant
  – Treatment benefit: low to moderate
  – Treatment risk: low to moderate
  – Alternatives: few proven options
  – If unsure, consider therapeutic trial

• All clinical guidelines support the use of opioids for palliation of dyspnea in cancer patients

• More research is needed!