Delirium in the ICU – Why All the Confusion?

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Objectives

- To provide the clinical features of delirium
- To review some of the adverse effects of delirium
- To review screening methods for delirium
- To review pharmacological options for the management of delirium
Delirium – Practice Guidelines

- Common – Loss of touch with reality/disorientation
- Fluctuating levels of arousal throughout the day
- Disturbed sleep-wake cycle
- Hallucinations
- Delusions (Paranoid)

- Types
  - Hypoactive
  - Hyperactive
  - Mixed
- May occur after sedative therapy
Delirium

Hughes C et al  Curr Opin Critical Care 2012;18:518-26
Is Delirium Bad?

Ely EW et al JAMA 2004;291:1753-62
Is Delirium Bad?

Girard TD et al Crit Care Med 2010;28:1513-20
Is Delirium Expensive?

Milbrandt EB et al Crit Care Med 2004;32:955-62
What Factors are Associated with the Development of Delirium?

Table 1  Risk variables significant on univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.069</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.0047</td>
</tr>
<tr>
<td>Active tobacco consumption</td>
<td>0.0123</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.0015</td>
</tr>
<tr>
<td>Variables on ICU admission</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Epidural catheter use</td>
<td>0.0017</td>
</tr>
<tr>
<td>Average opiate dose</td>
<td>0.0096</td>
</tr>
<tr>
<td>Average benzodiazepine dose</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average propofol dose</td>
<td>0.0023</td>
</tr>
<tr>
<td>Average indomethacin dose</td>
<td>0.044</td>
</tr>
<tr>
<td>ICU stay related factors</td>
<td></td>
</tr>
<tr>
<td>Coma (all types)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.0824</td>
</tr>
<tr>
<td>Pain</td>
<td>0.0020</td>
</tr>
</tbody>
</table>

Ouimet S et al Intensive Care Med 2007;33:66-73
Delirium

Delirium

Delirium

Inflammation and BBB Function

How do we Detect Delirium?

- Screening Tools
  - CAM-ICU – Confusion Assessment Monitor - ICU
  - ICDSC – Intensive Care Delirium Screening Checklist
ICDSC

<table>
<thead>
<tr>
<th>Patient evaluation</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of consciousness* (A–E)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If A or B do not complete patient evaluation for the period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination—delusion—psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor agitation or retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate speech or mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep/wake cycle disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (0–8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Level of consciousness:
A: No response, score: None
B: Response to intense and repeated stimulation (loud voice and pain), score: None
C: Response to mild or moderate stimulation, score: 1
D: Normal wakefulness, score: 0
E: Exaggerated response to normal stimulation, score: 1

Score >4 = Delirium

Bergeron N et al Intensive Care Med 2001;27:859-864
Appendix 1. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

Delirium is diagnosed when both Features 1 and 2 are positive, along with either Feature 3 or Feature 4.

Feature 1. Acute Onset of Mental Status Changes or Fluctuating Course
- Is there evidence of an acute change in mental status from the baseline?
- Did the (abnormal) behavior fluctuate during the past 24 hrs, that is, tend to come and go or increase and decrease in severity?

Sources of information: Serial Glasgow Coma Scale or sedation score ratings over 24 hrs as well as readily available input from the patient’s bedside critical care nurse or family.

Ely EW et al Crit Care Med 2001;29:1370-79
Delirium

Feature 2. Inattention
- Did the patient have difficulty focusing attention?
- Is there a reduced ability to maintain and shift attention?

*Sources of information:* Attention screening examinations by using either picture recognition or Vigilance A random letter test (see Methods and Appendix 2 for description of Attention Screening Examinations). Neither of these tests requires verbal response, and thus they are ideally suited for mechanically ventilated patients.

Ely EW et al Crit Care Med 2001;29:1370-79
Delirium

Feature 3. Disorganized Thinking

- 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?
- Was the patient able to follow questions and commands throughout the assessment?
  1. “Are you having any unclear thinking?”
  2. “Hold up this many fingers.” (examiner holds two fingers in front of the patient)
  3. “Now, do the same thing with the other hand.” (not repeating the number of fingers)

Ely EW et al Crit Care Med 2001;29:1370-79
Delirium

Feature 4. Altered Level of Consciousness

- Any level of consciousness other than “alert.”
- Alert—normal, spontaneously fully aware of environment and interacts appropriately
- Vigilant—hyperalert
- Lethargic—drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
- Stupor—difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly
- Coma—un arousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult or impossible even with maximal prodding
Delirium Management Approaches

First-generation antipsychotic
- Haloperidol\(^1\)

Second-generation antipsychotic
- Quetiapine\(^1\)
- Olanzapine\(^1\)
- Ziprasidone

\(\alpha2\)-Adrenoceptor agonist
- Clonidine
- Dexmedetomidine\(^1\)

Dopamine

Serotonine

Noradrenaline

Acetylcholine

Melatonine

NMDA

GABA

Cholinesterase inhibitors
- Rivastigmine\(^2\)
- Donepezil\(^2\)

Benzodiazepines
- Lorazepam\(^2\)
- Midazolam\(^2\)

1 Positive effect in prophylaxis or treatment shown in RCTs.
2 Negative associations in prophylaxis or treatment shown in RCTs.

Zaal IJ and Slooter AJC Drugs 2012;72:1457-71
Delirium

Hipp DH and Ely W Neurotherapeutics 2012;9:158-75
Atypical Antipsychotics

Table 1. Pharmacokinetics of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors</td>
<td>DA, 5-HT, α1, H1, M1</td>
<td>DA, 5-HT, α1, H1, M1</td>
<td>DA, 5-HT, α1,α2, H2</td>
<td>DA, 5-HT, α1</td>
<td>DA, 5-HT, α1, H1, M1</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>60</td>
<td>73</td>
<td>70-85</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>33</td>
<td>6</td>
<td>3-24</td>
<td>6.6</td>
<td>47-68</td>
</tr>
<tr>
<td>Usual starting dose (elderly patients may require lower dose)</td>
<td>5 mg daily</td>
<td>25 mg bid</td>
<td>0.5 mg bid</td>
<td>40 mg q6hr³</td>
<td>5 mg daily³</td>
</tr>
<tr>
<td>Renal adjustment</td>
<td>No</td>
<td>No</td>
<td>Yes, slower titration may be necessary</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Oral (tablet and SL), IM</td>
<td>Oral</td>
<td>Oral, IM</td>
<td>Oral, IM</td>
<td>Oral, IM</td>
</tr>
</tbody>
</table>

Gilchrist et al J Intens Care Med 2011
Atypical Antipsychotics

### Table 2. Side Effects of Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation</th>
<th>EPS</th>
<th>NMS</th>
<th>QTc Prolongation</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Moderate</td>
<td>Very low</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Low</td>
<td>Low to moderate</td>
<td>Low to moderate</td>
<td>Low</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Low</td>
<td>Low</td>
<td>Unknown</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Very low</td>
<td>Low</td>
<td>Very low</td>
<td>Low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Abbreviations: EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.
* Seen at doses >6 mg/day.
# RCTs of Delirium Management

## TABLE 1. Major Randomized Trials of Pharmacotherapeutic Interventions for Delirium in the ICU Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Primary Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
</table>
| I. Antipsychotics
  Olanzapine vs. haloperidol (Skrobik et al<sup>14</sup>) | 73 Medical/surgical ICU patients diagnosed with delirium randomized to olanzapine (n=28) or haloperidol (n=45) | Severity of delirium and benzodiazepine use over 5 days | No significant difference in delirium index or benzodiazepine use |
| MIND Trial (Girard et al<sup>15</sup>) | 101 Medical/surgical ICU patients randomized to haloperidol (n=35), ziprasidone (n=30), or placebo (n=36) for up to 14 days | Days alive without delirium or coma | No significant differences between groups |
| Quetiapine (Devlin et al<sup>17</sup>) | 36 Medical/surgical ICU patients diagnosed with delirium randomized to quetiapine (N=18) or placebo (n=18) until first resolution of delirium, for up to 10 days, or until ICU discharge, whichever came first | Time to first resolution of delirium | Quetiapine associated with a shorter time to first resolution of delirium |
| Risperidone (Prakanrattana et al<sup>36</sup>) | 126 Cardiac surgery patients (ICU) randomized to a single postoperative dose of risperidone (n=63) or placebo (n=63) | Incidence of post-operative delirium | Incidence of postop delirium lower in the risperidone group |
# RCTs of Delirium Management

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</tr>
</thead>
<tbody>
<tr>
<td>II. Cholinesterase Inhibitors</td>
<td>104 ICU patients diagnosed with delirium randomized to rivastigmine ( n=54 ) or placebo ( n=50 ) as an adjunct to haloperidol</td>
<td>Duration of delirium</td>
<td>Median duration of delirium was longer in the rivastigmine group Study prematurely stopped due to increased mortality in the rivastigmine group</td>
</tr>
<tr>
<td>Rivastigmine (Gambarini et al(^{38}))</td>
<td>120 Cardiac surgery patients (ICU) randomized to rivastigmine ( n=59 ) or placebo ( n=61 ) for 6 postoperative days</td>
<td>Incidence of postoperative delirium</td>
<td>Incidence of postop delirium higher in the rivastigmine group</td>
</tr>
</tbody>
</table>

# RCTs of Delirium Management

<table>
<thead>
<tr>
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<th>Characteristics</th>
<th>Primary Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>III. NMDA Antagonists Ketamine (Hudetz et al\textsuperscript{37})</td>
<td>58 Cardiac surgery patients (ICU) randomized to ketamine ((n=29)) or placebo ((n=29)) during anesthetic induction</td>
<td>Incidence of postoperative delirium</td>
<td>Incidence of postop delirium lower in the ketamine group</td>
</tr>
</tbody>
</table>

### RCTs of Delirium Management

**TABLE 1. Major Randomized Trials of Pharmacotherapeutic Interventions for Delirium in the ICU Population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Primary Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV. α-2 Agonists</td>
<td>30 Surgical ICU patients who underwent acute repair of thoracic aortic dissection randomized to clonidine ((n=15)) or placebo ((n=15)) infusion during weaning from mechanical ventilation</td>
<td>Incidence and severity of postoperative delirium</td>
<td>No statistically significant difference in incidence of delirium between groups. Severity of delirium lower in the clonidine group</td>
</tr>
</tbody>
</table>

### RCTs of Delirium Management

#### TABLE 1. Major Randomized Trials of Pharmacotherapeutic Interventions for Delirium in the ICU Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Primary Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmedetomidine vs. Haloperidol (Reade et al(^{27}))</td>
<td>20 Medical/surgical ICU patients who were difficult to extubate secondary to superimposed delirium randomized to a continuous infusion of dexmedetomidine ((n=10)) or haloperidol ((n=10))</td>
<td>Time to extubation</td>
<td>Dexmedetomidine group had a significantly shorter time to extubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexmedetomidine group had an increased proportion of time spent with minimal or no delirium symptoms with minimal or no delirium symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incidence of delirium was significantly lower in the dexmedetomidine group</td>
</tr>
<tr>
<td></td>
<td>118 Cardiac surgery patients (ICU) randomized to dexmedetomidine ((n=40)), propofol ((n=38)), or midazolam ((n=40)) for postoperative sedation</td>
<td>Incidence of postoperative delirium</td>
<td>Incidence of delirium was markedly higher in the propofol and midazolam groups</td>
</tr>
</tbody>
</table>
# RCTs of Delirium Management

## TABLE 1. Major Randomized Trials of Pharmacotherapeutic Interventions for Delirium in the ICU Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
<th>Primary Outcome Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXCOM Study (Shehabi et al(^3))</td>
<td>306 Cardiac surgery patients (ICU) randomized to dexmedetomidine ((n=154)) or morphine ((n=152)) for postoperative sedation/analgesia</td>
<td>Incidence of postoperative delirium</td>
<td>Incidence of postoperative delirium was statistically similar between groups</td>
</tr>
<tr>
<td>MENDS Trial (Pandharipande et al(^2))</td>
<td>106 Medical/surgical ICU patients randomized to dexmedetomidine ((n=54)) or lorazepam ((n=52)) for sedation</td>
<td>Days alive without delirium or coma</td>
<td>Duration of delirium was shorter in the dexmedetomidine group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexmedetomidine group had significantly more days alive without delirium or coma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexmedetomidine group had significantly more coma-free days but not delirium-free days</td>
</tr>
</tbody>
</table>

What can we do to prevent/ameliorate delirium?

- Wake them up!
Sedation Assessment

Richmond Agitation Sedation Assessment Scale

- +4 Overtly Combative
- +3 Very Agitated
- +2 Agitated
- +1 Restless
- 0
- Alert and Calm
- -1 Drowsy
- -2 Light Sedation
- -3 Moderate Sedation
- -4 Deep Sedation
- -5 Unarousable

Allowed for a targeted sedation level to be prescribed

Ely et al JAMA 2003;289:2983-2991
Daily Wake-up

Kress et al NEJM 2000;342(20):1471-7
Daily Wake-up

![Graph showing comparison between Wake Up and Control groups for CT Scan, MRI, LP, and Positive Test.]

Kress et al. NEJM 2000;342(20):1471-7
Daily Wake-up

Kress et al NEJM 2000;342(20):1471-7
Daily Wake-Up

TABLE 3. IMPACT OF EVENTS SCORES

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Difference in Means—Control Minus Intervention (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total impact of events score</td>
<td>27.3 ± 19.2</td>
<td>11.2 ± 14.9</td>
<td>16.1 (3.0 to 29.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Avoidance subscale score</td>
<td>15.7 ± 10.5</td>
<td>7.8 ± 9.2</td>
<td>8.0 (0.5 to 15.4)</td>
<td></td>
</tr>
<tr>
<td>Intrusive Thoughts Subscale score</td>
<td>13.8 ± 9.7</td>
<td>5.6 ± 7.3</td>
<td>8.2 (1.7 to 14.7)</td>
<td>0.055</td>
</tr>
<tr>
<td>Impact of Events Subgroup scores—MANOVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CI = confidence interval; MANOVA = multivariate analysis of variance.*

Less PTSD in Early Wake up

ABC Trial

Hipp DH and Ely W Neurotherapeutics 2012;9:158-75
## Wake-up and SBT

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (n=167)</th>
<th>Control group (n=168)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilator free days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.7 (0.9)</td>
<td>11.6 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median</td>
<td>20.0 (0 to 26.0)</td>
<td>8.1 (0 to 24.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to discharge (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From intensive care</td>
<td>9.1 (5.1 to 17.8)</td>
<td>12.9 (6.0 to 24.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>From hospital</td>
<td>14.9 (8.9 to 25.8)</td>
<td>19.2 (10.3 to NA)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>28-day mortality</strong></td>
<td>47 (28%)</td>
<td>58 (35%)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>1-year mortality</strong></td>
<td>74 (44%)</td>
<td>97 (58%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Duration of brain dysfunction (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>2 (0 to 4)</td>
<td>3 (1 to 7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Delirium</td>
<td>2 (0 to 5)</td>
<td>2 (0 to 6)</td>
<td>0.50</td>
</tr>
<tr>
<td>RASS at first successful SBT</td>
<td>-1 (-3 to 0)</td>
<td>-2.5 (-4 to 0)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any self-extubation</td>
<td>16 (10%)</td>
<td>6 (4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Self-extubation requiring reintubation‡</td>
<td>5 (3%)</td>
<td>3 (2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Reintubation‡</td>
<td>23 (14%)</td>
<td>21 (13%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>21 (13%)</td>
<td>34 (20%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Girard Lancet 2008;371:126-34

Low Incidence Of Delirium And Coma in Both Groups
Wake-up and Mobilize

<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>Time in ICU with delirium (%)</td>
<td>33% (0–58)</td>
<td>57% (33–69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital delirium (days)</td>
<td>2.0 (0.0–6.0)</td>
<td>4.0 (2.0–8.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital days with delirium (%)</td>
<td>26% (20)</td>
<td>41% (27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Barthel Index score at hospital discharge</td>
<td>75 (75–95)</td>
<td>55 (0–85)</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU-acquired paresis at hospital discharge</td>
<td>15 (31%)</td>
<td>27 (49%)</td>
<td>0.09</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>Duration of mechanical ventilation, survivors (days)</td>
<td>3.7 (2.3–7.7)</td>
<td>5.6 (3.4–8.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, non-survivors (days)</td>
<td>2.5 (2.4–5.5)</td>
<td>9.5 (5.9–14.1)</td>
<td>0.04</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>

Schweickert et al Lancet 2009;373:1874-82
Does Heavy Sedation Produce Less Myocardial Ischemia?

Hall et al Anesth Analg 1997;85:971-8
Do ICU Patients Handle Drugs Differently?

- Absorption
  - Impaired by gut wall edema
- Distribution
  - Altered protein binding
    - Renal Disease
    - Liver Disease
  - Redistribution
    - Context Sensitive Half Time
Context Sensitive Half Time

Hughes et al Anesthesiology 1992;76(3):334-341
Context Sensitive Half Time

Hughes et al Anesthesiology 1992;76(3):334-341
Do ICU Patients Handle Drugs Differently?

- Drug Metabolism and Excretion
  - CYP450 3A4/5
    - Midazolam – Multiple drug interactions including inhibition (e.g., macrolide antibiotics, propofol)
  - CRRT
  - Hypothermia
  - Inflammation
Midazolam Drug Interaction

Clarithromycin Inhibition of Midazolam Metabolism

Hypothermia and Midazolam Metabolism

Fukuoka et al. Resuscitation 2004;60(20):225-30
Do Sedative Drugs Have Harmful Effects?

- Prolonged Drug Effect
  - Increased risk of VAP
  - Impaired gut function and risk of aspiration

- Sleep Disturbance
  - Altered architecture similar to sleep deprivation
  - Rebound

- Effects on the Immune System
Sedatives Alter Sleep Patterns

Table 2—Patient Characteristics in Each Group on Day of Sleep Study*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Disrupted Sleep Group</th>
<th>Atypical Sleep Group</th>
<th>Coma Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>69 ± 10</td>
<td>62 ± 7</td>
<td>53 ± 19</td>
</tr>
<tr>
<td>M:F</td>
<td>6:2</td>
<td>2:3</td>
<td>4:3</td>
</tr>
<tr>
<td>ICU day</td>
<td>9 ± 10</td>
<td>13 ± 7</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>APS</td>
<td>6 ± 4</td>
<td>13 ± 4</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>Δ APS</td>
<td>−1 ± 6</td>
<td>1 ± 4</td>
<td>−4 ± 7</td>
</tr>
<tr>
<td>GCS</td>
<td>14 ± 3</td>
<td>10 ± 3</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>LIS</td>
<td>1.8 ± 0.6</td>
<td>1.0 ± 0.0</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Cultures, ±</td>
<td>5:3</td>
<td>5:0</td>
<td>1:6</td>
</tr>
<tr>
<td>Inotropes, ±</td>
<td>0:8</td>
<td>1:4</td>
<td>0:7</td>
</tr>
<tr>
<td>Muscle relaxants, ±</td>
<td>0:8</td>
<td>0:5</td>
<td>2:5</td>
</tr>
<tr>
<td>Benzodiazepines, ±</td>
<td>5:3</td>
<td>4:1</td>
<td>6:1</td>
</tr>
<tr>
<td>Lorazepam dose, μg/kg/h</td>
<td>1.0 ± 1.0</td>
<td>9.1 ± 18.2</td>
<td>19.5 ± 27.2</td>
</tr>
<tr>
<td>Opioids, ±</td>
<td>5:3</td>
<td>3:2</td>
<td>6:1</td>
</tr>
<tr>
<td>Morphine dose, μg/kg/h</td>
<td>8 ± 19</td>
<td>12.3 ± 18.1</td>
<td>139 ± 168</td>
</tr>
<tr>
<td>Neuroleptics, ±</td>
<td>4:4</td>
<td>1:4</td>
<td>2:5</td>
</tr>
<tr>
<td>Haloperidol dose, mg/kg/h</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.3 ± 0.6</td>
</tr>
</tbody>
</table>

Cooper et al Chest 2000;117(3):809-18
Rebound Insomnia

Midazolam 20 mg


1 week of drug administration
Sedatives and Pulmonary Function

- **Propofol**
  - Impaired response to hypoxemia and hypercarbia
  - Reductions in tidal volume and minute ventilation

Blouin et al. Anesthesiology 1993;79:1177-82
Sedatives and Pulmonary Function

- Sedative Induced Alterations in Rapid Shallow Breathing Index may mislead caregivers trying to wean patients and prolong MV

Khamiees et al Respir Care 2002;47:150-153
Sedatives and Pulmonary Function

- Impaired airway reflexes
  - Cough
  - Secretion Retention
  - Aspiration

Ventilator Acquired Pneumonia?

Ammonia Threshold ppm

Murphy et al. Anaesthesia 1994;49:105-110
Take Homes

- Delirium is:
  - Common
  - Lethal and Morbid
  - Expensive
  - Often Unrecognized – Screening tools may help
  - Difficult to manage with no clear preferred treatment – Haloperidol and/or Second generation antipsychotics
  - By altering our sedation practices we can reduce the delirium rate and improve outcomes
Conclusions

- Sedation is necessary in nearly all ICU patients at some time.
- Overuse can lead to a variety of consequences which may increase patient morbidity, duration of MV, Infection Risk, and ICU LOS.
- Daily wake up from sedation/analgesia allows an assessment to be made Re: efficacy and continued requirements.
Thanks!!

Questions?

Some useful references:

- Bar J et al Clinical practice guidelines for the management of pain, agitation and delirium in adult patients in the intensive care unit, Crit Care Med 2013;41:263-306
- Supplement to Crit Care Med 2013 Sept
- Roberts DJ, Haroon B, Hall R Sedation for critically ill or injured adults in the intensive care unit: A shifting paradigm Drugs 2012;72(14): 1881-1916
Sedation – Practice Guidelines

- Causes of Anxiety
  - Noise
  - Inability to communicate
  - Continuous lighting and disrupted sleep-wake cycle
  - Inadequate analgesia
  - Frequent vital signs/positioning
  - Immobility/ Restraints
  - Mechanical Ventilation and ETT
Sedation arose out of a requirement to facilitate surgery initially and then to facilitate mechanical ventilation.

- Crude mechanical ventilators often requiring neuromuscular blockade so as to allow patient-ventilator synchrony.
- Sedation employed as a comfort measure.
Historical Perspective

- Ventilator development allowed progressively more patient involvement in the mechanical ventilator process.

- CMV
  - IMV
  - SIMV → PEEP
  - PSV

  Fully sedated
  - In theory, less sedation required
  - In practice – Fully sedated
Daily Wake-up

No difference in General Health


<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SF-36 MANOVA</td>
<td>45.6 ± 25.8</td>
<td>44.6 ± 29.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>55.1 ± 23.6</td>
<td>60.2 ± 25.3</td>
<td></td>
</tr>
<tr>
<td>Role limitations caused by physical health problems</td>
<td>25.0 ± 39.3</td>
<td>46.2 ± 47.7</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>41.8 ± 17.9</td>
<td>44.5 ± 16.0</td>
<td></td>
</tr>
<tr>
<td>Overall general health</td>
<td>52.5 ± 15.5</td>
<td>45.4 ± 22.3</td>
<td></td>
</tr>
<tr>
<td>Vitality (energy/fatigue)</td>
<td>46.2 ± 47.7</td>
<td>45.4 ± 22.3</td>
<td></td>
</tr>
<tr>
<td>Role limitations caused by emotional problems</td>
<td>51.9 ± 40.0</td>
<td>48.7 ± 46.4</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>58.3 ± 26.4</td>
<td>63.5 ± 27.7</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>59.3 ± 17.8</td>
<td>66.8 ± 20.1</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval; MANOVA = multivariate analysis of variance; SF-36 = Medical Outcomes Study 36 item short-form health survey.
Daily Wake-up

Trend toward better social adjustment in Wake-up Group

ABC Trial

SAT reduced ventilator time by = 2 days

Patients Receiving Mechanical Ventilation (%)

Control (n=60)

Protocol (n=68)

Adjusted
p < 0.001

Hipp DH and Ely W Neurotherapeutics 2012;9:158-75
ABC Trial

Hipp DH and Ely W Neurotherapeutics 2012;9:158-75
ABC Trial

Hipp DH and Ely W Neurotherapeutics 2012;9:158-75
Wake-up and Mobilize

More Functional Independence

Schweickert et al Lancet 2009;373:1874-82
Wake-up and Mobilize

Higher No ADLs

Schweickert et al
Lancet
2009;373:1874-82
Take Home Message

- Critically ill patients benefit from having sedation levels minimized
  - More rapid mobilization
  - Shorter duration of mechanical intubation
  - Less investigative procedures
  - Less delirium
Sedation – Practice Guidelines

- Indications are not well defined
  - Adjuncts for the management of “anxiety and agitation”
  - Raised intracranial pressure
  - To facilitate certain forms of support e.g., ECMO
  - In the presence of neuromuscular blocking agents
  - To ameliorate the “Stress Response”
  - In the presence of hemodynamic instability
  - Intoxications
The Stress Response

Norepinephrine pg/ml

Hall et al Anesth Analg 1997;85:971-8
Opioids and The Stress Response

Cortisol nmol/L

Hall et al Anesth Analg 1997;85:971-8
Fentanyl inhibits Midazolam Metabolism

Dose Dependent
In Vitro Assay

Sedatives and Drug Metabolism

Serum from Critically Ill Patients Inhibits Midazolam Metabolism

Park et al Anaesthesia 1996;51:11-15
Sedatives and Drug Pharmacokinetics

Changes in Midazolam Concentration for Continuous Infusion over time

Shelley et al Anaesthesia 1987;42:619-626
Sedatives and Drug Metabolism

Percent of Control

Inflammatory Cytokines Inhibit CytP450

CytP450 3A

72 h culture In liver cells

Abdel-Razzak et al Mol Pharmacol 1993;44:707-15
Sedatives and Drug Pharmacokinetics

Tolerance

Shelly et al Eur J Anaesthesiol 1991;8:21-7
Take Home Message

- Critically ill patients handle drugs differently and the usual dosing regimens may not apply – particularly for sedative drugs given for prolonged durations.
Sedatives and Immunosuppression

Benzodiazepines

- Central receptors – immunoenhancing
- Peripheral Receptors – immunosuppression
  - Lymphocytes/Monocytes/Macrophages
- Inhibition of phagocytosis/bacterial killing by PMNs
- Impaired chemotaxis/superoxide production
- Impaired T cell function
Sedatives and Immunosuppression

Propofol reduced E. coli clearance

Do Sedative Drugs Have Harmful Effects?

- **Delirium**
  - Increased mortality
  - Increased duration of mechanical ventilation and hospital length of stay
- Increased Costs
- Increased risk of cognitive impairment
## Costs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preprotocol</th>
<th>Postprotocol</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts., n</td>
<td>604</td>
<td>610</td>
<td></td>
</tr>
<tr>
<td>Pts. assessable for delirium, n</td>
<td>539</td>
<td>564</td>
<td></td>
</tr>
<tr>
<td>Cost of drugs, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all pts., mean (SD)</td>
<td>59.97 (186.42)</td>
<td>46.02 (122.30)</td>
<td>0.01</td>
</tr>
<tr>
<td>median</td>
<td>8.48</td>
<td>6.56</td>
<td></td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>(2.51, 45.51)</td>
<td>(1.72, 31.68)</td>
<td></td>
</tr>
<tr>
<td>assessable pts., mean (SD)</td>
<td>57.21 (192.75)</td>
<td>47.95 (126.59)</td>
<td>0.202</td>
</tr>
<tr>
<td>median</td>
<td>7.16</td>
<td>6.66</td>
<td></td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>(2.14, 37.94)</td>
<td>(1.75, 31.66)</td>
<td></td>
</tr>
<tr>
<td>Cost of ICU hospitalization, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all pts., mean (SD)</td>
<td>6121.04 (7830.45)</td>
<td>5258.93 (6127.77)</td>
<td>0.04</td>
</tr>
<tr>
<td>median</td>
<td>3852.00</td>
<td>2889.00</td>
<td></td>
</tr>
<tr>
<td>IQR (Q1, Q3)</td>
<td>(1926, 7704)</td>
<td>(1926, 6741)</td>
<td></td>
</tr>
<tr>
<td>assessable pts., mean (SD)</td>
<td>3852.00</td>
<td>2889.00</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>(1926, 7704)</td>
<td>(1926, 6741)</td>
<td></td>
</tr>
<tr>
<td>Total cost, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all pts., mean (SD)</td>
<td>6212.64 (7846.86)</td>
<td>5279.90 (6263.91)</td>
<td>0.022</td>
</tr>
<tr>
<td>median</td>
<td>3854.03</td>
<td>2905.68</td>
<td></td>
</tr>
<tr>
<td>assessable pts., mean (SD)</td>
<td>3852.00</td>
<td>2909.14</td>
<td>0.044</td>
</tr>
<tr>
<td>median</td>
<td>6178.24 (7932.04)</td>
<td>5308.39 (6201.91)</td>
<td></td>
</tr>
</tbody>
</table>

ICU = intensive care unit; IQR = interquartile range.
*Expressed as 2004 Canadian dollars.
Opioid Metabolism

Bosilkova M et al Drugs 2012;72(12):1645-69

Fig. 2. Major enzymes involved in opioid drug metabolism. CYP = cytochrome P450; UGT = uridine 5’-diphosphate glucuronosyltransferase.
Sedation Assessment

Ely et al JAMA 2003;289:2983-2991
Sedation Assessment

Ely et al. JAMA 2003;289:2983-2991
Practice Guidelines

- Analgesia – the blunting or *absence* of sensation of pain or noxious stimuli

Sources of Pain

- Recent surgery
- Pre-existing Disease
- Monitoring Devices e.g., central lines
- Drains – urinary
- ETT
- Nursing care – suctioning/ dressing changes
- Immobilisation
Consequences of Pain

- Sleep deprivation
- Agitation
- Stress response
  - Tachycardia
  - Increased Myocardial Oxygen Consumption
  - Hypercoagulability
  - Immunosuppression
  - Catabolism
- Splinting
Pain Assessment

- The most reliable and valid indicator of pain is the patient’s self report
- Aggravating and Relieving factors
- Intensity
  - Verbal rating scores
  - Visual Analog Scales
  - Numeric Rating Scales
Pain Assessment

- Sedated and unconscious patients are very difficult to assess for pain – either its presence or intensity
- Over or Under-estimated with adverse consequences in either case
Opioids – Do We Have a Problem?

Rocker et al. Chest 1998;114:332S
Opioids – Do We Have a Problem?

VARIATION IN PRACTICE DURING WITHDRAWAL OF LIFE SUPPORT AMONG NURSES

(Number of Nurses)

bolus in mg /30 mins until comfort reached

Rocker et al. Chest 1998;114:332S
Recommendation

- All critically ill patients have the right to adequate analgesia and management of their pain


**Recommendation**

- *Pain assessment and response to therapy should be performed regularly by using a scale appropriate to the patient population and systematically documented.*

Recommendation

- The level of pain reported *by the patient* must be considered the current standard for assessment of pain and response to analgesia whenever possible.
Recommendation

- Patients who cannot communicate should be assessed through subjective observation of pain-related behaviours (movement, facial expression and posturing), and physiological indicators (heart rate, blood pressure, respiratory rate) and the changes in these parameters following analgesic therapy.

Treatment Modalities

- Proper Positioning
- Stabilization of Fractures
- Cold/Heat Application
- Pharmacology
  - NSAIDS – coagulation effects/renal effects/GI effects
  - Regional – coagulation
  - Acetaminophen – liver toxicity
  - Opioids by default
Opioids

- Currently recommended
  - Fentanyl
  - Morphine
  - Hydromorphone
Opioids

- Immunosuppression
- Gut Function
- Drug Metabolism and Interactions
- Respiratory Function
Opioids and Immunosuppression

- Sepsis is the leading cause of death in noncoronary ICU’s
Severe Sepsis: Comparative Incidence and Mortality

Incidence

- AIDS
- Breast Cancer
- 1st MI
- Severe Sepsis

Mortality

- AIDS
- Breast Cancer
- AMI
- Severe Sepsis

American Cancer Society. 2001.
Opioids and Immunosuppression

- **Mechanisms of Immunosuppression**
  - **Indirect** via activation of the HPA axis and production of corticosteroids and/or activation of the adrenergic nervous system
  - **Direct** via binding to opiate receptors on immune cells
Opioids and Immunosuppression

Stem Cell

Myeloid Progenitor
- RBC
- Megakaryocyte
- Eosinophil
- Neutrophil
- Macrophage

Morphine

NK Cell

M-CSF

Lymphoid Progenitor

Morphine

B

T

IL-2

Morphine

Anti bodies

Opioids and Immunosuppression

- Macrophage Cellular Effects
  - Inhibits polarisation
  - Inhibits chemotaxis
  - Inhibits Phagocytosis
  - Inhibits production of Biological Response Markers (IL-1, TNF)
  - Increases superoxide and hydrogen peroxide production
Opioids and Immunosuppression

- Inhibition of NKC effects
  - Volunteers underwent Morphine exposure for 36 h
  - Clinically relevant dose
  - Onset within 2 hr and in high dose group present beyond 48 h from discontinuation

Yeager et al Anesthesiology 1995;83:500-8
Opioids and Immunosuppression

Effects on Lymphocytes

- Reduced numbers of CD4+ (T helper) and CD8+ (T cytotoxic-suppressor) cells
- Impaired lymphocyte proliferation response
Opioids and Immunosuppression

Morphine and Endotoxin in Rats

Opioids and Gut Function

- Decreased Motility leading to Opioid Bowel Dysfunction
  - Constipation
  - Cramping
  - Bloating
  - Reflux
- Exacerbation of Post-operative Ileus
- Abdominal Distension Leading to Impaired Diaphragmatic Excursion
Opioids and The Biliary Tract

- Sphincter of Oddi
  - Constriction
  - Biliary Colic
  - ? Acalculous Cholecystitis
Opioids and Drug Pharmacokinetics

- Majority are metabolised by Cytochrome P450 3A4
  - Inhibition by
    - Macrolides
    - Propofol
    - Azole Antifungal Agents
    - Cimetidine but not ranitidine
  - Enhanced by
    - Rifampin
Surgical Stress Impairs Cytochrome P450

Opioids and Drug Pharmacokinetics

The longer the infusion, the longer the effect

Hughes et al. Anesthesiology 1992;76:334-41
Opioids and Drug Pharmacokinetics

Combes et al. Crit Care Med 2003;31:1373-81
Opioids and Drug Pharmacokinetics

- Phenylpiperidine Class (e.g., Fentanyl) are highly protein bound to Alpha$_1$-Acidglycoprotein (AGP)
  - AGP is an acute phase reactant
  - Reduced analgesic effect for the same dose as inflammation occurs
Opioids and Drug Pharmacokinetics

- P-glycoprotein
  - ATP-dependent efflux pump
  - Responsible for the Blood-Brain Barrier
  - Many CypP450 inhibitors affect P-glycoprotein in a similar manner
Opioids and Drug Pharmacokinetics

- Morphine metabolised to M3G and M6G
- Both accumulate over time
- M6G has analgesic properties
- M3G is a neuroexcitant and brain concentrations are increased in the presence of P-plycoprotein inhibition
- Seizures

Rat Study c ICV Injection

M3G Dose

Opioids and Pulmonary Function

Hypoxic Response

Hypercarbic Response

Weil et al NEJM 1975;292:1103-6
Opioids and Pulmonary Function

- Apnoea
- Cough Reflex
Consequences of Prolonged Opioid Administration?

Attributable Cost = $11897 US

Warren et al. Crit Care Med 2003;31:1312-17
In the management of anxiety and agitation, the first priority is to identify and treat the underlying physiological cause including hypoxemia, hypoglycemia, hypotension, pain, and drug withdrawal.

Sedatives are not intended to be used as a means of coercion, discipline, convenience, or retaliation by staff.

Sedation – Practice Guidelines

- *Without amnesia, many patients who recall their ICU stay report unpleasant or frightening memories which may contribute to the Post Traumatic Stress Disorder.*

**BUT**

Short of extubating all patients anesthetised, the very process of weaning will require some degree of awareness and co-operation in sentient patients, so while ideal, in practice difficult to attain. Particularly in patients who are difficult to wean.
Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes.

Recommendation

- A sedation goal or endpoint should be established and regularly defined for each patient. Regular assessment and response to therapy should be systematically documented.
- The use of a validated sedation assessment scale is recommended.

Sedation – Practice Guidelines

- Sedation Assessment – allows titration to defined end points
  - Few validated
  - Most not helpful in patients receiving NMB
  - Observer Variability High – *What is the difference between “Agitated” and “Very Agitated.”*
Sedation – Do We Have a Problem?

SEDATION VARIABILITY
(LORAZEPAM)

Number of Nurses

Rocker et al. Chest 1998;114:332S
Sedation – Practice Guidelines

- **Agents**
  - Benzodiazepines
    - Midazolam
    - Diazepam
    - Lorazepam
  - Propofol
  - Alpha 2 Agonists
    - Clonidine
    - Dexmedetomidine
Recommendation

- **Midazolam or diazepam should be used for rapid sedation of acutely agitated patients.**

- **Propofol is the preferred sedative when rapid awakening (e.g., for neurological assessment or extubation) is important**

- **Midazolam is recommended for short term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48-72 hours**

Recommendations

- Lorazepam is recommended for the sedation of most patients via intermittent iv administration or continuous infusion

Recommendation

- Triglyceride concentrations should be monitored after two days of propofol infusion, and total caloric intake from lipids should be included in the nutrition support prescription.

- Propofol Perfusion Syndrome

- The use of sedation guidelines, an algorithm, or a protocol is recommended

Recommendation

- The potential for opioid, benzodiazepine, and propofol withdrawal should be considered after high doses or more than approximately seven days of continuous therapy. Doses should be tapered systematically to prevent withdrawal symptoms.

Sedatives

- Immunosuppression
- Gut Function
- Drug Metabolism and Pharmacokinetics
- Respiratory Function
Sedatives and Immunosuppression

Propofol

- Inhibition of hydrogen peroxide production
- Inhibition of PMN chemotaxis
- Impaired Respiratory burst activity
- Increased release of proinflammatory cytokines from lymphocytes/monocytes/PMN
Sedatives and Gut Function

Benzodiazepines

- Antagonise effects of cholecystokinin (CCK<sub>2</sub>)
  - Digestive Tract Motility
  - Secretions – HCL/Pepsinogen
  - Gall Bladder Contraction
  - Exocrine pancreatic function

- No effect on Sphincter of Oddi
Sedatives and Gut Function

Propofol
- Impaired Contractility
- No effect on Sphincter of Oddi
Sedatives and Drug Pharmacokinetics

- Benzodiazepines
  - CytP450 3A4/5/3/7
  - Midazolam as 3A4 probe
  - 3A4 inhibited by many drugs used in critical care
    - Macrolide antibiotics
    - Propofol
    - Azole antifungal agents (e.g., fluconazole)
    - Cimetidine
    - Fentanyl
Recommendation

- The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to minimise prolonged sedative effects.
Something to Try?

- RCT in MICU
- Daily Awakening from Mid/Morph or Prop/Morph Infusion (n=68) vs Standard of Care (n=60)

Kress et al NEJM 2000;342:1471-7
Something to Try?

Daily wake up reduces time on MV

Kress et al NEJM 2000;342:1471-7
Something to Try?

Daily Wake up Reduces ICU LOS

Kress et al NEJM 2000;342:1471-7
Kress et al NEJM 2000;342:1471-7
Opioids and Immunosuppression

Sedatives and Drug Pharmacokinetics

- Propofol
  - CytP450 3A4/2B1/1A1/2E1
Sedation – Practice Guidelines

- Agitation
  - Anxiety
  - Delirium
  - Pain
  - *Adverse Drug Effects*
Recommendation

- Routine assessment for the presence of delirium is recommended. (The CAM-ICU is a promising tool for the assessment of delirium in ICU patients.)

**Recommendation**

- Haloperidol is the preferred agent for the treatment of delirium in critically ill patients.
- Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol.

Sedatives and Drug Pharmacokinetics

- Benzodiazepines
  - Cyp 3A4 inhibited by
    - Inflammation