A Live Educational Activity
Targeting Sedation and Analgesia

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Educational Purpose

This curriculum deck will update readers on recent advances regarding the use of analgesia and sedation in acute care settings.

Learning Objectives

Upon completion of this activity, participants should be able to

- Describe the rationale for the use of analgesia and sedation in acute care settings
- Compare the current analgesics and sedatives, and assess their benefits and limitations
- Review the clinical study evidence supporting the use of current agents for acute care sedation and analgesia
- Discuss the rationale for pharmacoeconomic analyses of therapeutic agents in various acute care settings
Program Overview

- General Anesthesia and Sedation Background
- Comfort Care in the Acute Care Setting
- Overview of Current Sedative and Analgesic Agents
- Dexmedetomidine
- Pharmacoeconomic Data
- Neurological Effects
- Pediatric Applications
- Dexmedetomidine in Bariatric Surgery
- Algorithms
- Summary
General Analgesia and Sedation Background
Purpose of Analgesia and Sedation in Acute Care Settings

- Provide adequate pain control\(^1\)
- Optimize safety for patients and their caregivers\(^2\)
- Enhance patient comfort\(^1\)
- Facilitate mechanical ventilation\(^3\)
- Reduce anxiety\(^1\)
- Prevent delirium\(^1\)
- Induce sleep when required\(^1\)
- Induce appropriate level of amnesia\(^3\)

Need for Analgesia and Sedation in Acute Care
Physiological and Neurobehavioral Considerations

• Failure to address pain in acute care patients may lead to
  – Agitation and anxiety
  – Hypermetabolic states
  – Increased endogenous catecholamine activity
  – Myocardial ischemia
• Acute care patients may demonstrate periods of disorientation during which psychotic behavior occurs
• Certain types of sedation can reduce the risk of harm to the patient or others

Factors Leading to Agitation

**Modifiable**
- Memory Loss
- Confusion
- Inconsiderate Providers
- Chemical/Physiologic Imbalance
- Medications
- Fear
- Lights/Temperature
- Sleep Deprivation

**Non-Modifiable**
- Mechanical Devices
- Alarms
- Age/History
- Loss of Control
- Surgical Stress
- Noises
- Nonchanging Environment

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Goals of Sedation and Analgesia

- Optimize safety for acute care patients and their caregivers\(^1,2\)
- Relieve pain and anxiety\(^1-3\)
- Attenuate the harmful adrenergic response\(^1,2\)
- Improve compliance with care\(^1,2\)
- Facilitate communication with caregivers and family members\(^1,2\)
- Avoid or reduce delirium\(^1,2,4\)

Characteristics of an Ideal Sedative

- Rapid onset of action allows rapid recovery after discontinuation\(^1\)
- Effective at providing adequate sedation with predictable dose response\(^1,2\)
- Easy to administer\(^1,3\)
- Lack of drug accumulation\(^1\)
- Few adverse effects\(^1-3\)
- Minimal adverse interactions with other drugs\(^1-3\)
- Cost effective\(^3\)
- Predictable dose response\(^2\)
- Promotes natural sleep\(^4\)

Targeting Patient Comfort

On-target sedation:
- Decreases weaning period\(^1\)
- Is not associated with muscular atrophy\(^1\)
- Decreases LOS and cost\(^2\)
- Provides cardiovascular\(^1\) and intraoperative hemodynamic stability\(^3\)
- Improves patient safety\(^1,3\)
- Facilitates neurological assessment\(^3\)

# Importance of Optimizing Levels of Sedation

<table>
<thead>
<tr>
<th>Undersedation</th>
<th>Oversedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Anxiety&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Prolonged weaning&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Ventilator dysynchrony&lt;sup&gt;2&lt;/sup&gt;</td>
<td>▪ Respiratory depression&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Dislodging invasive lines/devices&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Lack of patient cooperation for assessment and therapeutic measures&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ May increase posttraumatic stress syndrome&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Inability to communicate with health care providers or family members&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Increased O&lt;sub&gt;2&lt;/sub&gt; consumption&lt;sup&gt;1&lt;/sup&gt;</td>
<td>▪ Delirium&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Delirium&lt;sup&gt;2&lt;/sup&gt;</td>
<td>▪ Hypoactivity&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>▪ Hyperactivity&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>▪ Minimal amnesia&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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<sup>1</sup>McGaffigan PA. Crit Care Nursing. 2002; Feb Suppl:29-36.  
Incidence of Inadequate Sedation

- Continuous sedation carries the risks associated with oversedation and may increase the duration of mechanical ventilation (MV)\(^1,2\)

- MV patients accrue significantly more cost during their ICU stay than non-MV patients\(^3\)
  - $31,574 versus $12,931, \(P<.001\)\(^3\)

- Sedation should be titrated to achieve a cooperative patient and daily wake-up, a JCAHO requirement\(^2,3\)

Costs and Effects of Undersedation

- Increased staffing needs (nursing and respiratory care)\(^1\)
- Patient/family discomfort and dissatisfaction
- Decreased staff satisfaction
- Need for an appropriate use of paralysis
- Adverse physiologic consequences
- Reflex shift to oversedation

Costs and Effects of Oversedation

- Inability to adequately examine the patient
- Increased costs of diagnostic imaging and other tests
- Possible delayed diagnosis of treatable problems
- Prolonged mechanical ventilation time
- Prolonged stay in acute care settings
- Prolonged hospital stay

Guidelines and Standards

- JCAHO Standards
- 2002 SCCM Guidelines
- Anesthesia Patient Safety Foundation
- ASA Guidelines
- Institute of Medicine
Comfort Care in the Acute Care Setting
Assessing Pain

- Faces Pain Rating Scale
- Visual Analog Scale (VAS)
- Pain questionnaire
  - Qualitative aspects
- Sympathetic response to pain

Assessing Sedation

- Ramsay Sedation Scale
- Observer’s Assessment of Alertness/Sedation Scale (OAA/SS)
- Motor Activity Assessment Scale (MAAS)
- Riker’s Sedation-Agitation Scale (SAS)
- Richmond Agitation-Sedation Scale (RASS)
- Brain function monitoring
Assessing Anxiety and Delirium

- State-Trait Anxiety Inventory (STAI)\(^1\)
- Hamilton Rating Scales for Depression and Anxiety\(^2\)
- The Hospital Anxiety and Depression Scale\(^3\)
- Linear Analog Anxiety Scale\(^4\)
- Surrogate markers of stress response\(^5\)
- The Confusion Assessment Method for the Diagnosis of Delirium in the ICU (CAM-ICU)\(^6\)

Characteristics of Cooperative Sedation

- In cooperative sedation, patients easily transition from sleep to wakefulness and task performance when aroused\(^1\)
- Patients are able to resume rest when not stimulated\(^1\)
- Cooperative sedation is most useful during procedures in which communication with the patient must be maintained\(^1\)
- Facilitates participation in therapeutic maneuvers\(^2\)
- Allows for patient interaction in care decisions\(^2\)
- May contribute to shorter recovery room convalescence\(^3\)
- Reduces risk of developing drug-induced complications\(^3\)

http://health.enotes.com/medicine-encyclopedia/sedation
Examples of Cooperative Sedation

- Allows for accurate evaluation of the neuropsychological status of mechanically ventilated patients\(^1\)
- Facilitates direct evaluation of cerebral perfusion during carotid endarterectomy\(^2\)
- Patients are comfortable and responsive during cortical mapping\(^2\)

Negative Outcomes Associated With Poor Cooperative Sedation

- Pain that is not communicated in acute care settings can result in:\n  - Increased stress response
  - Guarding of muscles and muscle rigidity around area of pain, leading to pulmonary dysfunction
  - Exhaustion and disorientation
  - Poor patient cooperation

- Inability to assess patients can result in:
  - Increased number of diagnostic tests
  - Increased time on ventilator
  - Increased LOS
  - Increased overall costs

Institutional Effects of Implementing Rational Use Guidelines

- Prospective analysis of 156 ICU patients who required mechanical ventilation and continuous analgesia, sedation, and/or neuromuscular blockade
- One group (n = 84) was tracked after guidelines were implemented
- Length of hospital and ICU stay and duration of mechanical ventilation were all shorter in the guidelines group
- Institution of the guidelines led to a decline in mean drug costs across all drug classes studied

Implementation of Clinical Pathways
Clinical Outcome and Cost Burden

- Large-scale implementation project with comparison to historic controls\(^1\)
- Outcomes management study including evidence-based clinical pathways and protocols for weaning acute care patients\(^1\)
- Participants included 595 pre-outcomes management patients and 510 post-outcomes management patients mechanically ventilated for >3 consecutive days\(^1\)

Implementation of Clinical Pathways
Clinical Outcome and Cost Burden (Cont’d)

- Significant differences in clinical outcomes were demonstrated between the 2 groups\(^1\)
  - Decreased ventilator duration by 1 day (\(P=.0001\))\(^1\)
  - ICU stay reduced by 3 days (\(P=.0008\))\(^1\)
  - Hospital length of stay reduced by 2 days (\(P=.0001\))\(^1\)
  - Mortality rate declined from 38% to 31% (\(P=.02\))\(^1\)

- More than $3 million cost savings were realized in the OM group\(^1\)

Overview of Current Sedative and Analgesic Agents
# Overview of Current Sedative and Analgesic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Year FDA Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Morphine</td>
<td>Prior to 1938</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>1968</td>
</tr>
<tr>
<td>Butyrophenones</td>
<td>Haloperidol</td>
<td>1967</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam</td>
<td>1963</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>1963</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td>1985</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Propofol</td>
<td>1989</td>
</tr>
<tr>
<td>$\alpha_2$ Agonists</td>
<td>Clonidine</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td>Dexmedetomidine</td>
<td>1999</td>
</tr>
</tbody>
</table>

http://www.fda.gov/cder/ob/default.htm
# Opioids

### Clinical Effects

- Analgesia\(^1\)
- Sedation\(^1\)

### Adverse Effects

- Respiratory depression\(^1,2\)
- Hypotension\(^1,2\)
- Bradycardia\(^1,2\)
- Constipation\(^1\)
- Tolerance\(^1\)
- Withdrawal symptoms\(^1,2\)
- Dysphoria\(^3,4\)

---

![Fentanyl](image1.png)

![Morphine](image2.png)

---

\(^1\)Harvey MA. *Am J Crit Care.* 1996;5:7-16.


Haloperidol

Clinical Effects

- Hypnotic agent with antipsychotic properties\(^1\)
  - For treatment of delirium in critically ill adults\(^1\)
- Does not cause respiratory depression\(^1\)

Adverse Effects

- Dysphoria\(^2\)
- Adverse CV effects include QT interval prolongation, extrapyramidal symptoms, neuroleptic malignant syndrome (rare)\(^1\)
- Metabolism altered by drug-drug interactions\(^2\)

\(^1\)Harvey MA. *Am J Crit Care*. 1996;5:7-16.
Benzodiazepines

Lorazepam

Clinical Effects

- Sedation, anxiolysis, and amnesia\(^1\)
- Commonly used for long-term sedation\(^2\)

Adverse Effects

- Slower onset of action than midazolam\(^2,3\)
- Metabolic Acidosis (propylene glycol toxicity)\(^4,5\)
- Retrograde and anterograde amnesia can exceed desirability\(^6\)
- Delirium\(^7\)

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Benzodiazepines
Midazolam

**Clinical Effects**
- Sedation, anxiolysis, and amnesia\(^1\)
- Rapid onset of action intravenously\(^1\)

**Adverse Effects**
- May accumulate in liver and/or renal failure\(^1\)
- Anterograde amnesia\(^2\)
- Prolonged recovery after long-term use\(^3\)
- Combination with opioids increases hypotensive effects\(^1\)
- Respiratory depression\(^4\)
- Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability\(^4\)

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## Propofol

### Clinical Effects

- Sedation\(^1\)
- Hypnosis\(^1\)
- Anxiolysis\(^1\)
- Muscle relaxation\(^1\)
- ↓ ICP\(^1\)
- ↓ Cerebral metabolic rate\(^1\)
- Antiemetic\(^2\)

### Adverse Effects

- Respiratory depression (exacerbated by opioids)\(^1\)
- Hypotension\(^1\)
- Decreased myocardial contractility\(^3\)
- Preservative issues\(^4\)
- Potential for infection\(^4\)
- Tolerance\(^5\)
- Propofol infusion syndrome\(^6\)
- ↑ Serum triglycerides\(^4\)

---

\(^1\)Harvey MA. *Am J Crit Care*. 1996;5:7-16.


**α2 Agonists: Clonidine**

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antihypertensive(^1,^2)</td>
<td>- Bradycardia(^1)</td>
</tr>
<tr>
<td>- Analgesia(^1)</td>
<td>- Dry mouth(^1)</td>
</tr>
<tr>
<td>- Anxiolysis(^1)</td>
<td>- Hypotension(^3)</td>
</tr>
<tr>
<td>- Sedation(^1)</td>
<td>-</td>
</tr>
<tr>
<td>- ↓ Shivering(^1)</td>
<td>-</td>
</tr>
</tbody>
</table>

$\alpha_2$ Agonists: Dexmedetomidine

Clinical Effects

- Antihypertensive$^{1,2}$
- Sedative$^{1,2}$
- Analgesic$^{1,2}$
- ↓ Shivering$^3$
- Anxiolytic effects$^4$
- Patient rousability$^4$
- Potentiates effects of opioids, sedatives, and anesthetics$^2$
- Decreased sympathetic activity$^5$

Adverse Effects

- Bradycardia$^6$
- Hypotension$^6$
- Dry mouth$^2$
- Vasoconstriction with rapid infusion or at high doses$^2$
- Nausea$^2$

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Key Components of the Ascending Arousal System

Key Projections to the Ascending Arousal System

“Switch” Mechanisms of Alertness and Sleep

Clinical Characteristics of Dexmedetomidine

- Cooperative sedation\(^1\)
- Analgesia\(^2,3\)
- Organ Protection (ie, neural, renal, cardiac)\(^1\)
- Anxiolysis\(^2,3\)
- Controls hyperadrenergic response to stress\(^1-3\)
- Reduces shivering\(^3\)
- Diuretic action\(^4\)
- Mimics Natural Sleep\(^1\)

---

Physiology of Dexmedetomidine

α2A, α2C Locus Ceruleus

α2A Brainstem vasomotor center

α2B CNS-based thermoregulatory inhibition

α2B Cerebral vessels and peripheral vasculature

α2B Dorsal horn of the spinal cord

α2A Dorsal horn of the spinal cord

Bradycardia

Vagomimetic action

Decrease
Tachycardia

Blocks cardioaccelerator nerve

Anti-shivering

Vasoconstriction

X

α2A Peripheral smooth-muscle cells

α2B Diuresis

# Comparison of Clinical Effects

<table>
<thead>
<tr>
<th></th>
<th>Benzo-diazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Dexmedetomidine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Alleviate anxiety</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analgesic Properties</strong>&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Promote arousability during sedation</strong>&lt;sup&gt;2-4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Facilitate ventilation during weaning</strong>&lt;sup&gt;2-4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>No respiratory depression</strong>&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Control delirium</strong>&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>1</sup>Blanchard AR. *Postgrad Med*. 2002;111:59-74.<br>
<sup>2</sup>Kamibayashi T, et al *Anesthesiology*. 2000;95:1345-1349.<br>
## Comparison of Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Benzo-diazepines</th>
<th>Propofol</th>
<th>Opioids</th>
<th>Dexmedetomidine</th>
<th>Haloperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged weaning(^1)</td>
<td>X</td>
<td>X</td>
<td>X(^*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory depression(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension(^1-3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Constipation(^1)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Deliriogenic</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia(^1)</td>
<td></td>
<td></td>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia(^1)</td>
<td></td>
<td></td>
<td>Fentanyl</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^*\)Excluding remifentanil

\(^1\)Harvey MA. *Am J Crit Care.* 1996;5:7-16.


\(^3\)Maze M. *Crit Care Clin.* 2001;4:881;
Sedative-Analgesics
Risk for Transitioning to Delirium

- Evaluation of 198 mechanically ventilated patients to determine the probability of daily transition to delirium\(^1\)
  - As a function of sedative and analgesic dose administration during the previous 24 hours\(^1\)
- Lorazepam was an independent risk factor for daily transition to delirium\(^1\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Transitioning to Delirium Only Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>1.2 (1.1-1.4)</td>
<td>.003</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.7 (0.9-3.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.2 (1.0-1.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Morphine</td>
<td>1.1 (0.9-1.2)</td>
<td>.24</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.2 (0.9-1.7)</td>
<td>.18</td>
</tr>
</tbody>
</table>

## Serious Complications Associated With Delirium

<table>
<thead>
<tr>
<th>Response</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged ventilation</td>
<td>179 (20)</td>
</tr>
<tr>
<td>Patient injury</td>
<td>179 (20)</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>176 (19)</td>
</tr>
<tr>
<td>Self-extubation</td>
<td>80 (9)</td>
</tr>
<tr>
<td>Sepsis/shock</td>
<td>60 (7)</td>
</tr>
<tr>
<td>Prolonged LOS</td>
<td>58 (6)</td>
</tr>
<tr>
<td>Oversedation</td>
<td>52 (6)</td>
</tr>
<tr>
<td>Death</td>
<td>36 (4)</td>
</tr>
</tbody>
</table>

Incidence of ICU Delirium

- Evaluation of 90 patients undergoing cardiac surgery to determine the probability of development of postoperative delirium
- Post-operative sedation with dexmedetomidine may be associated with a lower incidence of delirium compared with more conventional forms of sedation

## Comparison of Pharmacokinetics

### Ranges Reported in Healthy Patients* and ICU Patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>Elimination Half-life (hr)</th>
<th>Systemic Clearance (mL/kg/min)</th>
<th>Potential for Accumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.0-5.5</td>
<td>8.6-23</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Fentanyl&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6.9-36.0</td>
<td>8.6-15.0</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Diazepam&lt;sup&gt;1&lt;/sup&gt;</td>
<td>21-120</td>
<td>0.4-0.9</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Midazolam&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3.4-11</td>
<td>4.3-6.6</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Lorazepam&lt;sup&gt;1&lt;/sup&gt;</td>
<td>10-15</td>
<td>1.2-4.1</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Propofol&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6.3-32</td>
<td>17-31</td>
<td>--</td>
</tr>
<tr>
<td>Clonidine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6-23</td>
<td>1.9-4.3</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Dexmedetomidine&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2</td>
<td>0.32-0.64 mL/hr/kg</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Haloperidol&lt;sup&gt;4&lt;/sup&gt;</td>
<td>28-38</td>
<td>10-13</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Aripiprazole&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td>75</td>
<td>3.45-4.5 L/h</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Olanzapine&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7</td>
<td>7.5</td>
<td>--</td>
</tr>
<tr>
<td>Ziprasidone&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7</td>
<td>7.5</td>
<td>Hepatic insufficiency</td>
</tr>
</tbody>
</table>

*Healthy patients: no renal or hepatic disease.

<sup>2</sup>Khan ZP, et al. *Anaesthesia*. 1999;54:146-165;  
<sup>4</sup>Prescribing information for respective drugs;  
Dexmedetomidine
Patients were infused with placebo or 1 of 2 doses of dexmedetomidine and monitored with the Bispectral Index System (BIS) before stimulation and immediately after being asked to perform cognitive and cold pressor tests\(^1\).

Patients receiving either infusion of dexmedetomidine could be completely aroused by a mild stimulus\(^1\).

Comparison of Dexmedetomidine With Propofol

- 20 adult ICU patients were randomized to either dexmedetomidine or propofol
  - Dexmedetomidine; 10-minute 2.5 mcg/kg/h loading dose, 0.2-2.5 mcg/kg/h maintenance dose
  - Propofol; ≤1 mg/kg 10-minute loading dose (if required), 1-3 mg/kg/h maintenance dose

- Additional analgesia, if necessary, was provided by alfentanil

- Depth of sedation was measured with RSS and BIS

- Dexmedetomidine and propofol produced an equivalent depth of sedation

Predictable Effects on Heart Rate and Arterial Pressure

- Significantly lower heart rates in the dexmedetomidine group during intubation ($P=.034$) but not after sedative discontinuation ($P=.15$)\(^1\)
  - Predictable 10% decrease with plateau\(^1\)
- No significant differences in systolic and diastolic blood pressures ($P=.60$)\(^1\)
- Attenuates postoperative tachycardia\(^2\)


Note: Reductions from baseline shown.
Postoperative Effects of Dexmedetomidine

Improved postoperative pain and greater sedation with dexmedetomidine compared with propofol.\(^1\)


**P**<.05 difference over time compared with baseline
\(\dagger\)P<.05 difference between groups
Morphine-Sparing Effects in Inpatient Surgery

- 34 patients scheduled for inpatient surgery
- Randomized to either dexmedetomidine or morphine
- Agents were started 30 minutes before the end of surgery
- Dexmedetomidine reduced the early postoperative need for morphine by 66%

Reduction of Postoperative Requirement for Epidural Opioids With Dexmedetomidine

- Prospective, randomized, double-blind study with 28 patients scheduled for thoracotomy for wedge resection, lobectomy, or pneumonectomy¹
- Bupivacaine was administered in an acute care setting through a thoracic epidural, and patients were randomized to receive either IV placebo or IV dexmedetomidine (20-minute, 0.5 mcg/kg loading dose plus infusion of 0.4 mcg/kg/h)¹
- Supplemental analgesia (fentanyl), vital signs, and blood gasses were monitored¹

Reduction of Postoperative Requirement for Opioids With Dexmedetomidine

The requirement for supplemental Epidural (ED) fentanyl analgesia was significantly greater in the placebo group¹

Dexmedetomidine is a potentially effective analgesic adjunct to thoracic ED bupivacaine infusion and may decrease the requirement for opioids and potential for respiratory depression¹

Injury and Liability Associated With Monitored Anesthesia Care

Bhananker and colleagues assessed the patterns of injury and liability associated with monitored anesthesia care (MAC; n = 121) compared with general (n = 1519) and regional anesthesia (n = 312).

- The proportion of claims for death and permanent brain damage was reduced in regional anesthesia compared with MAC.
- In contrast, the severity of injury was similar between MAC claims and those associated with general anesthesia.

Respiratory depression due to sedative, hypnotic, and/or analgesic overdose was responsible for 21% of MAC-related claims
- 24% occurred during endoscopic procedures
- Nearly 75% received a combination of two or more drugs
  - Either a benzodiazepine and an opioid or propofol plus others

Death or brain damage resulted in most of the claims related to oversedation

Resolution of legal claims associated with oversedation cost an average of $254,000 per patient
Pharmacoeconomic Data
Factors Affecting ICU Cost

- ICU stays account for nearly a third of total inpatient costs
- High ICU costs may be due to mechanical ventilation (MV) and/or delirium
- Sedatives have the potential to prolong MV and may increase healthcare costs
- Incorporation of a daily sedation interruption policy into a medical ICU guideline can significantly reduce ICU stays and days of MV

5 Wittbrodt ET. *Pharmacotherapy*. 2005;25(5 Pt 2):3S-7S.
Limitations of Pharmacoeconomic Studies on Sedation

- Small sample sizes
- Results not applicable to other clinical sites
- Too few have been conducted to date
- Most do not evaluate total cost

Pharmacoeconomic Analysis
Outcomes Analysis in Cardiac Surgery

- 12-month retrospective administrative claims database analysis (2003-2004)\(^1\)
- Nationally representative sample of 250 medical and surgical hospitals\(^1\)
- Comparison of patients receiving either midazolam plus propofol (M+P, \(n = 9996\)) or dexmedetomidine plus M+P (D+M+P, \(n = 356\))\(^1\)
  - Patients who were admitted to the hospital for either a cardiovascular valve or vessel procedure\(^1\)
  - Patient demographics and outcomes were obtained from the hospital billing claim form, UB-92\(^1\)
- Admissions with lengths of stay more than 100 days were excluded from all analyses

## Pharmacoeconomic Analysis
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M+P</th>
<th>D+M+P</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>n = 9996</strong></td>
<td><strong>n = 356</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean [SD])</td>
<td>65.6 (12.0)</td>
<td>61.0 (11.1)</td>
<td>&lt;.0001</td>
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<tr>
<td>Male</td>
<td>67.6%</td>
<td>78.9%</td>
<td>&lt;.0001</td>
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<tr>
<td>Patient Charlson Comorbidity Index</td>
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<tr>
<td>0</td>
<td>34.4%</td>
<td>40.2%</td>
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<tr>
<td>1</td>
<td>56.7%</td>
<td>53.7%</td>
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</tr>
<tr>
<td>2</td>
<td>7.6%</td>
<td>4.5%</td>
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<tr>
<td>3</td>
<td>1.0%</td>
<td>1.6%</td>
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</tr>
<tr>
<td>4</td>
<td>0.3%</td>
<td>0%</td>
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<td>Mechanical Ventilation/Intubation</td>
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<td></td>
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<tr>
<td>Patients</td>
<td>78.1%</td>
<td>98.0%</td>
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<tr>
<td>Duration, days</td>
<td>5.46</td>
<td>4.82</td>
<td>&lt;.01</td>
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</tbody>
</table>

Pharmacoeconomic Analysis
Reduced Mean Total Treatment Charges

12-month retrospective administrative claims database analysis
Comparison of patients receiving either midazolam plus propofol (M+P) or dexmedetomidine plus M+P (D+M+P)
The D+M+P cohort showed significant reductions in per patient total charges

M+P, n = 9996
D+M+P, n = 356

Pharmacoeconomic Analysis
Departmental Treatment Charges

ICU/CCU
- M+P: $17.7K, D+M+P: $2.8K, P < .0001

Operating Room
- M+P: $17.3K, D+M+P: $12.8K, P < .0001

Pharmacy
- M+P: $12.7K, D+M+P: $16.7K, P < .0001

Anesthesia
- M+P: $2.5K, D+M+P: $3.4K, P < .0001

Reductions in ICU and OR charges offset increases in other areas.

M+P, n = 9996
D+M+P, n = 356

Pharmacoeconomic Analysis
Reduced Hospitalization and Mortality

Mean Length of Stay

- M+P, n = 9996
- D+M+P, n = 356

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Length of Stay</th>
</tr>
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<tbody>
<tr>
<td>M+P</td>
<td>9.4</td>
</tr>
<tr>
<td>D+M+P</td>
<td>8.8</td>
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</table>

P < 0.0001

Mean Days in ICU/CCU

- M+P
- D+M+P

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Days</th>
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<td>M+P</td>
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<tr>
<td>D+M+P</td>
<td>1.4</td>
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</table>

P < 0.0001

Mortality Rate

- M+P
- D+M+P

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>M+P</td>
<td>3.0%</td>
</tr>
<tr>
<td>D+M+P</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

P = 0.0142

Pharmacoeconomic Analysis
Reduced Charges, Hospitalization, and Mortality in Patients With Cardiac Vessel Procedures

Mean Total Charges
- M+P: $97K
- D+M+P: $80K

Mean Length of Stay
- M+P: 8.9 days
- D+M+P: 8.1 days

Mortality Rate
- M+P: 2.5%
- D+M+P: 1.0%

M+P, n = 7577
D+M+P, n = 293

Pharmacoeconomic Analysis
Study Limitations

- Dosage
- Duration of therapies
- Influence of practice patterns/institutional variability unknown
- Lack of randomization of patients to treatment introduced risk of selection or channeling bias
- Assigning causality based on results not possible\(^1\)

Dexmedetomidine was added to standard sedative regimens (midazolam + propofol) under actual practice conditions\(^1\)

Largest study measuring the pharmacoeconomic and clinical outcomes of any sedation agent in this population

Potential demonstrable clinical and economic benefits of including dexmedetomidine in sedation regimens\(^1\)
  - Addition of dexmedetomidine to the standard of care was associated with significant reductions in total LOS, stay in ICU/CCU, and mortality\(^1\)
  - Significantly lower total treatment charges\(^1\)

Properties of Dexmedetomidine in Cardiovascular Surgery

- Lack of respiratory depression
- Cooperative sedation aids in assessing neurophysiological function during vascular procedures such as endarterectomy
- Hemodynamic stabilization is desirable during cardiovascular surgery
- Attenuates hypertension and tachycardia

Postoperative CABG Sedation
Dexmedetomidine Versus Propofol

Effects of Dexmedetomidine and Propofol on Heart Rate

Mean heart rates were similar between groups throughout the study period\(^1\)

Immediate Extubation Following Cardiac Surgery

- Horswell et al conducted a study of immediate extubation after off-pump coronary artery bypass graft (OPCAB) in 514 patients.
- Following surgery, each patient received 2 or more of the following: epidural anesthesia, IV morphine on demand, IV ketorolac on schedule, and/or continuous IV dexmedetomidine.
- All patients were successfully extubated immediately after dressing application.
- The investigators concluded that immediate extubation of OPCAB patients is feasible and probably safe\(^1\).

Use of Perioperative Dexmedetomidine in Vascular Surgery

- Significant between group changes from baseline for plasma epinephrine ($P<.05$) and norepinephrine ($P<.001$)
- Plasma norepinephrine concentrations were 2 to 3 times lower in the dexmedetomidine group at both tracheal extubation and at 60 min after arrival to PACU
- Plasma epinephrine concentrations were lower in the dexmedetomidine group only during tracheal extubation

Neurological Effects
Properties of Dexmedetomidine in Neurosurgery

- Intraoperative hemodynamic stability\(^1\)
- Lack of respiratory depression\(^1\)
- Patients easily transition from sleep to wakefulness and task performance when aroused, and then back to sleep when not stimulated\(^1\)
- Does not increase intracranial pressure\(^1\)
- Allows for consistent and reliable somatosensory evoked potential amplitudes or latencies\(^1\)

Examples of Cooperative Sedation

Neurological Examples

- Intracranial surgical procedures often require patient cooperation for functional assessment\(^1\)
  - The procedure is frequently limited by the location/spatial extent of the lesion and its relationship to functioning tissue\(^1\)
  - Surgeons balance the benefits of an aggressive resection with anticipated neurological dysfunction\(^1\)
- Intraoperative neurophysiological testing\(^1\)
  - Can verify that surgical target has been localized\(^1\)
  - Is used to assess the production of an intended functional change\(^1\)
- Carotid endarterectomy performed in awake patients allows evaluation of cerebral perfusion by continuous examination of neurologic function\(^2\)

Dexmedetomidine and Cerebral Blood Flow Clinical Data

- Reduced cerebral blood flow (CBF) has also been demonstrated in human studies:\(^1\)
  - Reduced CBF may be advantageous for situations such as traumatic brain injury or large brain tumors\(^1\)
- No detrimental effect on local brain tissue oxygenation in patients undergoing cerebral vascular surgery\(^1\)
- Under normotensive conditions in the setting of compromised cerebral circulation, dexmedetomidine has no apparent adverse effects\(^1\)
- It has been shown that dexmedetomidine is suitable for preoperative sedation of patients with subarachnoid hemorrhage (SAH)\(^2\)

Dexmedetomidine and Cerebral Blood Flow Decreased Cerebral Metabolic Rate

- Prielipp and colleagues analyzed data from nine supine volunteers to assess the potential for dexmedetomidine induced decreases in regional and global CBF
- Patients were infused with a 1 mcg/kg IV loading dose of dexmedetomidine, followed by an infusions of either
  - 0.2 mcg/kg/h (Low Dose)
  - 0.6 mcg/kg/h (High Dose)
Dexmedetomidine and Cerebral Blood Flow
Decreased Cerebral Metabolic Rate

- Both low and high doses
  - Reduced global CBF by one third
  - Decreased mean systemic BP, HR, and CO 15% to 20%
  - Increased PaCO₂ no more than 5 mm Hg
- CBF decreased from baseline throughout dexmedetomidine infusion and for at least 30 minutes thereafter

Note: Color intensity correlates with CBF

Dexmedetomidine and Cerebral Blood Flow
Cerebral Perfusion in Severe Head Injury

- Prospective study on the effect of dexmedetomidine in patients with severe head injury
  - 12 ICU patients (aged 15 to 64 years)
  - Glasgow Coma Scale ≤8
  - Intracranial pressure <20 mm Hg
  - \( \text{O}_2 \) saturation monitoring of blood from jugular bulb

- 3 hours of progressive IV dexmedetomidine perfusion (0.2, 0.4, 0.7 mcg/kg/h)
  - All other sedative-analgesic medications previously withdrawn

Dexmedetomidine and Cerebral Blood Flow
Cerebral Perfusion in Severe Head Injury (Cont’d)

- No significant changes from baseline in the following domains
  - Intracranial pressure
  - Mean arterial pressure
  - Cerebral profusion
  - Jugular bulb oxygenation
  - Cerebral oxygen extraction/supply
  - Heart rate

Pediatric Applications
Use of Dexmedetomidine in MRI

- 80 children aged 1-7 years\(^1\)
- Randomly assigned to either dexmedetomidine or midazolam\(^1\)
  - 10-minute loading doses:
    1 mcg/kg dexmedetomidine, 0.2 mcg/kg midazolam\(^1\)
  - Infusions: 0.5 mcg/kg/h dexmedetomidine, 6 mcg/kg/h midazolam\(^1\)
- The quality of MRI was significantly better (\(P<.001\)) and the rate of adequate sedation was significantly higher (\(P<.001\)) with dexmedetomidine\(^1\)

![Quality of MRI](image)

*\(P<.001\) compared with midazolam

Dexmedetomidine Superior to Midazolam in Pediatric Acute Care Patients

- 20 pediatric ICU patients randomized to either dexmedetomidine (starting dose 0.25 or 0.5 mcg/kg/h) or midazolam (starting dose 0.1 mg/kg/h)\(^1\)
- Morphine was used intermittently as needed\(^1\)
- 0.25 mcg/kg/h dexmedetomidine was equivalent to 0.22 mg/kg/h midazolam\(^1\)
- 0.5 mcg/kg/h dexmedetomidine provided more effective sedation than 0.22 mg/kg/h midazolam\(^1\)
  - Less morphine use\(^1\)
  - Decrease in the number of Ramsay scores of 1 (fewer patients oversedated) [Data not shown]\(^1\)

Propofol Black Box Warnings for Pediatric Use

- Not recommended for
  - Induction of anesthesia in patients aged <3 years\(^1\)
  - Maintenance of anesthesia in patients aged <2 months\(^1\)

- Pediatric use
  - Not indicated for ICU sedation or for MAC sedation for surgical, nonsurgical, or diagnostic procedures\(^1\)
  - Co-administration of fentanyl and propofol may result in serious bradycardia\(^1\)

Dexmedetomidine in Bariatric Surgery
Intraoperative Use of Dexmedetomidine in Bariatric Surgery

- Rising incidence of morbid obesity is increasing the need for bariatric surgery\(^1,\)\(^2\)
- Respiratory comorbidities in morbid obesity may profoundly impact anesthetic management\(^1,\)\(^2\)
  - Opioid use may lead to severe respiratory depression\(^1,\)\(^2\)
  - Ideal analgesics should be free of significant/long-lasting respiratory effects\(^1,\)\(^2\)
- In one center, over 2000 bariatric procedures have been performed safely using the perioperative administration of dexmedetomidine, which was shown to be cardioprotective and neuroprotective while providing a hemodynamically stable course and reducing the need for opioids and inhalational agents\(^3\)

Dexmedetomidine Attenuates Blood Pressure in Bariatric Surgery

- Feld and colleagues evaluated whether dexmedetomidine infusion could replace fentanyl in open gastric bypass surgery.

- During surgery, blood pressure and heart rate were significantly decreased with dexmedetomidine compared with fentanyl.

- Dexmedetomidine was associated with significantly lower postoperative pain and morphine use.

Algorithms
Dexmedetomidine Sedation Algorithm

Initial assessment of patient’s sedation level
Is the patient comfortable, cooperative, and communicative? SAS ≤ 4?

N

Is the patient agitated or in pain? SAS > 4?

Y

Initiate Dexmedetomidine
• Begin infusion: 0.2 mcg/kg/hr
  (If SAS < 6 and hemodynamics are normal or depressed)
• If hyperdynamic and SAS > 6: Bolus, 1.0 mcg/kg over 10-20 minutes

Ongoing assessment of patient’s sedation level
• SAS > 4
• Patient is agitated or in pain?

N

Dexmedetomidine infusion rate < 0.7 mcg/kg/hr

Y

Assess pain and implement supplemental opioid protocol as needed

Y

Increase dexmedetomidine infusion rate < 0.1 mcg/kg/hr

N

Implement supplemental agitation protocol (dexmedetomidine < 2.0 mcg/kg/hr) if patient demonstrates agitation on assessment (SAS > 4)

N

If the patient is somnolent or unresponsive with SAS < 3, assess for CNS event, metabolic process, and drugs. If dexmedetomidine infusion is ongoing, decrease by 0.1 mcg/kg/hr with ongoing assessment of sedation.

N

Y

Y

Y

Transitioning Long-Term Sedation to Dexmedetomidine

- Titrate propofol every hour with orders not to increase
- Administer dexmedetomidine infusion, 0.4 mcg/kg/hr
  - Titrate dexmedetomidine according to HR and BP with allowed increases of 0.2 mcg/kg/hr
  - Increase dose of dexmedetomidine in PM to optimize natural sleep and circadian rhythm
- If extreme agitation occurs, add benzodiazepine (synergistic with dexmedetomidine)
- If patient is agitated on waking, administer more benzodiazepine (requirement is less with dexmedetomidine on board)

Courtesy of Daniel L. Herr, MD.
Abdominal Aortic Aneurysm

- Patients undergoing endovascular repair of abdominal aortic aneurysms with general (n = 217; 22 used for direct comparison) versus dexmedetomidine (n = 14) sedation

- Dexmedetomidine sedation resulted in
  - Reduced time for surgery
  - Reduced time for anesthesia
  - Reduced opioid requirement

Induce as usual; when stable, start dexmedetomidine at 0.7 mcg/kg/h

After 15 mins reduce inhalant anesthetic to half MAC

Opioid use
Routine dose of fentanyl at induction of anesthesia

Hemodynamics indicative of adequate analgesia?

Five minutes prior to end of procedure, reduce dexmedetomidine to 0.2 mcg/kg/h

Awaken patient and extubate

Titratedexmedetomidine after extubation to patient comfort (usually 0.2 – 0.5 mcg/kg/h)
Perioperative Bariatric Surgery Algorithm
Preoperative Protocol

Assess cardiac functioning
Indications of cardiomegaly, cardiac failure, CAD, or pulmonary HTN?

- Y Optimize cardiac state
- N Assess airway/respiratory system

Obstruction of airway by adipose tissue?

- Y Awake fiberoptic intubation
  - Y Administer Dexmedetomidine (<0.7 mcg/kg/h) plus topical anesthetic
  - Y Correct head positioning
    Use “back up” position at induction of anesthesia and subsequent recovery
  - N Proceed to Intraoperative Procedure

- N Obstructive sleep apnea? O₂ Desaturation Risk?
  - ↓ Lung Volumes
    - Functional residual capacity
    - Expiratory reserve
    - Forced vital capacity
  - N Proceed to Intraoperative Procedure

Courtesy of M. Ramsay, MD.
Perioperative Bariatric Surgery Algorithm
Intraoperative Protocol

**Brief Procedure**

- **Y**
  - Laproscopic gastric bypass or gastric banding
  - Administer Dexmedetomidine Loading Dose
    - 0.5 to 0.75 mcg/kg and monitor for transient hypertension

- **N**
  - Roux-en Y gastric bypass
    - Dexmedetomidine solution
      - 400 mcg/100 mL of 0.9% sodium chloride at 4 mcg/mL
      - Initiate dexmedetomidine infusion
        - (0.4 to 0.7 mcg/kg/h)
        - 1 hour before completion of surgery
      - Reduce infusion at end of surgery
        - (approximately 5 min prior to completion)
      - Allow patient to gradually awaken
  - Proceed to Postoperative Procedure

*Courtesy of M. Ramsay, MD.*
Perioperative Bariatric Surgery Algorithm

Postoperative Protocol

- Continue infusion in the recovery room during and after intubation
- Titrate to 0.7 mcg/kg/h for pain control
- Discontinue dexmedetomidine at discharge from recovery unit
- No postoperative opioids needed

Courtesy of M. Ramsay, MD.
Overall Summary

- Patient care and safety, as well as physiological and neurobehavioral considerations, reinforce the need for sedation in acute care settings.
- Attenuating reactions to pain and stress while optimizing patient communication are important acute care goals.
- Inappropriate sedation and analgesic therapy in acute care settings leads to poor clinical and economic outcomes.
- Guidelines, standards, clinical pathways, and algorithms clarify the manner in which sedatives should be used in acute care settings.
  - Institutions should have multidisciplinary agreements to use scale assessment and documentation.
Overall Summary (Cont’d)

- Ongoing developments influence changes in guidelines and standards
  - It is anticipated that JCAHO will add new sedation criteria
  - Currently under revision, new SCCM guidelines are expected in 2007

- Implementation of rational use guidelines in acute care sedation can result in improved LOS and reduced costs for medications

- The addition of dexmedetomidine to the current standard of care is associated with improved clinical outcomes and reduced total hospital costs