Interventions that Lack an Evidence-base for Treating Dyspnea, Nausea, and Death Rattle
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Disclosures
Margaret Campbell has no real or perceived conflicts of interest that relate to this presentation.

Objectives
• Identify non-beneficial or equivocal palliative care treatments that are in common use
• Describe the evidence, strengths, limitations and gaps for select palliative care treatments
Case study #1
Melissa is near death following bilateral ischemic stroke. On patient rounds you note noisy upper airway sounds (death rattle). Sounds are audible at the foot of the bed. Melissa is not conscious and has no signs of distress.

Her family have been visiting round the clock and ask you about the noisy breathing.

How will you respond?
A. Prescribe or recommend transdermal scopolamine
B. Prescribe or recommend atropine drops by mouth
C. Prescribe or recommend SQ Glycopyrrolate
D. Prescribe or recommend no medication

Death rattle
• Naturally occurring upper airway sound from retained pharyngeal secretions
• Patients near death become drowsy and/or unconscious and unable to clear secretions
• Small volumes resonate in airway generating noise
• Noise intensity varies
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Hospice and Palliative Nurses Association (HPNA) Clinical Practice Forum – October 23-24, 2015

Death rattle prevalence

• 44% of inpatient palliative care unit patients (Heisler, et al. J Pain Symptom Manage, 2013)

• 45% of inpatient palliative care/hospice patients (Campbell, et al. J Pall Med, 2013)

Distress

• Bereaved relatives – semi-structured interviews (Wee, et al., Palliative Med, 2006)

  n = 27; 12 had experienced death rattle

  50% were distressed by the sound
  • “It was soul-destroying to see her there... she was lying there in a sort of daze but all she was doing was like this horrible noise from her mouth”

  50% were neutral or found it a helpful signal of impending death
  • “I wasn’t distressed by it. I had heard that people who were near the end did breathe a bit oddly”

• Hospice staff and volunteers – focus group (Wee, et al., Palliative Med, 2008)

  Seven meetings with 41 total participants (nursing, medical, chaplaincy, housekeeping, and volunteers)

  Some were matter-of-fact
  • “I think it’s kind of a natural progression... deep down they’re quite comfortable, aren’t they?”

  Most reported negative responses
  • “I can’t imagine that if that was present at death, you won’t continue to hear that because it’s such a horrible noise...I think I would because it’s so horrible”
Distress

• Patients – prospective observation (Campbell, et al., J Pall Med, 2013)
  - 71 patients who were near death

• Measures
  - Death rattle intensity
  - Respiratory Distress Observation Scale©

Results

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<th>Variable</th>
<th>No death rattle</th>
<th>Death rattle</th>
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<tr>
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</tr>
<tr>
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<td>17 women</td>
<td>13 women</td>
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<td>Pulmonary 2</td>
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<td>Cardiac 3</td>
<td>Cardiac 2</td>
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<td>Other 7</td>
<td>Other 5</td>
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<td>&lt; .01</td>
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</table>

Death Rattle Treatment

• Cochrane review: Interventions for noisy breathing in patients near to death (Wee, et al., 2012)

• Selection criteria
  - Randomized controlled trials
  - Controlled before-after studies
  - Interventions – atropine, scopolamine, glycopyrrolate

• Results – n = 4 studies
  - No evidence that any intervention is superior to placebo
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Medication alternatives

• Side-lying positioning

• No treatment
  . Advise listeners about “naturalness” of the sounds
  . Advise listeners about “no patient distress”
  . Advise listeners about limited/no medication benefit
  . Medications have adverse effects but patient cannot report them
  . Consider that medicating patient to soothe family (or staff) is ethically problematic

Case study #1

Melissa is near death following bilateral ischemic stroke. On patient rounds you note noisy upper airway sounds (death rattle). Sounds are audible at the foot of the bed. Melissa is not conscious and has no signs of distress.

Her family have been visiting round the clock and ask you about the noisy breathing.

Has your response changed?

A. Transdermal scopolamine
B. Atropine drops by mouth
C. SQ Glycopyrrolate
D. No medication

Case study #2
Howard is dying from advanced COPD and lung cancer. He is hypersomnolent, rouses briefly to touch, breathing 12-14 breaths/minute, with no signs of respiratory distress. He uses oxygen by nasal cannula at 3 l/min. He can no longer use his metered-dose inhalers. He can no longer swallow.

On home visit his wife reports no recent use of prn morphine and nothing to eat or drink. You conclude that death is imminent and he is comfortable.

His wife asks if the oxygen can be discontinued?

How will you respond?
A. Discontinue oxygen
B. Maintain oxygen
C. Reduce flow rate
D. Measure peripheral oxygen saturation

Oxygen benefits
• Correct hypoxemia
• Reduce dyspnea
• Prolong life
COPD and long-term oxygen

- >15 hours/day
- Increased survival of patients with resting dyspnea
- \( \text{PaO}_2 < 55 \text{ mm Hg} \)
- \( \text{SaO}_2 < 88\% \)

Global Initiative for Chronic Obstructive Lung Disease, 2013

Oxygen burdens

- Decreased mobility
- Nasal drying
  - Nosebleed
- Feeling of suffocation
- Prolongs dying
  - Extends caregiver days
  - Increases health care costs
- Flammability risks around open flame

Oxygen therapy for dyspnea in adults

- Cochrane review (Cranston et al., 2009)
  - Eight RCTs with 144 participants
    - Cancer \( n = 97 \)
    - Heart failure \( n = 35 \)
    - Kyphoscoliosis \( n = 12 \)
  - No consistent beneficial effect of oxygen inhalation over air inhalation

Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnea: a double-blind, randomized controlled trial (Abernethy et al., Lancet, 2010)

- 239 terminally ill patients with refractory dyspnea, PaO2 >55 mm Hg
- Random assignment to oxygen or air via nasal cannula for 7 days for at least 15 hours/day
- Dyspnea by NRS (0-10) morning and evening
- Oxygen provided no additional symptomatic benefit in non-hypoxemic, dyspneic patients

Symptomatic oxygen for non-hypoxemic COPD

- Cochrane review (Uronis, et al., 2011)
- RCTs comparing oxygen to air in mildly or non-hypoxemic patients with COPD
  - 28 studies with 702 patients
- Slight improvement in dyspnea with oxygen

Oxygen is non-beneficial for most patients who are near death (Campbell, et al., J Pain Symptom Manage, 2013)

- Repeated measures, double – blinded, randomized cross-over, using the patient as his/her own control
- 32 inpatient palliative care patients and inpatient hospice patients near death with one or more of COPD, heart failure, lung cancer or pneumonia; comfortable at baseline
- Random application of oxygen, medical air, or no flow via nasal cannula every 10 minutes with respiratory distress measurement
  - 27 (84%) had oxygen flowing at baseline
  - 91% patients experienced no distress during the protocol
  - No differences in patient comfort were seen across gas and flow conditions (F = 0.55, p = 0.74)
  - 3 patients were restored to baseline oxygen

Oxygen Conclusions

• Declining oxygen saturation is naturally occurring and expected
• Declining oxygen saturation may predict but does not signify respiratory distress
• The routine application of oxygen to most patients who are near death is not supported
• An n of 1 trial of oxygen is appropriate in the face of respiratory distress

Case study #2

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Case study #3
Lucretia has advanced ovarian cancer with abdominal carcinomatosis. Her pain is well-controlled but nausea has been an ongoing problem. She gags whenever she tries to swallow medication. Even sips of water have been problematic.

You see ABH gel in the compounding pharmacy formulary. Perhaps this topical compound will resolve Lucretia’s nausea.

Nausea
• Multi-factorial etiology
• Difficult to manage
  • Many patients unable to take oral medications
• Granisetron is an effective topical agent
  • Very expensive ($360/patch)
• An effective, inexpensive topical agent could improve care

ABH gel
Ativan®, Benadryl®, and Haldol®
• Compounded formula in a topical gel
• Efficacy shown in case reports (Moon, Int J Pharm Compd, 2006; Fields, Pharm Times, 2007)
• Efficacy shown in two uncontrolled trials (Bleicher, et al., J Support Onc, 2008)
### Does it work?  (Smith, et al., J Pain Symptom Manage, 2012)

10 healthy volunteers

- Standard dose
  - 2mg lorazepam, 25mg diphenhydramine, 2mg haloperidol
  - Rubbed on volar surface of wrists by the participant
  - Plasma concentrations sampled at 0, 30, 60, 90, 120, 180, and 240 minutes
- No lorazepam or haloperidol detected in any sample from any volunteer
- Sub-therapeutic levels of diphenhydramine in 5 volunteers
- RCT needed

### A randomized trial of the effectiveness of topical “ABH gel” vs. placebo in cancer patients with nausea  (Fletcher, et al., J Pain and Symptom Manage, 2014)

- 20 patients with cancer
  - Self-reported nausea score of at least 4/10 at evaluation time
  - No changes to anti-emetic regimen in previous 12 hours
- Randomized, double-blind, placebo-controlled, crossover clinical trial
- Measures
  - Difference in nausea score at baseline and at end-point of 60 minutes
  - Number of episodes of emesis
- Results
  - Small mean change in nausea; no difference between conditions
  - Evidence of placebo-effect

### ABH gel evidence summary

- Medication is not absorbed
- Effect no better than placebo
- Although inexpensive and easy to use there is no scientific basis for this formulation
Case study #3

Lucretia has advanced ovarian cancer with abdominal carcinomatosis. Her pain is well-controlled but nausea has been an ongoing problem. She gags whenever she tries to swallow medication. Even sips of water have been problematic. You see ABH gel in the compounding pharmacy formulary. Perhaps this topical compound will resolve Lucretia’s nausea.

Tradition vs. Evidence

• Our field is becoming more sophisticated with regard to evidence-based practice
• Changing tradition remains slow
• What will you consider changing in your practice?