Delirium in Advanced Cancer: An Evidence Based Update

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Outline

• Introduction

• Treatment
  – Setting therapeutic goals
  – Treatment of underlying causes
  – Non-pharmacologic approaches
  – Pharmacologic approaches

• Summary
# Cardinal Features

## DSM-IV Criteria

A. Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.

B. A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

## DSM-5 Criteria

A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).

D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.
Delirium is Common

- Patient characteristics are different
- Etiology may be different
- Outcomes are different

<table>
<thead>
<tr>
<th>Setting</th>
<th>Incidence at Admission</th>
<th>Incidence During Admission</th>
<th>Incidence Before Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>General inpatient</td>
<td>10-31%</td>
<td>11-42%</td>
<td></td>
</tr>
<tr>
<td>Geriatric postop</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care vented</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative care inpatient</td>
<td>13-42% at adm</td>
<td>26-62% during adm</td>
<td>59-88% before death</td>
</tr>
</tbody>
</table>

Causes and Outcomes

Drugs
Infections
Metabolic changes
Structural abnormalities

Underlying disease, frailty, & comorbidities

Delirium

Associated Complications
- Increased morbidity
- Increased safety concerns
- Increased distress
- Increased length of stay
- Increased healthcare costs
- Increased institutionalization
- Increased mortality

Increased distress
# Delirium Recall and Related Distress

99 patients recovered from delirium

- 73 (74%) had delirium recall
- 59 (81%) reported it was distressing
- 21 (26%) had no delirium recall
- 11 (42%) reported it was distressing

## Recalled Symptom Frequency

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No.</th>
<th>Median (Q1-Q3) Patient</th>
<th>No.</th>
<th>Median (Q1-Q3) Family</th>
<th>P</th>
<th>No.</th>
<th>Median (Q1-Q3) Patient</th>
<th>No.</th>
<th>Median (Q1-Q3) Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory hallucinations</td>
<td>18</td>
<td>2 (1-2)</td>
<td>30</td>
<td>2 (2-3)</td>
<td>0.14</td>
<td>17</td>
<td>3 (2-3)</td>
<td>29</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>Delusional thoughts</td>
<td>33</td>
<td>2 (1-3)</td>
<td>46</td>
<td>2 (1-3)</td>
<td>0.20</td>
<td>31</td>
<td>3 (1-4)</td>
<td>45</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Time orientation</td>
<td>57</td>
<td>3 (2-4)</td>
<td>79</td>
<td>3 (2-4)</td>
<td>0.87</td>
<td>56</td>
<td>3 (1-3.5)</td>
<td>77</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>Place orientation</td>
<td>52</td>
<td>2 (1-4)</td>
<td>75</td>
<td>2 (2-4)</td>
<td>0.74</td>
<td>52</td>
<td>3 (1-4)</td>
<td>73</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>55</td>
<td>2 (2-4)</td>
<td>82</td>
<td>3 (2-4)</td>
<td>0.43</td>
<td>54</td>
<td>3 (2-4)</td>
<td>80</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Tactile hallucinations</td>
<td>12</td>
<td>2 (1-2.5)</td>
<td>25</td>
<td>2 (1-3)</td>
<td>0.79</td>
<td>12</td>
<td>3.5 (2-4)</td>
<td>23</td>
<td>3 (1-4)</td>
</tr>
<tr>
<td>Visual hallucinations</td>
<td>50</td>
<td>2 (1-3)</td>
<td>55</td>
<td>2 (1-3)</td>
<td>0.93</td>
<td>49</td>
<td>2 (1-3)</td>
<td>53</td>
<td>3 (2-4)</td>
</tr>
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</table>

## Distress Score

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patient</th>
<th>No.</th>
<th>Median (Q1-Q3)</th>
<th>P</th>
<th>Family Caregiver</th>
<th>No.</th>
<th>Median (Q1-Q3)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Auditory hallucinations</td>
<td>0.38</td>
<td>17</td>
<td>3 (2-3)</td>
<td>0.14</td>
<td>29</td>
<td>3 (1-4)</td>
<td>.38</td>
<td></td>
</tr>
<tr>
<td>Delusional thoughts</td>
<td>0.31</td>
<td>31</td>
<td>3 (1-4)</td>
<td>0.20</td>
<td>45</td>
<td>3 (2-4)</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Time orientation</td>
<td>0.69</td>
<td>56</td>
<td>3 (1-3.5)</td>
<td>0.87</td>
<td>77</td>
<td>3 (1-4)</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>Place orientation</td>
<td>0.19</td>
<td>52</td>
<td>3 (1-4)</td>
<td>0.74</td>
<td>73</td>
<td>3 (1-4)</td>
<td>.19</td>
<td></td>
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<tr>
<td>Psychomotor agitation</td>
<td>0.09</td>
<td>54</td>
<td>3 (2-4)</td>
<td>0.43</td>
<td>54</td>
<td>4 (3-4)</td>
<td>.09</td>
<td></td>
</tr>
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<td>0.68</td>
<td>12</td>
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<td>.68</td>
<td></td>
</tr>
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<td>Visual hallucinations</td>
<td>0.01</td>
<td>49</td>
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<td>0.93</td>
<td>53</td>
<td>3 (2-4)</td>
<td>.01</td>
<td></td>
</tr>
</tbody>
</table>

Bruera et al. *Cancer* 2008
"I'VE BEEN HAVING HALLUCINATIONS AGAIN, DOCTOR."
Delirium Assessment
Missed Delirium

Missed Delirium
61%

Reversible Delirium
67%

252/771 (33%) patients who had an inpatient palliative care consult found to have delirium by the palliative care team. 99 (39%) diagnosed with delirium by oncology team.

55/82 (67%) patients with reversible delirium had a missed diagnosis initially.

Routine screening is key!

De La Cruz et al. Supp Care Cancer 2015
## Delirium Assessment

### Screening Tools

<table>
<thead>
<tr>
<th>Screening Tool</th>
<th>Burden</th>
<th>Sens</th>
<th>Spc</th>
<th>LR- (95% CI)</th>
<th>LR+ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion Assessment Method (CAM)</td>
<td>4 items &lt;5 min</td>
<td>86%</td>
<td>93%</td>
<td>0.16 (0.09, 0.29)</td>
<td>9.6 (5.8, 16)</td>
</tr>
<tr>
<td>Delirium Rating Scale (DRS)</td>
<td>10 items Cutoff ≥10/32</td>
<td>95%</td>
<td>79%</td>
<td>0.07 (0.03, 0.37)</td>
<td>4.3 (2.1, 9.1)</td>
</tr>
<tr>
<td>Memorial Delirium Assessment Scale (MDAS)</td>
<td>10 items &lt;10 min</td>
<td>92%</td>
<td>92%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cutoff ≥10/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium Observation Screening Scale (DOS/DOSS)</td>
<td>13/25 items &lt;5/10 min</td>
<td>92%</td>
<td>82%</td>
<td>0.1 (0.03, 0.37)</td>
<td>5.2 (2.7, 9.9)</td>
</tr>
</tbody>
</table>

Greer et al. VA-ESP Project #09-009 2011
Outline

• Introduction

• Treatment
  – Setting therapeutic goals
  – Treatment of underlying causes
  – Non-pharmacologic approaches
  – Pharmacologic approaches

• Summary
Prognosis-Based Decision Making
Delirium in Advanced Cancer

Advanced cancer (months to years)

Post-Op Delirium
Transient, reversible
Goals: prevention, short term treatment

Far advanced cancer (weeks to months)

Medical Delirium
Possibly reversible
Goals: treat underlying cause, control delirium symptoms

Actively dying (days to weeks)

Terminal Delirium
Often less reversible
Part of dying process
Goals: palliation, control agitation

“End of life”, “terminally ill”: months or less of survival

Medical/Surgical Settings

Palliative Care Settings

Hui et al. Curr Opin Supp Palliat Care 2016
Delirium Management

Setting Realistic Goals

Variable level of evidence in different care settings

Prevention of delirium

Reversal of delirium

Palliation of delirium symptoms

Reduce delirium related distress

Non-Pharmacologic Interventions

Pharmacologic Interventions

Treat reversible causes

Non-Pharmacologic Interventions
Reversibility of Delirium
Palliative Care Setting

- 71 patients with advanced cancer admitted to palliative care developed delirium
  - Reversal in 46/94 (49%) episodes
  - Terminal delirium in 46/52 (88%) APCU deaths
  - Median survival ~25 days

<table>
<thead>
<tr>
<th>Categories†</th>
<th>No. (%) of Episodes</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reversed (n = 40)</td>
<td>Nonreversed (n = 31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Psychotropic drugs</td>
<td>38 (95)</td>
<td>15 (48)</td>
<td>8.85</td>
</tr>
<tr>
<td>Dehydration</td>
<td>26 (65)</td>
<td>8 (26)</td>
<td>2.35</td>
</tr>
<tr>
<td>Miscellaneous other causes</td>
<td>7 (18)</td>
<td>7 (23)</td>
<td>0.69</td>
</tr>
<tr>
<td>Nonrespiratory infection</td>
<td>10 (25)</td>
<td>8 (26)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hypoxic encephalopathy</td>
<td>11 (28)</td>
<td>22 (71)</td>
<td>0.39</td>
</tr>
<tr>
<td>Metabolic</td>
<td>10 (25)</td>
<td>18 (58)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hematologic</td>
<td>5 (13)</td>
<td>7 (23)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Lawlor et al. Arch Intern Med 2001
## Reversibility of Delirium
### Thiamine Deficiency

- Wernicke encephalopathy diagnosed clinically and treated before lab values confirmed

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>71yo M</td>
<td>66yo F</td>
<td>77yo F</td>
</tr>
<tr>
<td>DRS baseline</td>
<td>21</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Gradual</td>
<td>Gradual</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Ocular</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Thiamine lvl</td>
<td>18ng/ml</td>
<td>15ng/ml</td>
<td>NA</td>
</tr>
<tr>
<td>Reversed after tx</td>
<td>Yes</td>
<td>After 3 days</td>
<td>After 3 days</td>
</tr>
</tbody>
</table>

- 70 year old woman with delirium, disorientation, cognitive impairment but no ocular changes or gait abnormalities
  - Thiamine level 14 (normal 20-50 ng/ml), started IV thiamine 100 mg/day
  - Day 1: DRS 24
  - Day 2: improvement in cognition and insomnia
  - Day 3: able to communicate
  - Day 4: DRS 3. Thiamine level 679 ng/ml
  - Died 10 days later

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Onishi et al. *Supp Care Cancer* 2004

Yae et al. *Palliat Supp Care* 2005
Treat Underlying Cause(s)

Take Home Message

Risks

Benefits

Investigations needed

Reversibility of delirium

Improves comorbidities
Delirium Management
Setting Realistic Goals

- Prevention of delirium
- Reversal of delirium
- Palliation of delirium symptoms
- Reduce delirium related distress

Variable level of evidence in different care settings

- Non-Pharmacologic Interventions
- Pharmacologic Interventions

- Treat reversible causes
- Non-Pharmacologic Interventions
- Pharmacologic Interventions

- Pharmacologic Interventions
- Pharmacologic Interventions

- Pharmacologic Interventions
Non-Pharmacologic Measures
Hydration for Delirium Prevention

Double blind, randomized controlled trial

129 cancer patients in hospice

1000 mL per day until off study

100 mL per day until off study
Non-Pharmacologic Measures
Hydration for Delirium Prevention

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Change between Baseline and Day 4</th>
<th>Change between Baseline and Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydration N=49</td>
<td>Placebo N=51</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>Hydration N=44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo N=49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-value</td>
</tr>
<tr>
<td>Composite outcome [fatigue, drowsiness, hallucinations, myoclonus], mean (95% confidence interval)</td>
<td>-3.3 (-1.1, -5.4)</td>
<td>-2.8 (-0.2, -5.3)</td>
</tr>
<tr>
<td>MDAS, median (IQR)</td>
<td>1 (-2, 5.8)</td>
<td>3.5 (-0.3, 14.5)</td>
</tr>
<tr>
<td>NuDESC, median (SD)</td>
<td>0 (-1, 1)</td>
<td>0 (-1, 2)</td>
</tr>
<tr>
<td>Day</td>
<td>0 (-1, 1)</td>
<td>0 (-1, 2)</td>
</tr>
<tr>
<td>Evening</td>
<td>0 (-1, 1)</td>
<td>0 (-1, 2)</td>
</tr>
<tr>
<td>Night</td>
<td>0 (-1, 0)</td>
<td>0 (-1, 2)</td>
</tr>
</tbody>
</table>

**Caveats**

- Only patients with mild-moderate dehydration
- Delirium was a secondary outcome (floor effect)
- Patients with days-weeks of survival
- May need multi-model intervention

Bruera et al. *J Clin Oncol* 2013
Multicomponent Intervention
Delirium Prevention

Open label, matched cohort study

852 geriatric hospitalized patients at intermediate/high risk of delirium*

Elder Life Program (intervention unit)
- Interdisciplinary team (geriatrician, nurse specialist, recreation specialist, Elder life specialists, physical therapy, volunteers)
- Targeted 6 risk factors (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, dehydration)

Usual Care (control units) with same attending physician

* Four risk factors: visual impairment, severe illness, cognitive impairment, high BUN/Cr
  - Intermediate risk: 1-2 risk factors
  - High risk: 3-4 risk factors

Inouye et al. NEJM 1999
## Multicomponent Intervention

### Delirium Prevention

<table>
<thead>
<tr>
<th>Domain</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation protocol</td>
<td>Board with names of care team members listed, communication to reorient to surroundings. Therapeutic activities protocol TID, as tolerated; includes family involvement and structured reminiscence.</td>
</tr>
<tr>
<td>Sleep protocol</td>
<td>Warm drink at bedtime, relaxation music, unit-wide noise reduction strategies, schedule adjustments to allow sleep (rescheduling of vitals, medications, and procedures).</td>
</tr>
<tr>
<td>Mobilization protocol</td>
<td>Physical/occupational therapy assessment, minimal use of immobilizing equipment.</td>
</tr>
<tr>
<td>Vision protocol</td>
<td>Visual aids (e.g., glasses or magnifying lenses), adaptive equipment (e.g., large illuminated telephone keypads) for patients with visual impairments, reinforcement of their use.</td>
</tr>
<tr>
<td>Hearing protocol</td>
<td>Portable amplifying devices, special communication techniques for patients with hearing impairments, daily reinforcement of these adaptations.</td>
</tr>
<tr>
<td>Dehydration protocol</td>
<td>Early recognition of dehydration and volume repletion (e.g., encourage oral intake or parenteral hydration).</td>
</tr>
</tbody>
</table>
### Multicomponent Intervention

#### Delirium Prevention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Group</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Usual Care</td>
</tr>
<tr>
<td>All matched patients (n=852)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode of delirium — no. of patients (%)</td>
<td>42 (9.9)</td>
<td>64 (15.0)</td>
</tr>
<tr>
<td>Total days of delirium§</td>
<td>105</td>
<td>161</td>
</tr>
<tr>
<td>No. of episodes of delirium¶</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>Patients with delirium (n=106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD delirium-severity score</td>
<td>3.85±1.27</td>
<td>3.52±1.44</td>
</tr>
<tr>
<td>Recurrence (two or more episodes) — no. of patients (%)</td>
<td>13 (31.0)</td>
<td>17 (26.6)</td>
</tr>
</tbody>
</table>

Inouye et al. *NEJM* 1999
Delirium Prevention
Systematic Review and Metaanalysis

- Multicomponent Intervention (RR 0.63, 95% CI 0.43-0.92)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>MCI</th>
<th>Control</th>
<th>Risk Ratio MCI-1</th>
<th>Weight</th>
<th>Risk Ratio MCI-1</th>
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</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abizanda 2011</td>
<td>27/186</td>
<td>39/184</td>
<td></td>
<td>12.8 %</td>
<td>0.68 [0.44, 1.07]</td>
</tr>
<tr>
<td>Bonaventura 2007</td>
<td>0/30</td>
<td>5/30</td>
<td></td>
<td>0.3 %</td>
<td>0.09 [0.01, 1.57]</td>
</tr>
<tr>
<td>Jeffs 2013</td>
<td>15/305</td>
<td>21/343</td>
<td></td>
<td>6.1 %</td>
<td>0.80 [0.42, 1.53]</td>
</tr>
<tr>
<td>Martínez 2012</td>
<td>8/144</td>
<td>19/143</td>
<td></td>
<td>4.0 %</td>
<td>0.42 [0.19, 0.92]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>665</td>
<td>700</td>
<td></td>
<td>23.3 %</td>
<td>0.63 [0.43, 0.92]</td>
</tr>
</tbody>
</table>

Total events: 50 (MCI), 84 (Control)
Heterogeneity: Tau² = 0.03; Ch² = 3.53, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 2.40 (P = 0.016)

- Pharmacologic therapies (inadequate evidence)
  - Antipsychotics (RR 0.73, 95% CI 0.33-1.59)
    - Haloperidol (RR 1.05, 95% CI 0.69-1.60)
    - Olanzapine (RR 0.36, 95% CI 0.24-0.52)
  - Melatonin (RR 0.41 95% CI 0.09-1.89)
  - Cholinesterase inhibitors (RR 0.68 95% CI 0.17-2.62)

Siddiqi et al. Cochrane Database 2016
## Multicomponent Intervention Delirium Treatment

### 4 geriatric, unblinded randomized controlled trials

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention (vs. usual care)</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cole et al. CMAJ 1994</strong>&lt;br&gt;88 pts with delirium&lt;br&gt;Medical unit&lt;br&gt;Age 75 or older</td>
<td>Consultation by geriatrician or psychiatrist and followup by liaison nurse (environment, orientation, familiarity, communication, activities) during admission</td>
<td>Crichton Geriatric Behavioural Rating Scale (-8.1 vs. -3.5, P&lt;0.05) over 8 wks&lt;br&gt;Short Portable Mental Status Questionnaire (-0.5 vs. -0.6, p=0.06)&lt;br&gt;No difference in restraints, length of stay, discharge outcomes or mortality</td>
<td>Non-pharm on delirium; mixed findings and limited improvement</td>
</tr>
<tr>
<td><strong>Cole et al. CMAJ 2002</strong>&lt;br&gt;227 pts with delirium&lt;br&gt;Medical units&lt;br&gt;Age 65 or older</td>
<td>Consultation by geriatrician or psychiatrist and followup by liaison nurse (environment, orientation, familiarity, communication, activities) during admission</td>
<td>Time to improvement (HR 1.1, 95% 0.74-1.63)&lt;br&gt;Delirium improvement (48% vs. 45%)&lt;br&gt;No difference in Delirium Index score, Barthel Index score, length of stay, discharge outcomes or survival</td>
<td>Non-pharm on delirium; no improvement</td>
</tr>
<tr>
<td><strong>Lundstrom et al. JAGS 2005</strong>&lt;br&gt;125 pts with delirium&lt;br&gt;275 pts without delirium&lt;br&gt;Medical service&lt;br&gt;Age 70 or older</td>
<td>2 day course in geriatric medicine focusing on delirium&lt;br&gt;Education concerning caregiver-patient interaction&lt;br&gt;Reorganization of nursing care&lt;br&gt;Guidance for nursing staff once a month</td>
<td>Complete remission rate on day 7 (70% vs. 40%, P=0.001)&lt;br&gt;Able to return to home (78% vs. 60%, P=0.05)&lt;br&gt;Length of stay (11 d vs. 21 d)&lt;br&gt;Lower mortality (3% vs. 14%, P=0.03)</td>
<td>Educational/system change; lots of improvement</td>
</tr>
<tr>
<td><strong>Pitkala et al. J Gerontology 2006</strong>&lt;br&gt;174 pts with delirium&lt;br&gt;Medical services&lt;br&gt;Age 69 or older</td>
<td>Comprehensive geriatric assessment at baseline, avoid conventional neuroleptics, orientation, physiotherapy, geriatric interventions (nutrition supplements, calcium, hip protectors), cholinesterase inhibitors</td>
<td>Mortality at 1 year (61% vs. 64%, P=0.64)&lt;br&gt;Days in hospital (126 vs. 140, P=0.69)&lt;br&gt;Delirium MDAS improvement by day 8 (~50% vs. ~20%)&lt;br&gt;MMSE 6 months (8.4 vs. 15.8, P=0.047)&lt;br&gt;Barthel Index 6 months (70.2 vs. 63.8, P=0.14)</td>
<td>Non-pharm; Delirium secondary endpoint and positive</td>
</tr>
</tbody>
</table>

Ahraha et al. *PLOS One* 2015
Multicomponent Intervention

Take Home Message

Prevention

- Risks
  - Hard to standardize

- Benefits
  - Improves comorbidities
  - Strong evidence to prevent delirium by 30-40%

Treatment

- Risks
  - Paucity of evidence
  - Hard to standardize

- Benefits
  - Potentially useful to treat delirium
  - Improves comorbidities
Delirium Management

Setting Realistic Goals

Variable level of evidence in different care settings

- Prevention of delirium
  - Non-Pharmacologic Interventions
  - Pharmacologic Interventions

- Reversal of delirium
  - Treat reversible causes
  - Non-Pharmacologic Interventions
  - Pharmacologic Interventions

- Palliation of delirium symptoms
  - Pharmacologic Interventions

- Reduce delirium related distress
  - Pharmacologic Interventions

Reversibility
Length of delirium
Severity of delirium

Reduce delirium related distress
Pharmacologic Interventions
Delirium Prevention

- Antipsychotics (RR 0.73, 95% CI 0.33-1.59)
  - Haloperidol (RR 1.05, 95% CI 0.69-1.60)
  - Olanzapine (RR 0.36, 95% CI 0.24-0.52)

- Melatonin (RR 0.41 95% CI 0.09-1.89)

- Cholinesterase inhibitors (RR 0.68 95% CI 0.17-2.62)

Siddiqi et al. Cochrane Database 2016
Pharmacologic Interventions
Delirium Prevention

• Antipsychotics for prevention of post-op delirium
  – 2 of 3 haloperidol trials +ve (Kaneko et al. 1999 ICU; Wang et al. 2012 ICU)
  – 2 of 2 risperidone trials +ve (Prakanrattana et al. 2007 ICU; Hakim et al. 2012 ICU)
  – 1 of 1 olanzapine trial +ve (Larsen et al. 2010 Geriatric)

• Cholinesterase inhibitors for prevention of post-op delirium
  – 0 of 3 donepezil trials +ve
  – 0 of 2 rivastigmine trials +ve

Friedman et al. *Am J Psych* 2014
Pharmacologic Interventions

Delirium Treatment

• Antipsychotics for treatment of delirium
  – 0 of 1 haloperidol-placebo trial +ve (Girard et al. 2010 ICU)
  – 0 of 1 ziprasidone-placebo trial +ve (Girard et al. 2010 ICU)
  – 0 of 2 quetiapine-placebo trial +ve (Devlin et al. 2010, Tahir et al. 2010)

• Miscellaneous treatments
  – 0 of 1 melatonin trial +ve (Al Aama et al. 2011)
  – 0 of 1 ketamine trial +ve (Hudetz et al. 2009)
Neuroleptics
Delirium Treatment

Response rate at the study endpoint

Delirium severity scales scores on the endpoint

Conclusion
Our results suggested that antipsychotic medications were superior to PLA/UC in efficacy outcomes. Moreover, SGAs are more beneficial for the treatment of delirium regarding efficacy and safety outcomes compared with haloperidol. However, because the studies included in the meta-analysis were small, further study using larger samples is required.

Kishi et al. J Neurol Neurosurg Psychiatry 2016
Neuroleptics

Delirium Prevention and Treatment

12 treatment trials: 10 RCTs, 5 had placebo
7 prevention trials: all post-operative setting

B Delirium Duration in Hospitalized Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antipsychotics Mean</th>
<th>SD</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devlin 2010</td>
<td>1.8</td>
<td>1.8</td>
<td>18</td>
<td></td>
<td>18</td>
<td>11.4%</td>
<td>-3.30 [-5.12, -1.48]</td>
</tr>
<tr>
<td>Girard 2010</td>
<td>5.1</td>
<td>4</td>
<td>30</td>
<td></td>
<td>35</td>
<td>8.9%</td>
<td>0.30 [-2.04, 2.64]</td>
</tr>
<tr>
<td>Girard 2010</td>
<td>4.9</td>
<td>3.7</td>
<td>35</td>
<td></td>
<td>48</td>
<td>9.4%</td>
<td>0.10 [-2.12, 2.32]</td>
</tr>
<tr>
<td>Hakim 2012</td>
<td>3</td>
<td>1.5</td>
<td>51</td>
<td></td>
<td>3</td>
<td>19.1%</td>
<td>0.00 [-0.47, 0.47]</td>
</tr>
<tr>
<td>Han 2004</td>
<td>4.2</td>
<td>2.5</td>
<td>12</td>
<td></td>
<td>4.2</td>
<td>11.3%</td>
<td>0.00 [-1.85, 1.85]</td>
</tr>
<tr>
<td>Kalisvaart 2005</td>
<td>5.4</td>
<td>4.9</td>
<td>32</td>
<td></td>
<td>11.8</td>
<td>6.6%</td>
<td>-6.40 [-9.38, -3.42]</td>
</tr>
<tr>
<td>Larsen 2010</td>
<td>2.2</td>
<td>1.3</td>
<td>28</td>
<td></td>
<td>1.6</td>
<td>18.9%</td>
<td>0.60 [0.10, 1.10]</td>
</tr>
<tr>
<td>Page 2013</td>
<td>5.3</td>
<td>3.8</td>
<td>71</td>
<td></td>
<td>5.3</td>
<td>14.4%</td>
<td>0.00 [-1.31, 1.31]</td>
</tr>
</tbody>
</table>

Total (95% CI) 277
Heterogeneity: Tau^2 = 1.14; Chi^2 = 35.67, df = 7 (P < 0.00001); I^2 = 80%
Test for overall effect: Z = 1.36 (P = 0.17)

C Delirium Severity in Hospitalized Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antipsychotics Mean</th>
<th>SD</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breibtart 1996</td>
<td>11.6</td>
<td>6.1</td>
<td>11</td>
<td></td>
<td>11.9</td>
<td>6.7</td>
<td>8.0%</td>
</tr>
<tr>
<td>Grover 2011</td>
<td>10.1</td>
<td>6.4</td>
<td>10</td>
<td></td>
<td>11.7</td>
<td>7.2</td>
<td>8.4%</td>
</tr>
<tr>
<td>Grover 2011</td>
<td>10.1</td>
<td>6.4</td>
<td>10</td>
<td></td>
<td>12</td>
<td>6.8</td>
<td>8.5%</td>
</tr>
<tr>
<td>Han 2004</td>
<td>21.8</td>
<td>4.4</td>
<td>12</td>
<td></td>
<td>23.5</td>
<td>4.2</td>
<td>7.9%</td>
</tr>
<tr>
<td>Kalisvaart 2005</td>
<td>14.4</td>
<td>3.4</td>
<td>32</td>
<td></td>
<td>18.4</td>
<td>4.3</td>
<td>11.3%</td>
</tr>
<tr>
<td>Larsen 2010</td>
<td>16.4</td>
<td>3.7</td>
<td>28</td>
<td></td>
<td>14.5</td>
<td>2.7</td>
<td>12.1%</td>
</tr>
<tr>
<td>Maneeton 2013</td>
<td>-21.7</td>
<td>6.7</td>
<td>28</td>
<td></td>
<td>-22.9</td>
<td>6.9</td>
<td>10.8%</td>
</tr>
<tr>
<td>Tahir 2010</td>
<td>7.1</td>
<td>3.3</td>
<td>21</td>
<td></td>
<td>7.4</td>
<td>3.3</td>
<td>10.1%</td>
</tr>
<tr>
<td>Yoon 2013</td>
<td>8.5</td>
<td>4.6</td>
<td>7</td>
<td></td>
<td>8.8</td>
<td>6</td>
<td>7.3%</td>
</tr>
<tr>
<td>Yoon 2013</td>
<td>8.5</td>
<td>4.6</td>
<td>8</td>
<td></td>
<td>9.8</td>
<td>6.7</td>
<td>7.8%</td>
</tr>
<tr>
<td>Yoon 2013</td>
<td>8.5</td>
<td>4.6</td>
<td>8</td>
<td></td>
<td>7.6</td>
<td>3.7</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Total (95% CI) 175
Heterogeneity: Tau^2 = 0.18; Chi^2 = 25.55, df = 10 (P = 0.004); I^2 = 61%
Test for overall effect: Z = 0.65 (P = 0.52)
Neuroleptics
Terminally Ill Patients

[Intervention Review]

Drug therapy for delirium in terminally ill adult patients

Bridget Candy¹, Kenneth C Jackson², Louise Jones¹, Baptiste Leurent¹, Adrian Tookman¹, Michael King³

There is limited evidence from clinical trials on the role of drug therapy for the treatment of delirium in terminally ill patients. The key feature of delirium is a decreased level of consciousness (awareness). People may experience impaired memory, thinking and judgement, and become disorientated. They may experience distressing hallucinations or delusions. It occurs frequently in patients with terminal illness, and may be caused by the illness itself or occur as a side effect of drug treatments for symptom management. Our search of the international literature for trials of drug therapies for the treatment of delirium in patients with terminal illness yielded one small study, and therefore it was not possible to assess the effectiveness of drug treatment options. It is hoped that this review will provide an incentive for further research.
Are You Confused Yet?
Delirium Literature
It is Confusing!

• Different patient populations and settings
• Different doses and dosing schedules
• Different comparison arms
• Different outcome measures (variable degree of validation)

• Different systematic reviews included different studies
• Different quality of studies
• Different languages

Result: Different opinions!
Benzodiazepines
Delirium Treatment

No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition. Because of the scarcity of trials with randomization of patients, placebo control, and adequate concealment of allocation of subjects, it is clear that further research is required to determine the role of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.

• Pandharipande et al. JAMA 2017
  – Dexmedetomidine vs. lorazepam
  – Only study included in systematic review

• Breitbart et al. Am J Psych 1996
  – Haloperidol vs. chlorpromazine vs. lorazepam
  – Not included as lorazepam arm terminated early

• Christensen et al. JAGS 1998
  – Haloperidol vs. alprazolam
  – Not included because mixed dementia/delirium/amnesic/cognitive disorder

Lonergen et al. Cochrane 2009
Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

Double-blind, randomized controlled trial

30 HIV patients with delirium (mean KPS 52%)

- Haloperidol x6d, N=11
- Chlorpromazine x6d, N=14
- Lorazepam x6d, N=6

Outcomes
- Delirium Rating Scale
- Mini-Mental State Examination
- Extrapyramidal Symptom Rating Scale
- Other Side Effects
- Karnofsky Performance Status
- Medical Status Profile

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

- **Mean drug doses in first 24 h**
  - Haloperidol 3.8 (2.4) mg
  - Chlorpromazine 50 (23.1) mg
  - Lorazepam 3 (3.6) mg

- **Mean maintenance drug doses**
  - Haloperidol 1.4 (1.2) mg
  - Chlorpromazine 36 (18.4) mg
  - Lorazepam 4.6 (4.7) mg

**TABLE 1. Drug Dosing Protocol for Treatment of Delirium in Hospitalized AIDS Patients**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Oral</th>
<th>Intramuscular</th>
<th>Oral</th>
<th>Intramuscular</th>
<th>Oral</th>
<th>Intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Chlorpromazine</td>
<td>Lorazepam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td>0.125</td>
<td>10</td>
<td>5</td>
<td>0.50</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
<td>0.50</td>
<td>20</td>
<td>10</td>
<td>1.00</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>0.50</td>
<td>40</td>
<td>20</td>
<td>1.50</td>
<td>0.70</td>
</tr>
<tr>
<td>4</td>
<td>2.00</td>
<td>1.00</td>
<td>80</td>
<td>40</td>
<td>2.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>2.50</td>
<td>1.50</td>
<td>100</td>
<td>50</td>
<td>2.50</td>
<td>1.25</td>
</tr>
<tr>
<td>6</td>
<td>2.50</td>
<td>1.50</td>
<td>100</td>
<td>50</td>
<td>2.50</td>
<td>1.25</td>
</tr>
<tr>
<td>7</td>
<td>2.50</td>
<td>1.50</td>
<td>100</td>
<td>50</td>
<td>2.50</td>
<td>1.25</td>
</tr>
<tr>
<td>8</td>
<td>5.00</td>
<td>3.00</td>
<td>200</td>
<td>100</td>
<td>4.00</td>
<td>2.00</td>
</tr>
<tr>
<td>9</td>
<td>5.00</td>
<td>3.00</td>
<td>200</td>
<td>100</td>
<td>4.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Day 1: Increase dose to next level every hour if DRS >13
Day 2-6: Give total dose from day 1, div BID

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

- Improvement seen within 24 hours of treatment in haloperidol and chlorpromazine arms
- All 6 patients on lorazepam arm developed treatment limiting side effects (sedation, disinhibition, ataxia, increased confusion)

Haloperidol vs. Chlorpromazine vs. Lorazepam: HIV Patients, Front Line

• Strengths
  – First delirium study in palliative care setting
  – Rapid titration to identify optimal doses

• Limitations
  – No placebo group
  – Small sample size
  – Intensive titration schedule
  – Lorazepam arm terminated early (n=6)

Main implication: Neuroleptics are superior to benzodiazepine for delirium in the palliative care setting
Risperidone vs. Haloperidol vs. Placebo
Palliative Care, Front Line

Double-blind, randomized controlled trial

247 patients with life limiting illness, symptomatic delirium (MDAS >=7, DSM IV-R)

Risperidone PO 1 mg loading, then 0.5 mg BID, max 4 mg/d (halved if age >65), midazolam 2.5 mg SC q2h PRN

Haloperidol PO 1 mg loading, then 0.5 mg BID, max 4 mg/d (halved if age >65), midazolam 2.5 mg SC q2h PRN

Placebo PO, midazolam 2.5 mg SC q2h PRN

Outcomes
• Primary: NuDesc inappropriate behaviour, inappropriate communication, illusions/hallucinations at 72 h
• Patient/caregiver/health professional rated distress
• Dosage or length of administration
• Toxicity (extrapyramidal effects, sedation)
• Pathophysiologic correlates (S100B, cytochrome C, caspase 3, neuron specific enolase)

Agar et al. JAMA Intern Med 2017
### Risperidone vs. Haloperidol vs. Placebo

**Palliative Care, Front Line**

<table>
<thead>
<tr>
<th></th>
<th>Risperidone vs. Placebo</th>
<th>P-value</th>
<th>Haloperidol vs. Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delirium symptoms</strong></td>
<td>0.48 (0.09, 0.86)</td>
<td>0.02</td>
<td>0.24 (0.06, 0.42)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>MDAS scores/day</strong></td>
<td>0.96 (0.16, 1.77)</td>
<td>&lt;0.001</td>
<td>0.76 (-0.03, 1.51)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>RASS/day</strong></td>
<td>-0.05 (-0.19-0.09)</td>
<td>0.52</td>
<td>-0.14 (-0.28, 0)</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>Extrapyramidal effects</strong></td>
<td>0.73 (0.09, 1.37)</td>
<td>0.03</td>
<td>0.79 (0.17, 1.41)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Overall survival (HR)</strong></td>
<td>1.29 (0.91, 1.84)</td>
<td>0.14</td>
<td>1.73 (1.20, 2.50)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Median survival</strong></td>
<td>17 d vs. 26 d</td>
<td></td>
<td>16 d vs. 26 d</td>
<td></td>
</tr>
</tbody>
</table>

*Agar et al. JAMA Intern Med 2017*
Risperidone vs. Haloperidol vs. Placebo
Palliative Care, Front Line

• Midazolam use (placebo vs. neuroleptics)
  – Day 1: 13/75 (17%) vs. 50/144 (35%), P=0.007
  – Day 2: 11/68 (17%) vs. 40/121 (33%), P=0.01
  – Day 3: 9/66 (14%) vs. 32/108 (30%), P=0.02

• Midazolam dose/day (among pts who got it)
  – Placebo: median 2.5 mg (2.5-5.0 mg)
  – Risperidone: median 2.5 mg (2.5-5.0 mg)
  – Haloperidol: median 4 mg (2.5-5.0 mg)

Implications:
1. Neuroleptics are inferior to placebo for delirium in the palliative care setting
2. Benzodiazepines alone may be considered for rescue

Agar et al. JAMA Intern Med 2017
Risperidone vs. Haloperidol vs. Placebo
Palliative Care, Front Line

• Primary outcome
  – Has not been validated
  – Observed difference statistically significant but clinical significant unknown

• Patient population
  – Relatively low MDAS scores (median 13.7-15.1 – placebo best)
  – Did not exclude dementia patients

• Adverse effects
  – Despite very small doses for short duration (72 h)
  – Secondary outcomes = hypothesis generating only

How I feel right now
How about agitation...

RASS +1
Restless

RASS +2
Agitated

RASS +3
Aggressive
Haloperidol ± Lorazepam
Palliative Care, Persistent Agitation

- Double-blind, randomized controlled trial
- Single dose instead of repeated dosing
  - Short survival (i.e. hours to days)
  - Uncertain risks associated with lorazepam in a frail population
- Study outcomes:
  - Richmond Agitation Sedation Scale (1°)
  - Use any additional psychotropics agents
  - Perceived patient comfort
  - MDAS, ESAS, DEQ
  - Communication capacity
  - Adverse effects
  - Discharge outcomes, survival

Cancer patients in APCU with mixed/hyperactive delirium despite regular haloperidol use (<8 mg/d)

Haloperidol 2 mg q6h and q1h PRN

First occurrence of RASS ≥+1 & meds needed

Haloperidol 2 mg PLUS Lorazepam 3 mg x1 dose

Haloperidol 2 mg PLUS Placebo x1 dose

Hui et al. ASCO 2017
Haloperidol ± Lorazepam
Palliative Care, Persistent Agitation

- Lorazepam/haloperidol was associated with a significantly greater reduction of RASS compared to placebo
  - 0-30 min: mean Δ -2.0, 95% CI -2.9, -1.1, P<0.001
  - 0-8 h: mean Δ -1.9, 95% CI -2.8, -0.9, P<0.001

Hui et al. ASCO 2017
Haloperidol ± Lorazepam
Palliative Care, Persistent Agitation
Placebo + Haloperidol

Hui et al. ASCO 2017
Haloperidol ± Lorazepam
Palliative Care, Persistent Agitation
Lorazepam + Haloperidol

Hui et al. ASCO 2017
# Haloperidol ± Lorazepam

## Palliative Care, Persistent Agitation

## Neuroleptic use during the first 8 hours

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam + Haloperidol (n=29)</th>
<th>Placebo + Haloperidol (n=29)</th>
<th>Difference between arms (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheduled HEDD, median (IQR), mg</td>
<td>2.0 (2.0, 4.0)</td>
<td>2.0 (2.0, 4.0)</td>
<td>-0.1 (-0.9, 0.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>Rescue HEDD, median (IQR), mg</td>
<td>2.0 (2.0, 2.0)</td>
<td>4.0 (2.0, 5.0)</td>
<td>-2.2 (-3.8, -0.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Total HEDD, median (IQR), mg</td>
<td>6.0 (4.0, 6.0)</td>
<td>6.0 (4.0, 8.0)</td>
<td>-2.3 (-4.2, -0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of rescue doses, median (IQR), mg</td>
<td>1.0 (1.0, 1.0)</td>
<td>2.0 (1.0, 2.0)</td>
<td>-0.9 (-1.6, -0.2)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

## Need for chlorpromazine during first 8 hours, No./total No. of observations (%)

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam + Haloperidol (n=29)</th>
<th>Placebo + Haloperidol (n=29)</th>
<th>Difference between arms (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/29 (6.9%)</td>
<td>4/29 (13.8%)</td>
<td>-0.1 (-0.3, 0.2)</td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

## Change in MDAS, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam + Haloperidol (n=29)</th>
<th>Placebo + Haloperidol (n=29)</th>
<th>Difference between arms (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>-2.4 (2.7)</td>
<td>-1.7 (4.2)</td>
<td>-0.7 (-3.6, 2.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.1 (1.9)</td>
<td>-1.8 (3.2)</td>
<td>1.9 (-0.7, 4.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Nausea</td>
<td>-0.7 (3.4)</td>
<td>-2.7 (3.9)</td>
<td>2.0 (-1.7, 5.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Depression</td>
<td>-1.4 (4.0)</td>
<td>0.2 (2.9)</td>
<td>-1.6 (-5.3, 2.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-3.4 (3.8)</td>
<td>-2.1 (4.7)</td>
<td>-1.3 (-5.0, 2.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1.9 (3.5)</td>
<td>-2.0 (3.1)</td>
<td>3.9 (0.8, 7.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

## Change in Edmonton Symptom Assessment Scale, mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Lorazepam + Haloperidol (n=29)</th>
<th>Placebo + Haloperidol (n=29)</th>
<th>Difference between arms (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of Breath</td>
<td>-1.0 (2.2)</td>
<td>-0.4 (4.5)</td>
<td>-0.6 (-3.3, 2.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Appetite</td>
<td>0.6 (1.6)</td>
<td>2.1 (3.2)</td>
<td>-1.5 (-3.6, 0.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sleep</td>
<td>-2.9 (3.8)</td>
<td>-2.4 (3.8)</td>
<td>-0.5 (-4.0, 3.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Feeling of Well-being</td>
<td>-2.3 (3.3)</td>
<td>-1.5 (3.3)</td>
<td>-0.8 (-4.2, 2.6)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Hui et al. ASCO 2017
Patients on lorazepam/haloperidol arm were perceived to be more comfortable after the study medication by blinded caregivers and nurses.
Haloperidol ± Lorazepam
Palliative Care, Persistent Agitation

• No significant difference in
  – Delirium recall
  – Communication capacity
  – Adverse effects
  – Discharge outcomes
  – Overall survival

Median survival
68 h vs. 73 h, P=0.56
HR 1.2 (95% CI 0.7-2.2)

Hui et al. ASCO 2017
Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

• Lorazepam and haloperidol, given to the right individuals for the right reason at the right time, may reduce agitation and improve comfort.

• Limitations:
  – Single center study
  – Small study not powered to examine secondary outcomes
  – Only examined a single dose of lorazepam (3 mg)

• Further research is needed to examine the role of benzodiazepines and neuroleptics in delirium management.
# Placebo-Controlled Trials
## Delirium Treatment

<table>
<thead>
<tr>
<th>Agents</th>
<th>ICU</th>
<th>Medical/Surgical</th>
<th>Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Girard Crit Care Med 2010</td>
<td></td>
<td>Agar JAMA Intern Med 2017</td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Agar JAMA Intern Med 2017</td>
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<tr>
<td>Ziprasidone</td>
<td>Girard Crit Care Med 2010</td>
<td></td>
<td></td>
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<tr>
<td>Quetiapine</td>
<td>Devlin Crit Care Med 2010</td>
<td>Tahir J Psychosom Res 2010</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lorazepam</td>
<td></td>
<td></td>
<td>Hui (submitted)</td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacologic Therapies

Take Home Message

**Risks**

Neuroleptics:
- Some studies suggest harm
- Adverse effects

Benzodiazepines:
- Some studies suggest harm
- Adverse effects

**Benefits**

Neuroleptics:
- Some studies suggest improvement
- May reduce agitation

Benzodiazepines:
- Some studies suggest benefits
- May reduce agitation

**Prevention:** Mixed evidence

**Treatment:** Limited evidence; however, *may be* considered for selected patients given limited options

**Prevention:** No evidence

**Treatment:** Some evidence for agitation control; use with great caution
Neuroleptic Rotation
Palliative Care, Persistent Agitation

- **Haloperidol use**
  - Initial doses 5 (3-7) mg
  - Median duration 5 (3-7) days

- **Chlorpromazine use**
  - Initial dose 150 (100-150) mg
  - Median duration 3 (2-6) days

Delirium in APCU (n=167)

- **Haloperidol only** (n=128, 77%)
  - Reduced symps (n=91, 71%)
  - Rotated to chlorpromazine (n=37, 29%)
    - Reduced symps (n=13, 33%)
    - Did not improve (n=24, 67%)

- **Haloperidol + another agent** (n=39, 23%)

Shin et al. *Cancer Treat Res* 2015
Neuroleptics
Impact on Delirium Recall and Related Distress

Effective therapy

Ineffective therapy

Reactive therapy

HEDD (mg)

Distress

HEDD (mg)

Distress

HEDD (mg)

Distress
# Neuroleptics

## Impact on Delirium-Related Distress

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Caregivers</th>
<th>Nurses</th>
<th>PC specialists</th>
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<tbody>
<tr>
<td><strong>Disorientation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to place</td>
<td>H</td>
<td>2.6 (N=36)</td>
<td>2.0 (N=55)</td>
<td>7.0 (N=8)</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>1.8 (N=48)</td>
<td>2.8 (N=35)</td>
<td>3.3 (N=13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.48</td>
<td>p=0.24</td>
<td>p=0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5 (N=65)</td>
<td>2.0 (N=76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.002</td>
<td>p=0.32</td>
</tr>
<tr>
<td>to time</td>
<td>H</td>
<td>2.5 (N=40)</td>
<td>1.8 (N=52)</td>
<td>7.0 (N=6)</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>2.7 (N=45)</td>
<td>3.0 (N=41)</td>
<td>3.7 (N=16)</td>
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<tr>
<td></td>
<td></td>
<td>p=0.94</td>
<td>p=0.54</td>
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<td></td>
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<td>2.5 (N=69)</td>
<td>2.0 (N=75)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.008</td>
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<td><strong>Hallucinations</strong></td>
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<tr>
<td></td>
<td>H</td>
<td>3.5 (N=33)</td>
<td>3.2 (N=47)</td>
<td>4.6 (N=6)</td>
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<td>1.7 (N=43)</td>
<td>7.5 (N=10)</td>
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<td>p=0.14</td>
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<td>2.0 (N=79)</td>
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<td></td>
<td></td>
<td></td>
<td>p=0.20</td>
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<td><strong>Delusions</strong></td>
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<tr>
<td></td>
<td>H</td>
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<td>1.8 (N=36)</td>
<td>4.3 (N=7)</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>2.5 (N=57)</td>
<td>2.8 (N=49)</td>
<td>4.0 (N=9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.90</td>
<td>p=0.52</td>
<td>p=0.90</td>
</tr>
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<td></td>
<td>2.3 (N=64)</td>
<td>2.0 (N=80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.041</td>
<td>p=0.75</td>
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<tr>
<td><strong>Agitation</strong></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>2.5 (N=45)</td>
<td>2.5 (N=69)</td>
<td>6 (N=11)</td>
</tr>
<tr>
<td></td>
<td>L</td>
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<td>1.6 (N=22)</td>
<td>4.3 (N=23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.27</td>
<td>p=0.36</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.9 (N=62)</td>
<td>1.9 (N=69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.001</td>
<td>p=0.006</td>
</tr>
</tbody>
</table>

Hui et al. *J Pain Symp Manage* 2010
Onset of delirium

Early interventions
- Treat reversible causes
- Non-pharmacologic measures
- More effective pharmacologic measures

Worsening delirium symptoms

Delirium related distress

Patients and caregivers

Administration of neuroleptics

RNs and PC specialists
Treatment of Delirium
NCCN Clinical Practice Guideline

**Estimated Life Expectancy**
- Assess for delirium (e.g., DSM criteria)
- Hyperactive
- Hypoactive
- Screen for and treat underlying reversible causes
- Metabolic causes and medication withdrawal
- Dehydration
- Unrelieved pain
- Hypoxia
- Bowel obstruction/obstipation
- Infection
- Brain metastases (consider palliative RT) or other CNS events
- Bladder outlet obstruction
- Medication or substance effect or withdrawal (e.g., benzodiazepines, opioids, anticholinergics or non-prescribed substances)
- Assess, screen for, and maximize nonpharmacologic interventions (e.g., reorientation, cognitive stimulation, sleep hygiene)

**Delirium Interventions**
- Reduce or eliminate delirium-inducing medications as possible (e.g., steroids, anticholinergics, benzodiazepines)
- Administer haloperidol
- Administer alternative antipsychotic medications
- If agitation is refractory to high doses of neuroleptics, consider adding benzodiazepine
- Titrate starting dose to optimal effect with lowest possible dose
- Consider opioid dose reduction or rotation
- Support caregivers

**Reassessment**
- Acceptable:
  - Adequate delirium symptom management
  - Reduction of patient/family distress
  - Relief of caregiver burden

- Unacceptable
  - Intensify palliative care interventions
  - Consider consultation with a palliative care specialist or psychiatrist

- Ongoing reassessment

---

Dans et al. NCCN Palliative Care v1.2017
Delirium Literature

More Research is Needed

• Better understanding of pathophysiology
  – Classify subtypes
  – Identify novel interventions

• More validated outcomes are needed
  – Appropriate outcome based on goals of care
  – Minimal clinically important difference

• Interventions
  – Dose-finding studies
  – Multimodal interventions

• Control arms
  – Placebos are needed

• More adequately powered studies needed
  – Homogeneous populations
  – We need funding and collaborations

Hui et al. J Palliat Care 2014
Summary

• Think Delirium!
  – Routine screening
  – Match setting with goals of care

• Prevention
  – Treat potential contributors of delirium (if any)
  – Multicomponent intervention – high quality evidence in most settings
  – Pharmacologic therapy – nothing definitive yet!

• Treatment
  – Treat reversible causes (up to 50% even in palliative care setting)
  – Non-pharmacologic approaches – limited evidence but limited harm
  – Neuroleptics – consider for agitation, optimal dose undefined
  – Benzodiazepines – consider for agitation, optimal dose undefined
  – Dexmedetomidine – limited to intensive care
## Delirium Management by Setting

<table>
<thead>
<tr>
<th>Prevention of delirium</th>
<th>Reversal of delirium</th>
<th>Palliation of delirium symptoms (agitation)</th>
<th>Reduce delirium related distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Op (months-years)</td>
<td>Medical (weeks-months)</td>
<td>Palliative Care (days-weeks)</td>
<td></td>
</tr>
<tr>
<td>Multi-component</td>
<td>Multi-component</td>
<td>?Multi-component</td>
<td></td>
</tr>
<tr>
<td>Treat etiology</td>
<td>Treat etiology</td>
<td>Treat etiology</td>
<td></td>
</tr>
<tr>
<td>??Neuroleptics</td>
<td>??Neuroleptics</td>
<td>??Neuroleptics ??Benzos</td>
<td></td>
</tr>
</tbody>
</table>
ありがとうございました

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  - Dr. Daniel Epner
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  - Dr. Suresh Reddy
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