DELIРИАМ

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Saint Louis University
Division of Geriatrics
Financial Conflicts of Interest

None

Non-FDA approved use of a pharmacological agent

Dexmedetomidine

Antipsychotics
Objectives

1. Question why Delirium has such negative consequences
   ➢ Why do delirious patients die?

2. Judge the usefulness/non-usefulness of antipsychotics in Delirium based on the proposed neuropathophysiology of Delirium and the current research in the area of Delirium

3. Manage and treat patients at risk for Delirium or with Delirium
“Delirium constitutes a ubiquitous and thus clinically important sign of cerebral functional decompensation caused by physical illness”
A. 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 a 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).

The neurocognitive disorders (NCDs) (referred to in DSM-IV as “Dementia, Delirium, Amnestic, and Other Cognitive Disorders”)

Delirium: DSM-5 Diagnostic Criteria
D. The disturbances in Criteria A and C are not better explained by another preexisting, 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.
Prevalence and Incidence

- 20-31% of admissions
- 20-35% while in hospital
- 32-66% not identified

Siddiqi N. Age Ageing, 2006 (Syst. Rev. 42 studies; 8 high qual/ within 24 hours)
Francis J, et al. JAMA, 1990
Delirium: sites of care

• Hospital
  – Medicine
  – Surgery
  – ICU
  – Neurology
  – Oncology

• ED

• Pediatrics

• Palliative care
Treating Delirium: An Often Missed Diagnosis

by JOSEPH SHAPIRO

Listen to the Story
Morning Edition [4 min 22 sec]

August 10, 2009

Virginia Helton says her husband is a "brilliant" man. He's a scientist who can explain complex chemistry and physics. But when he was in the hospital last February, she didn't recognize the man acting so bizarrely — talking wild nonsense and taking off his clothes.
Objectives

1. Question why Delirium has such negative consequences
   ➢ Why do delirious patients die?

2. Judge the usefulness/non-usefulness of antipsychotics in Delirium based on the proposed neuropathophysiology of Delirium and the current research in the area of Delirium

3. Manage and treat patients at risk for Delirium or with Delirium
Consequences of Delirium*

- Hosp. complications
- Loss of function
- ↑ NH placement
- ↑ hospital stay
- ↑ mortality
- LTCI
- PTSD

*Compared to patients without delirium
## Delirium & ↑ mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Non-delirious</th>
<th>Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsay</td>
<td>1991</td>
<td>14%</td>
<td>62%*</td>
</tr>
<tr>
<td>Zanocchi</td>
<td>1998</td>
<td>9.9%</td>
<td>24.6%*</td>
</tr>
<tr>
<td>Francis</td>
<td>1990</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Inouye</td>
<td>1998</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Edlund</td>
<td>2006</td>
<td>1.8%</td>
<td>8.8%*</td>
</tr>
<tr>
<td>Villalpando-Berumen</td>
<td>2003</td>
<td>2.3%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

All medical inpatients; Controlled for confounding factors, previous cognitive impairment, comorbidities

*P < .05
### Delirium & ↑ mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Non-delirious</th>
<th>Delirious</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francis</td>
<td>1990</td>
<td>10%</td>
<td>14.3%</td>
<td>6 mo</td>
</tr>
<tr>
<td>O'Keefe</td>
<td>1997</td>
<td>15%</td>
<td>31%</td>
<td>6 mo</td>
</tr>
<tr>
<td>Edlund</td>
<td>2006</td>
<td>20%</td>
<td>36%*</td>
<td>12 mo</td>
</tr>
<tr>
<td>McCusker</td>
<td>2001</td>
<td>14%</td>
<td>42%*</td>
<td>12 mo</td>
</tr>
<tr>
<td>Ramsay</td>
<td>1991</td>
<td>37%</td>
<td>77%*</td>
<td>12 mo</td>
</tr>
</tbody>
</table>

All medical inpatients; Controlled for confounding factors, previous cognitive impairment, comorbidities

*P < .05
Long-Term Cognitive Impairment after Critical Illness

- N=821
- ICU, medical or surgical, respiratory failure or shock
- Only 6% had cognitive impairment at baseline
- 74% developed delirium
- Assessed at 3 and 12 months
  - Global cognition (RBANS= Repeatable Batter for the Assessment of Neuropsychological Status)
  - Executive function (Trail Making Test, Part B)

Global Cognition Scores in Survivors of Critical Illness.
Duration of Delirium and Global Cognition Score at 12 Months.


Adjusted RBANS Global Cognition Score at 12 Mo

N=382
P=0.04
Table 2. Effect of Duration of Delirium, Duration of Coma, and Exposure to Sedative or Analgesic Agents on Global Cognition and Executive Function.*

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Percentile</th>
<th>RBANS Global Cognition Score</th>
<th>Trails B Executive-Function Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25th</td>
<td>75th</td>
<td>At 3 Mo</td>
</tr>
<tr>
<td>Duration of delirium (days)</td>
<td>0</td>
<td>5</td>
<td>-6.3 (−10.3 to −2.3)</td>
</tr>
<tr>
<td>Duration of coma (days)</td>
<td>0</td>
<td>4</td>
<td>-1.5 (−7.0 to 4.1)</td>
</tr>
<tr>
<td>Mean daily dose of sedative or analgesic agent†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine (mg)</td>
<td>0</td>
<td>7.88</td>
<td>0.3 (−2.9 to 3.5)</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>0</td>
<td>804</td>
<td>0.5 (−2.2 to 3.3)</td>
</tr>
<tr>
<td>Dexmedetomidine (µg)</td>
<td>0</td>
<td>3826</td>
<td>-4.0 (−11.7 to 3.7)</td>
</tr>
<tr>
<td>Opiate (mg)</td>
<td>13.3</td>
<td>1238.8</td>
<td>3.5 (0.1 to 6.9)</td>
</tr>
</tbody>
</table>

* Results shown are from linear regression models in which outcome variables were global cognition scores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; on a scale from 40 to 160, with lower scores indicating worse performance) or the Trail Making Test, Part B (Trails B; with scores ranging from 0 to 100, and lower scores indicating worse executive function), the independent variables were duration of delirium, duration of coma, and mean dose of sedative or analgesic medications (all included simultaneously in the model), and the covariates were the following potential confounders, which were selected a priori: age, educational level, coexisting conditions, preexisting cognitive impairment, apolipoprotein E genotype, stroke risk, and ICU variables, including the mean scores for the severity of illness, mean haloperidol dose, duration of severe sepsis, duration of hypoxemia, and an interaction between delirium and coma.

† Differences (point estimates) in the RBANS and the Trails B scores in the linear regression analyses reflect a comparison between the 25th and the 75th percentile values for each variable among all 821 patients in the original cohort (with the exception of dexmedetomidine dose; because more than 85% of patients received no dexmedetomidine, we used the minimum and maximum doses instead). For example, in a comparison of patients with no delirium and those with 5 days of delirium, with all other covariates held constant, patients with 5 days of delirium had RBANS global cognition scores that were 5.6 points lower at 12 months than did those with no delirium. This represents a decrease of approximately 0.5 SD, which is considered to be a clinically significant decline (see the Supplementary Appendix). A similar comparison of executive-function scores at 3 and 12 months showed a decrease of 0.5 SD in the scores for patients with 5 days of delirium, which is a clinically significant decline according to the neuropsychology literature. CI denotes confidence interval.

‡ We used restricted cubic splines for all continuous variables, which allows for a nonlinear relationship between covariates and outcomes but requires multiple beta coefficients to estimate the effect. The most appropriate P value is one that takes into consideration all these beta coefficients together. Although the P value may indicate significance (and is correct), the comparison of the 25th and 75th percentiles may yield a point estimate with a confidence interval that crosses zero, or vice versa.
Duration of Delirium Matters
From: The CAM-S: Development and Validation of a New Scoring System for Delirium Severity in 2 Cohorts

The CAM-S Score for Delirium Severity


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**Table 3. Association of CAM-S Score With Posthospital Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Death Within 90 d ( (n = 919) )†</th>
<th>Adjusted Mean Cost per Day for First 90 d ( (95% \text{ CI}) ), $ ( (n = 831) )‡</th>
<th>Death or Nursing Home Residence at 90 d ( (n = 844) )‡</th>
<th>Functional Decline at 30 d ( (n = 712) )$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, ( n/N ) (%)</td>
<td>Adjusted RR ( (95% \text{ CI}) )</td>
<td>Patients, ( n/N ) (%)</td>
<td>Adjusted RR ( (95% \text{ CI}) )</td>
</tr>
<tr>
<td>CAM-S short-form severity rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None ( (n = 598) )</td>
<td>39/598 (7)</td>
<td>Referent</td>
<td>81/544 (15)</td>
<td>Referent</td>
</tr>
<tr>
<td>Low ( (n = 91) )</td>
<td>14/91 (15)</td>
<td>2.0 (1.1–3.5)</td>
<td>27/82 (33)</td>
<td>1.9 (1.3–2.7)</td>
</tr>
<tr>
<td>Moderate ( (n = 128) )</td>
<td>20/128 (16)</td>
<td>1.8 (1.1–3.2)</td>
<td>48/121 (40)</td>
<td>2.1 (1.5–2.9)</td>
</tr>
<tr>
<td>High ( (n = 102) )</td>
<td>28/102 (27)</td>
<td>3.3 (2.1–5.1)</td>
<td>49/97 (51)</td>
<td>2.5 (1.9–3.3)</td>
</tr>
<tr>
<td>( P \text{ value for trend} )</td>
<td>–</td>
<td>&lt;0.001</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| CAM-S long-form severity rating |||| |
| None \( (n = 205) \) | 14/205 (7) | Referent | 35/175 (20) | Referent |
| Low \( (n = 288) \) | 20/288 (7) | 0.8 (0.4–1.5) | 37/263 (14) | 1.0 (0.6–1.6) |
| Moderate \( (n = 234) \) | 25/234 (11) | 1.3 (0.7–2.4) | 57/217 (26) | 1.6 (1.0–2.5) |
| High \( (n = 192) \) | 42/192 (22) | 2.3 (1.3–4.1) | 87/183 (48) | 2.5 (1.6–3.7) |
| \( P \text{ value for trend} \) | – | <0.001 | – | <0.001 |

\( RR = \text{relative risk} \)

* Analyses were conducted in the Project Recovery sample. The maximum CAM-S score during each patient’s hospitalization was used in all analyses. All models were adjusted for age, sex, race, Acute Physiology and Chronic Health Evaluation II score, Charlson comorbidity index score, and baseline dementia. All models, except the one for functional decline, were also adjusted for baseline impairment in activities of daily living.

† Includes all in-hospital deaths.

‡ Medicare data were missing for 75 patients (including those receiving care in HMOs). The cost-per-day analyses also excluded 13 patients who died during hospitalization. See text for details.

§ Defined as a partial or complete decline in \( \geq 1 \) activity on the standard 7-item Activities of Daily Living (ADL) scale between baseline and 30 d. These analyses included all 728 patients who were available for telephone follow-up interviews at 1 mo but excluded 16 with missing ADL data.

|| 0 (none), 1 (mild), 2 (moderate), or 3–7 (severe) points.
| 0–1 (none), 2 (mild), 3–4 (moderate), or 5–19 (severe) points.

Date of download: 4/15/2014
Modified CAM = CAM-S

Acute Onset
1. Is there evidence of an acute change in mental status from the patient’s baseline?
   Yes = 1, No = 0, Unknown = U

Fluctuation
2. Did the patient’s behavior or mental status fluctuate (tend to come and go) during the day/night or interview?
   Yes = 1, No = 0

Inattention
3. Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
   Marked = 2; Mild = 1; No = 0

Disorganized Thinking
4. Was the patient’s thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
   Marked = 2; Mild = 1; No = 0

Altered Level of Consciousness
5. Overall, how would you rate this patient’s level of consciousness:
   0 Alert (normal)
   If any of the following are present, circle them, and give overall score for this section as:
   Marked = 2; Mild = 1
   Vigilant (hyper-alert, sensitive to stimuli)
   Lethargic (drowsy, easily arouse)
   Stupor (difficult to arouse)
   Coma (unarousable)
Severity of Delirium Matters
Loss of Brain on MRI:
49 y/o Patient 2 years after ICU stay for Sepsis
(had been normal at ICU discharge)

Patient’s pre-illness IQ was 140; following her sepsis and delirium, her IQ was 110 at 6 months and 118 at 2 years
Delirium ≠ Dementia

• The pathogenesis of Delirium is NOT the same as pathogenesis of Dementia
Vantaa 85+ study

• Neuropathological markers of dementia in patients with and without a history of delirium.
• 553 individuals (92% of those eligible) aged ≥85 years at baseline, 3, 5, 8 and 10 years.
• Brain autopsy was performed in 52%.
• Delirium
  – increased the risk of incident dementia, OR 8.7 (95% CI, 2.1-35).
  – associated with worsening dementia severity, OR 3.1 (1.5-6.3)
  – deterioration in global function score, OR 2.8 (1.4-5.5).

Longitudinal trajectory of change in MMSE score over time. Predicted trajectory of MMSE change for those with or without a history of delirium at baseline. Co-efficients and P-values are shown. The estimates for the intercept and slope are given when all covariates = 0. The estimate changes with the addition of each covariate, subtracting the appropriate β co-efficient where: delirium = yes; age per year; sex = female; functional status per increase in five-point scale. The full model, along with 95% CIs for each estimate, and related graphs are given in the Supplementary material.
Figure 3

Relationship between delirium, dementia and neuropathology/genotype. Display of logistic regression models, with 95% CIs. The relationship between dementia and pathology (or genotype), adjusted by age at death and sex. Markers were treated as dichotomous variables, and this relationship is given for the whole population, and then stratified by delirium history ($n = 58$ with history of delirium; $n = 232$ no delirium). Syn = synucleinopathy.
Vantaa 85+ study

• Neuropathological markers of dementia in patients with and without a history of delirium.

• In individuals with dementia and no history of delirium (n = 232), all pathologies were significantly associated with dementia.

• In individuals with delirium and dementia (n = 58), no relationship between dementia and these markers was found.

Vantaa 85+ study

- Neuropathological markers of dementia in patients with and without a history of delirium.

- In individuals with dementia and no history of delirium (n = 232), all pathologies were significantly associated with dementia.
- In individuals with delirium and dementia (n = 58), no relationship between dementia and these markers was found.

- Delirium is a strong risk factor for incident dementia and cognitive decline in the oldest-old.
- However, in this study, the relationship did not appear to be mediated by classical neuropathologies associated with dementia.

Objectives

I. Question why Delirium has such negative consequences

- Direct brain injury?
- Missed/delayed diagnosis
  - Of delirium and underlying cause of delirium
- Patients can’t get diagnostic tests/treatments they need
Mental Status is the 6th Vital Sign

“clinically important sign of cerebral functional decompensation”

The VA Delirium Working Group, June 2007
Immune System

CV System

Respiratory System

CN System
Step 1
State patient’s name and ask patient to open eyes and look at speaker. 
Ask ‘Describe how you are feeling today’
• If answers with short answer (<10 seconds), cue with second open ended question
• If no response to verbal cue, physically stimulate patient by shaking shoulder

Step 2
Score modified RASS below

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>No attention; overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Very distractible; repeated calling or touch required to get or keep eye contact or attention.; cannot focus; pulls or removes tube(s) or catheter(s); aggressive; fights environment not people</td>
</tr>
<tr>
<td>+2</td>
<td>Slightly agitated</td>
<td>Easily distractible; rapidly loses attention; resists care or uncooperative; frequent non-purposeful movement</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Slightly distractible; pays attention most of the time; anxious, but cooperative; movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Pays attention; makes eye contact; aware of surroundings; responds immediately and appropriately to calling name and touch</td>
</tr>
<tr>
<td>-1</td>
<td>Wakes easily</td>
<td>Slightly drowsy; eye contact&gt;10 sec; not fully alert, but has sustained awakening; eye-opening/eye contact to voice &gt;10 seconds</td>
</tr>
<tr>
<td>-2</td>
<td>Wakes slowly</td>
<td>Very drowsy; pays attention some of the time; briefly awakens with eye contact to voice &lt;10 seconds</td>
</tr>
<tr>
<td>-3</td>
<td>Difficult to wake</td>
<td>Repeated calling or touch required to get or keep eye contact or attention; needs repeated stimuli (touch or voice) for attention, movement, or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>Can’t stay awake</td>
<td>Arousable but no attention; no response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>
Serial administration of a Modified Richmond Agitation and Sedation Scale for Delirium Screening

- Single assessment paired with expert eval:
  - any abnormal score:
    - sensitivity of 64%; specificity of 93%

- Serial assessments paired with expert eval:
  - any change in the RASS:
    - sensitivity of 85%; specificity of 92%
Pilot Study of 6th Vital Sign

- Admission to the ACE Unit
- Age >65 years
- N = 30; 7/30 patients had delirium based on DSM-4 criteria

- Interrater reliability
- Average difference between raters: 0.667
- Median difference between rates: 0

- A change in faces score of 3 or more
- Sensitivity: 37.5%
- Specificity: 94%

- Positive Predictive Value: 60%
- Negative Predictive Value: 87%

Abdullah Shoaib MS2, Ellen Kaehr MD
Preliminary results of October 2014; study ongoing
If you DON'T have delirium, there's a 94% chance that the test will say you don't.
If you don't have a change in your faces score of more than 3 points, you're 87% likely not to have delirium.
Objectives

1. Question why Delirium has such negative consequences

2. Judge the usefulness/non-usefulness of antipsychotics in Delirium based on the proposed neuropathophysiology of Delirium and the current research in the area of Delirium

3. Manage and treat patients at risk for Delirium or with Delirium
Fig. 1. A basic pathoetiologic model of delirium.
Fig. 1. A basic pathotiological model of delirium.
Fig. 1. A basic pathophysiological model of delirium.
Antipsychotics

Fig. 1. A basic pathoetiological model of delirium.
Use of antipsychotics may increase mortality risk 1.6-1.7 times. …
Complex interplay between inflammatory mediators and cholinergic system in delirium pathogenesis.

IGF = insoluble growth factor; APOE = apolipoprotein E; CRP = C-reactive protein; SAA = Serum anticholinergic activity; IL = interleukin; NSE = neuro-specific enolase
Antipsychotics in the Treatment of Delirium among Older Hospitalized Patients: A Systematic Review

- MEDLINE (January 1980 through December 2010) and Cochrane Databases
  - keywords ‘delirium’ and ‘antipsychotics’
- Study selection criteria
  - prospective studies
  - >10 patients (in treatment arms)
  - mean age >60 years
  - standardized criteria for diagnosing delirium
  - validated delirium rating scales for reporting outcomes.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Treatment</th>
<th>N</th>
<th>Gender (Male:Female)</th>
<th>Mean age±SD (age range)*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breitbart W, 2002</td>
<td>Olanzapine</td>
<td>79</td>
<td>40:39</td>
<td>61±17 (19-89)</td>
<td>MDAS ≤10: 45% by time 2 (day 2-3), 76% by time 3 (day 4-7)</td>
</tr>
<tr>
<td>Parellada E, 2004</td>
<td>Risperidone</td>
<td>64</td>
<td>40:24</td>
<td>67±11</td>
<td>DRS &lt;13 by day three: 91%</td>
</tr>
<tr>
<td>Sasaki Y, 2003</td>
<td>Quetiapine</td>
<td>12</td>
<td>10:2</td>
<td>67±15 (37-84)</td>
<td>DRS-J &lt;12: 4.8±3.5 days</td>
</tr>
<tr>
<td>Kim KY, 2003</td>
<td>Quetiapine</td>
<td>12</td>
<td>12:0</td>
<td>74±4 (64-88)</td>
<td>“Stabilization” determined by psychiatrist: 5.9±2 days</td>
</tr>
<tr>
<td>Pae CU, 2004</td>
<td>Quetiapine</td>
<td>22</td>
<td>13:9</td>
<td>69±10 (48-85)</td>
<td>DRS-R-98 ≤15: 7±4 days, &gt;50% reduction in DRS-R-98: 86%</td>
</tr>
<tr>
<td>Takeuchi T, 2007</td>
<td>Perisperone</td>
<td>38</td>
<td>31:7</td>
<td>69±10</td>
<td>&gt;50% reduction in DRS-R-98: 71%</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>N</td>
<td>Mean ± SD (Range)</td>
<td>50% Reduction in DRS</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Nakamura J, 1997 (30)</td>
<td>Haloperidol</td>
<td>Mianserin</td>
<td>17</td>
<td>68±15 (40-92)</td>
<td>64±13 (23-86)</td>
</tr>
<tr>
<td>Han CS, 2004 (31)</td>
<td>Haloperidol</td>
<td>Risperidone</td>
<td>12</td>
<td>67±16</td>
<td>66±8</td>
</tr>
<tr>
<td>Hu H, 2004 (37)</td>
<td>Haloperidol</td>
<td>Olanzapine</td>
<td>72</td>
<td>74±8 (65-99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim JY, 2005 (32)</td>
<td>Haloperidol</td>
<td>Risperidone</td>
<td>24</td>
<td>71±7 (60-86)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td></td>
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<tr>
<td>Lee KU, 2005 (33)</td>
<td>Amisulpride</td>
<td>Quetiapine</td>
<td>16</td>
<td>61±18</td>
<td>63±15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(No P value given)</td>
<td></td>
</tr>
<tr>
<td>Kim SW, 2010 (34)</td>
<td>Risperidone</td>
<td>Olanzapine</td>
<td>17</td>
<td>67±12</td>
<td>68±11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tahir TA, 2010 (35)</td>
<td>Quetiapine</td>
<td>Placebo</td>
<td>21</td>
<td>84±9 (58–95)</td>
<td>84±7 (71–98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Conclusion

– Due to severe methodological limitations, the studies in this review do not support the use of antipsychotics in the treatment of delirium among older hospitalized patients.

– Additional well-designed randomized placebo-controlled trials are needed.
Delirium: sites of care

• Hospital
  – Medicine
  – Surgery
  – ICU
  – Neurology
  – Oncology

• ED

• Pediatrics

• Palliative care
Medicine

• Identify causes and contributing factors
• Prevention
  – HELP
• Management
  – Delirium Room
DDx and Contributing Factors to Delirium

- Drugs
- Eyes, Ears
- Low O2 States (MI, Stroke, PE)
- Infection
- Retention (Urine or Feces)
- Ictal
- Underhydration, Undernutrition
- Metabolic
- Subdural
Drugs that can cause an ACUTE CHANGE IN MS

ANTIPARKINSON CV DRUGS INSOMNIA MUSCLE Relax
CORTICOSTER. H2 BLOCKERS NSAIDS
URIN INCONT H A NTIBIOTICS SEIZURE
THEOPHLLYLEINE NARCOTICS
EMPTYING DRUGS GERO-PSYCH ENT

Flaherty JH. Clinics in Geriatric Medicine, 1998
84 year old man, 
Admitted for CHF. 
Day 3 he feels better (less short breath) 
Day 4 he suddenly becomes agitated, 
uncooperative, confused. 
His urine output is less than before. 
Diagnosis?

Blackburn & Dunn, 
Arch Int Med 1990
Cystocerebral Syndrome
(Urinary Retention)

Symptoms: pain, agitated delirium, overflow incontinence, acute renal failure

Blackburn & Dunn,
Arch Int Med 1990
A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients

Inouye, Sharon K.; Bogardus, Sidney T. Jr.; Charpentier, Peter A.; Leo-Summers, Linda; Acampora, Denise; Holford, Theodore R.; Cooney, Leo M. Jr.
Be Aware & Prevent

• B Baseline dementia?
• E Eye problems?
• A Altered sleep/wake cycle
• W Water or dehydration problems
• A Adding >3 meds, esp sed/psychoactive
• R Restricted mobility?
• E Ear problems

Be Aware & Prevent

- P Protocol for sleep
- R Replenish fluids/recognize volume depletion
- E Ear aids (amplifiers, pt’s hearing aids)
- V Visual aids
- E Exercise or ambulation asap
- N Name person, place, time for reorientation
- T Taper or d/c unnecessary meds

Results

• Intervention
  • N=426
  • 9.9% Delirium

• Usual care
  • N=426
  • 15% Delirium

$$\text{OR} = 0.60 \ (95\% \ CI, 0.39-0.92)$$
Welcome to the redesigned HELP Web Site, and to the new phase of the Hospital Elder Life Program!

If you are new to HELP, please click the "Sign In / Register" link to register a new HELP account.

If you are a registered HELP site, you may use your current account. If you don't know your site account name, you may simply create a new account using any name you like.

All registrants - old and new - will be required to read and agree to the terms of the HELP Disclaimer and usage agreement. After that, you will have full access to all of the HELP program documentation, business tools, training videos, and much more!

Welcome!

When older adults are ill and hospitalized, their daily routines are disrupted and they can lose their bearings and become mentally confused and disoriented.
The Delirium Room


The Delirium Room

• “Close Observation Room”
• 4-bed unit within the ACE* Unit
• Restraint Free
• 24-hour nursing

*Acute Care of the Elderly
<table>
<thead>
<tr>
<th></th>
<th>Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=51</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Expected DRG LOS</strong></td>
<td>4.9±1.6</td>
</tr>
<tr>
<td><strong>Actual LOS</strong></td>
<td>5.0±3.3</td>
</tr>
<tr>
<td><strong>Hospital (Charges/Day)</strong></td>
<td>$1,640</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Not Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=51</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Expected DRG LOS</strong></td>
<td>4.8±1.7</td>
</tr>
<tr>
<td><strong>Actual LOS</strong></td>
<td>5.2±3.1</td>
</tr>
<tr>
<td><strong>Hospital (Charges/Day)</strong></td>
<td>$1,850</td>
</tr>
</tbody>
</table>

| **P value** | NS | NS | NS |

## Delirium & ↑ LOS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Non-delirious</th>
<th>Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasquez</td>
<td>2000</td>
<td>7</td>
<td>10*</td>
</tr>
<tr>
<td>Francis</td>
<td>1990</td>
<td>7</td>
<td>12*</td>
</tr>
<tr>
<td>Villalpando</td>
<td>2003</td>
<td>10</td>
<td>13*</td>
</tr>
<tr>
<td>Edlund</td>
<td>2006</td>
<td>10</td>
<td>15*</td>
</tr>
<tr>
<td>Thomas</td>
<td>1988</td>
<td>11</td>
<td>21*</td>
</tr>
<tr>
<td>O’Keefe</td>
<td>1997</td>
<td>11</td>
<td>21*</td>
</tr>
<tr>
<td>Adamis</td>
<td>2006</td>
<td>14</td>
<td>28*</td>
</tr>
</tbody>
</table>

All medical inpatients;  
*P < .05
## Drug Use

**DR (only while in DR)**

\[ n = 51 \]

<table>
<thead>
<tr>
<th>Drug Use</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only Antipsychotic*</td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>Only BDZ**</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
<td>26%</td>
</tr>
</tbody>
</table>

*haloperidol or risperidone; **all lorazepam;
### Delirious vs. Not Delirious

<table>
<thead>
<tr>
<th></th>
<th>Delirious</th>
<th>Not Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>44</td>
<td>104</td>
</tr>
<tr>
<td><strong>Adm ADL</strong></td>
<td>4.1±4.6</td>
<td>7.4±4.7</td>
</tr>
<tr>
<td><strong>D/C ADL</strong></td>
<td>6.1±3.9</td>
<td>6.9±4.5</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>&lt;.05</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Actual LOS</strong></td>
<td>6.4±3.1</td>
<td>5.9±3.6</td>
</tr>
</tbody>
</table>

(ADLs: feeding, bathing, oral care, transfer, toilet: 0-10. 2=indep, 1=assist, 0=max assist)

# Delirium & ↑ mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Non-delirious</th>
<th>Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsay</td>
<td>1991</td>
<td>14%</td>
<td>62%*</td>
</tr>
<tr>
<td>Zanocchi</td>
<td>1998</td>
<td>9.9%</td>
<td>24.6%*</td>
</tr>
<tr>
<td>Francis</td>
<td>1990</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Inouye</td>
<td>1998</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Edlund</td>
<td>2006</td>
<td>1.8%</td>
<td>8.8%*</td>
</tr>
<tr>
<td>Villalpando-Berumen</td>
<td>2003</td>
<td>2.3%</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

All medical inpatients; Controlled for confounding factors, previous cognitive impairment, comorbidities

*P <.05
<table>
<thead>
<tr>
<th></th>
<th>SLU</th>
<th>Delirious</th>
<th>Not Delirious</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>n=51</td>
<td>0 (0%)</td>
<td>5 (9.8%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>DesPeres</td>
<td>Delirious</td>
<td>n=44</td>
<td>Not Delirious</td>
<td>P value</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (4.5%)</td>
<td>2/104 (1.9%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Eeles 2011    | Brisbane, Australia | • “COU”, 19-bed unit with 3 4-bed rooms, 1 is the COU  
• 5 month pre/post  
• 1 extra “AIN” and significant training |
| Mudge 2012    | Brisbane, Australia | • Gen med unit with 4-bed “Delirium Bay”  
• 4 month; control group gen med unit 4&5  
• Significant training |
| Niam 2009     | Perth, Australia | • “DASU”, 10-bed unit, 2-bed per room  
• Closed circuit TV and “PSGs”, geri assessment, guidelines  
• 13 month pre/post |

delirium and surveillance unit; patient supervision guard
## Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Cases</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eeles 2011</td>
<td>Brisbane, Australia</td>
<td>25/175</td>
<td>10/237</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Mudge 2012</td>
<td>Brisbane, Australia</td>
<td>5/27</td>
<td>0/19</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.5%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Niam 2009</td>
<td>Perth, Australia</td>
<td>4/48</td>
<td>6/180</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>
Objectives

1. Question why Delirium has such negative consequences
   - Missed/delayed diagnosis
     - Of delirium and underlying cause of delirium
   - Patients can’t get diagnostic tests/treatments they need

2. Why do delirious patients die?
Principles of care in the DR

- Every action has meaning

“The patient’s perception is their reality”
Principles of care in the DR- TADA

• Tolerate

• Anticipate

• Don’t Agitate
Principles of care in the DR- TADAAA

• Tolerate

• Anticipate

• Don’t Agitate
• Activate
• Ambulate
Objectives

1. Question why Delirium has such negative consequences
   - Why do delirious patients die?

2. Judge the usefulness/non-usefulness of antipsychotics in Delirium based on the proposed neuropathophysiology of Delirium and the current research in the area of Delirium

3. Manage and treat patients at risk for Delirium or with Delirium
Questions?
Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al., 2014

Part A: Threshold Criteria:
1. Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 days?
   OR did the patient have a “+” BAL upon admission?
   If the answer to either is YES, proceed with test:

Part B: Based on patient interview:
2. Have you ever experienced previous episodes of alcohol withdrawal?
3. Have you ever experienced alcohol withdrawal seizures?
4. Have you ever experienced delirium tremens or DT’s?
5. Have you ever undergone alcohol rehabilitation treatment?
   (i.e., in-patient or out-patient treatment programs or AA attendance)
6. Have you ever experienced blackouts?
7. Have you combined alcohol with other “downers” like benzodiazepines or barbiturates during the last 90 days?
8. Have you combined alcohol with any other substance of abuse during the last 90 days?

Part C: Based on clinical evidence:
9. Was the patient’s blood alcohol level (BAL) on presentation > 200?
10. Is there evidence of increased autonomic activity?
    (e.g., HR > 120 bpm, tremor, sweating, agitation, nausea)

Total Score:

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndromes. A score of ≥ 4 suggests HIGH RISK for moderate to severe AWS; prophylaxis and/or treatment may be indicated.
A Picture of ICU Delirium

© Peter E. Spronk – Geire Hospitals ICU. Apeldoorn, the Netherlands. Miriam B. Spronk (design)
The “Wake Up and Breathe” Trial

• **Purpose**: to see if a “wake up and breathe” approach (less exposure to sedatives) yielded better patient outcomes

• **Multicenter Investigation called the Awakening Breathing Controlled (ABC) Trial**:
  – Vanderbilt University Medical Center
  – Saint Thomas Hospital, Nashville
  – University of Chicago Hospitals
  – Hospital of the Univ. of Pennsylvania
  – Penn Presbyterian Medical Center
Patient Outcomes from ABC trial

- Patients given the “wake up and breathe” protocol each day in the ICU compared to control patients had the following:
  - 4 days less in ICU
  - 4 days less in hospital
  - 32% less likelihood of dying at 1 year
  (hazard of death was 0.68; 95% CI, 0.50 to 0.92)

Improved one-year survival in ABC Trial

Patients Alive (%)

Days

Standard Care (n=168)

Wake up and Breathe (n=167)

$p=0.01$

Lancet 2008
Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=49)</th>
<th>Control (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>57.7 (36.3–69.1)</td>
<td>54.4 (46.5–66.4)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>29 (59%)</td>
<td>23 (42%)</td>
</tr>
<tr>
<td><strong>Black race</strong></td>
<td>30 (61%)</td>
<td>31 (56%)</td>
</tr>
<tr>
<td><strong>Barthel Index score</strong></td>
<td>100 (85–100)</td>
<td>100 (90–100)</td>
</tr>
<tr>
<td><strong>Body-mass index (kg/m²)</strong></td>
<td>27.4 (25.1–32.4)</td>
<td>28.0 (23.5–34.1)</td>
</tr>
<tr>
<td><strong>APACHE II score</strong></td>
<td>20.0 (15.8–24.0)</td>
<td>19.0 (13.3–23.0)</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>42 (86%)</td>
<td>45 (82%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>18 (37%)</td>
<td>18 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention (n=49)</th>
<th>Control (n=55)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from intubation to first PT/OT session (days)</td>
<td>1.5 (1.0–2.1)</td>
<td>7.4 (6.0–10.9)</td>
</tr>
<tr>
<td>Time from intubation to milestones achieved (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out of bed</td>
<td>1.7 (1.1–3.0)</td>
<td>6.6 (4.2–8.3)</td>
</tr>
<tr>
<td>Standing</td>
<td>3.2 (1.5–5.6)</td>
<td>6.0 (4.5–8.9)</td>
</tr>
<tr>
<td>Marching in place</td>
<td>3.3 (1.6–5.8)</td>
<td>6.2 (4.6–9.6)</td>
</tr>
<tr>
<td>Transferring to a chair</td>
<td>3.1 (1.8–4.5)</td>
<td>6.2 (4.5–8.4)</td>
</tr>
<tr>
<td>Walking</td>
<td>3.8 (1.9–5.8)</td>
<td>7.3 (4.9–9.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=49)</th>
<th>Control (n=55)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to independent functional status at hospital discharge</td>
<td>29 (59%)</td>
<td>19 (35%)</td>
<td>0·02</td>
</tr>
<tr>
<td>ICU delirium (days)</td>
<td>2·0 (0·0–6·0)</td>
<td>4·0 (2·0–7·0)</td>
<td>0·03</td>
</tr>
<tr>
<td>Ventilator-free days*</td>
<td>23·5 (7·4–25·6)</td>
<td>21·1 (0·0–23·8)</td>
<td>0·05</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>3·4 (2·3–7·3)</td>
<td>6·1 (4·0–9·6)</td>
<td>0·02</td>
</tr>
<tr>
<td>Length of stay in ICU (days)</td>
<td>5·9 (4·5–13·2)</td>
<td>7·9 (6·1–12·9)</td>
<td>0·08</td>
</tr>
<tr>
<td>Length of stay in hospital (days)</td>
<td>13·5 (8·0–23·1)</td>
<td>12·9 (8·9–19·8)</td>
<td>0·93</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>9 (18%)</td>
<td>14 (25%)</td>
<td>0·53</td>
</tr>
</tbody>
</table>

Future of Delirium

• More “management” studies
• More “targeted” approach
  – Neurophysiological types of delirium
• Better “target” drug
• European Delirium Association
  – 9th Annual Meeting, Italy
• American Delirium Society
  – 4th Annual Meeting, Baltimore, MD
Objectives

1. Identifying Delirium
2. Question why Delirium has such negative consequences
3. Judge the usefulness/non-usefullness of antipsychotics in Delirium based on the proposed neuropathophysiology of Delirium and the current research in the area of Delirium
4. Manage patients at risk for Delirium or with Delirium based on current practice and clinical studies
Improving quality of delirium care in a general medical service with established interdisciplinary care: a controlled trial

- N= 206 medical patients (age >65)
- 22% delirious at admission
- Significantly fewer intervention participants were discharged with persistent delirium (32% vs 71%, p=0.016), with trends to reduced inpatient mortality (0% vs 18.5%, p=0.07) and falls (11% vs 22%, p=0.16)
- But longer medical ward stay (16 vs 8 days, p=0.01).

Postop Delirium


Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs; n = 229) or placebo (n = 228) was randomly administered from intensive care unit admission.

<table>
<thead>
<tr>
<th></th>
<th>Haldol</th>
<th>Placebo</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delirium</strong></td>
<td>15.1%</td>
<td>16.5%</td>
<td>.91 (.59-1.44)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Highest DRS score</strong></td>
<td>14.4±3.4</td>
<td>18.4±4.3</td>
<td>4.0 (2.0-5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Delirium Duration</strong></td>
<td>5.4±4.9</td>
<td>11.8±7.5</td>
<td>6.4 (4.0-8.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Hospital Days</strong></td>
<td>17.1±11.1</td>
<td>22.6±16.7</td>
<td>5.5 (1.4-2.3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*DRS Score 0-45 points  

Does 4 point difference translate to easier care for caregivers?

Perioperative Cognitive Protection - Dexmedetomidine and Cognitive Reserve

The “Dexlirium Trial”
Sites

- Mount Sinai School of Medicine, New York, New York
- Cleveland Clinic, Cleveland, Ohio
- Englewood Hospital, Englewood, New Jersey
- Johns Hopkins School of Medicine, Baltimore, Maryland
- Maimonides Medical Center, Brooklyn, New York
- Mayo Clinic School of Medicine, Rochester, Minnesota
- University of Miami School of Medicine, Miami, Florida
- Saint Louis University Hospital, DesPeres Hospital, St. Louis, Missouri
Dexlirium Study Schematic

**Visit 0**
Screening

**Pre-Op**
- **DEX Group**
  - N=350
  - DEXMEDETOMIDINE Infusion*
    - (0.5 mcg/kg/hr fixed rate)
- **PBO Group**
  - N=350
  - PBO Infusion*
    - (0.5 mcg/kg/hr fixed rate)

**O.R.**
- Anesthesia
- Morphine PRN
- Induction

**PACU**
- Morphine PRN

**Follow-Up**
- Hospital Stay
- 3 & 6 Month test

**End of Study**
<table>
<thead>
<tr>
<th>Location, time for recruitment</th>
<th>Treatment</th>
<th>Placebo?</th>
<th>Goal N</th>
<th>Site</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands 2013-2015</td>
<td>Prophylactic Use of Haloperidol in Critically Ill Patients With a High Risk for Delirium</td>
<td>No</td>
<td>2145</td>
<td>ICU</td>
<td>Mortality; Delirium incidence during ICU stay; Number of delirium free days;</td>
</tr>
<tr>
<td>Canada 2013-2014</td>
<td>Haloperidol, Quetiapine and Placebo in the Pharmacological Treatment of Delirium</td>
<td>Yes</td>
<td>45</td>
<td>ICU</td>
<td>Time to resolution of delirium; Delirium days; Severity (highest Nu-DESC score)</td>
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<tr>
<td>USA Northeastern Univ</td>
<td>Preventing ICU Subsyndromal Delirium Conversion to Delirium With Haloperidol</td>
<td>Yes</td>
<td>68</td>
<td>ICU</td>
<td>Conversion; number of hours spent agitated (SAS ( \geq 5 )) while on drug; Duration of mechanical ventilation</td>
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<tr>
<td>Location, time for recruitment</td>
<td>Treatment</td>
<td>Placebo?</td>
<td>Goal N</td>
<td>Site</td>
<td>Outcome</td>
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<tr>
<td>Netherlands</td>
<td><strong>Haloperidol Prophylaxis</strong></td>
<td>Yes</td>
<td>600</td>
<td>ED</td>
<td>Change from baseline in the mean Delirium Observation Screening (DOS)</td>
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<td>VU University</td>
<td><strong>in Older Emergency Department Patients</strong></td>
<td></td>
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<tr>
<td>Medical Center</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2012-2014</td>
<td></td>
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</tr>
<tr>
<td>USA</td>
<td><strong>The Modifying the Impact of ICU-Associated Neurological Dysfunction-USA (MIND-USA) Study</strong></td>
<td>Yes</td>
<td>876</td>
<td>ICU</td>
<td>Delirium/coma free days; Survival; Delirium duration;</td>
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<tr>
<td>Vanderbilt University</td>
<td></td>
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<td></td>
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<td>2011-2016</td>
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<tr>
<td>USA</td>
<td><strong>Pharmacological Management of Delirium</strong></td>
<td>No</td>
<td>428</td>
<td>ICU</td>
<td>Delirium severity, days free of delirium and coma (DRS-R-98, CAM-ICU,</td>
</tr>
</tbody>
</table>
Dexmedetomidine vs Lorazepam

- Dexmedetomidine patients had more days alive without delirium or coma (median, 7 vs 3; P = .01)

- About 30% fewer patients experienced coma in the dexmedetomidine group than in the lorazepam group (63% vs 92%; P < .001).

Dexmedetomidine vs Lorazepam

- NS differences were noted between the dexmedetomidine and lorazepam groups in 28-day mortality (17% vs 27%; P = .18).

- NS differences ventilator-free days (22 vs 18 days alive and free of mechanical ventilation; P = .22).

Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials.
Fraser GL¹, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, Kress JP, Davidson JE, Spencer FA.

Abstract

BACKGROUND:
Use of dexmedetomidine or propofol rather than a benzodiazepine sedation strategy may improve ICU outcomes. We reviewed randomized trials comparing a benzodiazepine and nonbenzodiazepine regimen in mechanically ventilated adult ICU patients to determine if differences exist between these sedation strategies with respect to ICU length of stay, time on the ventilator, delirium prevalence, and short-term mortality.

METHODS:
We searched CINAHL, MEDLINE, the Cochrane databases, and the American College of Critical Care Medicine's Pain, Agitation, Delirium Management Guidelines' literature database from 1996 to 2013. Citations were screened for randomized trials that enrolled critically ill, mechanically ventilated adults comparing an IV benzodiazepine-based to a nonbenzodiazepine-based sedative regimen and reported duration of ICU length of stay, duration of mechanical ventilation, delirium prevalence, and/or short-term mortality. Trial characteristics and results were abstracted in duplicate and independently, and the Cochrane risk of bias tool was used for quality assessment. We performed random effects model meta-analyses where possible.

RESULTS:
We included six trials enrolling 1,235 patients: midazolam versus dexmedetomidine (n = 3), lorazepam versus dexmedetomidine (n = 1), midazolam versus propofol (n = 1), and lorazepam versus propofol (n = 1). Compared to a benzodiazepine sedative strategy, a nonbenzodiazepine sedative strategy was associated with a shorter ICU length of stay (n = 6 studies; difference = 1.62 d; 95% CI, 0.68-2.55; I² = 0%; p = 0.0007) and duration of mechanical ventilation (n = 4 studies; difference = 1.9 d; 95% CI, 1.70-2.09; I² = 0%; p < 0.00001) but a similar prevalence of delirium (n = 2; risk ratio = 0.83; 95% CI, 0.61-1.11; I² = 84%; p = 0.19) and short-term mortality rate (n = 4; risk ratio = 0.98; 95% CI, 0.76-1.27; I² = 30%; p = 0.88).

CONCLUSIONS:
Current controlled data suggest that use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepine-based sedation regimen in critically ill adults may reduce ICU length of stay and duration of mechanical ventilation. Larger controlled studies are needed to further define the impact of nonbenzodiazepine sedation strategies on delirium and mortality.
d. Delirium prevention

i. We recommend performing early mobilization of adult ICU patients whenever feasible to reduce the incidence and duration of delirium (+1B).

ii. We provide no recommendation for using a pharmacologic delirium prevention protocol in adult ICU patients, as no compelling data demonstrate that this reduces the incidence or duration of delirium in these patients (0,C).

iii. We provide no recommendation for using a combined nonpharmacologic and pharmacologic delirium prevention protocol in adult ICU patients, as this has not been shown to reduce the incidence of delirium in these patients (0,C).

iv. We do not suggest that either haloperidol or atypical antipsychotics be administered to prevent delirium in adult ICU patients (−2C).

v. We provide no recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients, as there is no compelling evidence regarding its effectiveness in these patients (0,C).
Delirium treatment

i. There is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (No Evidence).

ii. Atypical antipsychotics may reduce the duration of delirium in adult ICU patients (C).

iii. We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (−1B).

iv. We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QTc interval, patients receiving concomitant medications known to prolong the QTc interval, or patients with a history of this arrhythmia) (−2C).

v. We suggest that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions be administered for sedation to reduce the duration of delirium in these patients (+2B).


Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E.

Author information

Abstract

OBJECTIVE:
To compare the efficacy and safety of scheduled quetiapine to placebo for the treatment of delirium in critically ill patients requiring as-needed haloperidol.

DESIGN:
Prospective, randomized, double-blind, placebo-controlled study.

SETTING:
Three academic medical centers.

PATIENTS:
Thirty-six adult intensive care unit patients with delirium (Intensive Care Delirium Screening Checklist score > or = 4), tolerating enteral nutrition, and without a complicating neurologic condition.

INTERVENTIONS:
Patients were randomized to receive quetiapine 50 mg every 12 hrs or placebo. Quetiapine was increased every 24 hrs (50 to 100 to 150 to 200 mg every 12 hrs) if more than one dose of haloperidol was given in the previous 24 hrs. Study drug was continued until the intensive care unit team discontinued it because of delirium resolution, therapy > or = 10 days, or intensive care unit discharge.

MEASUREMENTS AND MAIN RESULTS:
Baseline characteristics were similar between the quetiapine (n = 18) and placebo (n = 18) groups. Quetiapine was associated with a shorter time to first resolution of delirium [1.0 (interquartile range [IQR], 0.5-3.0) vs. 4.5 days (IQR, 2.0-7.0; p =.001)], a reduced duration of delirium [36 (IQR, 12-87) vs. 120 hrs (IQR, 60-195; p =.006)], and less agitation (Sedation-Agitation Scale score > or = 5) [6 (IQR, 0-38) vs. 36 hrs (IQR, 11-66; p =.02)]. Whereas mortality (11% quetiapine vs. 17%) and intensive care unit length of stay (16 quetiapine vs. 16 days) were similar, subjects treated with quetiapine were more likely to be discharged home or to rehabilitation (89% quetiapine vs. 56%; p =.06). Subjects treated with quetiapine required fewer days of as-needed haloperidol [3 [(IQR, 2-4)] vs. 4 days (IQR, 3-8; p =.05)]. Whereas the incidence of QTc prolongation and extrapyramidal symptoms was similar between groups, more somnolence was observed with quetiapine (22% vs. 11%; p =.66).

CONCLUSIONS:
Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation. Future studies should evaluate the effect of quetiapine on mortality, resource utilization, post-intensive care unit cognition, and dependency after discharge in a broader group of patients.
Figure 2. Proportion of patients with first resolution of delirium over time between quetiapine (n = 18) and placebo (n = 18) groups. Both groups of patients were treated using the same as-needed intravenous haloperidol protocol.
258 patients screened

222 excluded
- 46 Prior antipsychotic use within 30 days
- 38 Not receiving enteral nutrition
- 28 Primary neurological condition
- 16 Advanced liver disease
- 12 Alcohol withdrawal
- 12 Inability to conduct ICDSC
- 11 No delirium
- 11 Inability to obtain informed consent
- 10 Moribund
- 8 Irreversible brain disease
- 7 Current drug therapy w/agents affecting quetiapine concentrations
- 6 Current drug therapy with Class la, lc or III antiarrhythmics
- 5 Baseline QTc interval ≥500msec
- 5 Attending physician refusal for enrollment
- 7 Other

36 subjects randomized

- Quetiapine 50 mg NG twice daily (N=18)
- Placebo 50 mg NG twice daily (N=18)

As needed haloperidol therapy, usual sedation and analgesia therapy at the discretion of the subject’s physician

Dose Titration
Increase quetiapine or placebo dose by 50 mg every 12 hours on a daily basis if the subject received ≥ 1 dose of as needed haloperidol in the previous 24 hours. (Maximum dose=200 mg every 12 hours)

Discontinuation of study drug
- 1 Subject was deemed by the attending intensivist to be no longer demonstrating signs of delirium, therefore, therapy no longer required
- 2 10 days of therapy had elapsed
- 3 ICU discharge prior to 10 days of therapy
- 4 Serious adverse event potentially attributable to the study drug
Use of antipsychotics may increase mortality risk 1.6-1.7 times…..
### Delirium & ↑ LOS

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Non-delirious</th>
<th>Delirious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inouye</td>
<td>1998</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Jitapunkkul</td>
<td>1992</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Rockwood</td>
<td>1989</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Kolbeinssons</td>
<td>1993</td>
<td>17</td>
<td>20</td>
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<tr>
<td>Rockwood</td>
<td>1993</td>
<td>28</td>
<td>32</td>
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</tbody>
</table>

All medical inpatients; None of these studies showed a statistically significant difference.
The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): Systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome.

Maldonado JR1, Sher Y2, Ashouri JF3, Hills-Evans K4, Swendsen H5, Lolak S6, Miller AC7.

Author information

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3Internal Medicine (Rheumatology), University of California, San Francisco, CA, USA.

4Stanford University School of Medicine, Stanford, CA, USA.

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6Psychiatry, George Washington University School of Medicine & Health Sciences, Washington, DC, USA.

7Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Abstract

BACKGROUND:
To date, no screening tools for alcohol withdrawal syndromes (AWS) have been validated in the medically ill. Although several tools quantify the severity of AWS (e.g., Clinical Institute Withdrawal Assessment for Alcohol [CIWA]), none identify subjects at risk of AWS, thus missing the opportunity for timely prophylaxis. Moreover, there are no validated tools for the prediction of complicated (i.e., moderate to severe) AWS in the medically ill.

OBJECTIVES:
Our goals were (1) to conduct a systematic review of the published literature on AWS to identify clinical factors associated with the development of AWS, (2) to use the identified factors to develop a tool for the prediction of alcohol withdrawal among patients at risk, and (3) to conduct a pilot study to assess the validity of the tool.

METHODS:
For the creation of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS), we conducted a systematic literature search using PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines for clinical factors associated with the development of AWS, using PubMed, PsychInfo, MEDLINE, and Cochrane Databases. Eligibility criteria included: (i) manuscripts dealing with human subjects, age 18 years or older, (ii) manuscripts directly addressing descriptions of AWS or its predisposing factors, including case reports, naturalistic case descriptions, and all types of clinical trials (e.g., randomized, single-blind, or open label studies), (iii) manuscripts describing characteristics of alcohol use disorder (AUD), and (iv) manuscripts dealing with animal data (which were considered only if they directly dealt with variables described in humans). Obtained data were used to develop the Prediction of Alcohol Withdrawal Severity Scale, in order to assist in the identification of patients at risk for complicated AWS. A pilot study was conducted to assess the new tool's psychometric qualities on patients admitted to a general inpatient medicine unit over a 2-week period, who agreed to participate in the study. Blind to PAWSS results, a separate group of researchers retrospectively examined the medical records for evidence of AWS.

RESULTS:
The search produced 2802 articles describing factors potentially associated with increased risk for AWS, increased severity of withdrawal symptoms, and potential characteristics differentiating subjects with various forms of AWS. Of these, 446 articles met inclusion criteria and...
In this prospective observational cohort study, patients aged 65 years or older were enrolled at an academic, tertiary care ED from July 2009 to February 2012. An emergency physician (EP) and research assistants (RAs) performed the CAM-ICU. The reference standard for delirium was a comprehensive (~30 minutes) psychiatrist assessment using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria. All assessments were blinded to each other and were conducted within 3 hours. Sensitivities, specificities, and likelihood ratios were calculated for both the EP and the RAs using the psychiatrist's assessment as the reference standard. Kappa values between the EP and RAs were also calculated to measure reliability.

**Results**

Of 406 patients enrolled, 50 (12.3%) had delirium. The median age was 73.5 years old (interquartile range [IQR] = 69 to 80 years), 202 (49.8%) were female, and 57 (14.0%) were nonwhite. The CAM-ICU's sensitivities were 72.0% (95% confidence interval [CI] = 58.3% to 82.5%) and 68.0% (95% CI = 54.2% to 79.2%) in the EP and RAs, respectively. The CAM-ICU's specificity was 98.6% (95% CI = 96.8% to 99.4%) for both raters. The negative likelihood ratios (LR–) were 0.28 (95% CI = 0.18 to 0.44) and 0.32 (95% CI = 0.22 to 0.49) in the EP and RAs, respectively. The positive likelihood ratios (LR+) were 51.3 (95% CI = 21.1 to 124.5) and 48.4 (95% CI = 19.9 to 118.0), respectively. The kappa between the EP and RAs was 0.92 (95% CI = 0.85 to 0.98), indicating excellent interobserver reliability.