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

References:
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

- overshedation
- undersedation

- 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\(^3\)

\(^1\) McGaffigan PA. *Crit Care Nursing*. 2002; Feb Suppl:29-36.
## Importance of Optimizing Levels of Sedation

<table>
<thead>
<tr>
<th>Undersedation</th>
<th>Oversedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anxiety(^1)</td>
<td>• Prolonged weaning(^3)</td>
</tr>
<tr>
<td>• Ventilator dysynchrony(^2)</td>
<td>• Respiratory depression(^4)</td>
</tr>
<tr>
<td>• Dislodging invasive lines/devices(^1)</td>
<td>• Lack of patient cooperation for assessment and therapeutic measures(^1)</td>
</tr>
<tr>
<td>• May increase posttraumatic stress syndrome(^1)</td>
<td>• Inability to communicate with health care providers or family members(^1)</td>
</tr>
<tr>
<td>• Increased O(_2) consumption(^1)</td>
<td>• Delirium(^2)</td>
</tr>
<tr>
<td>• Delirium(^2)</td>
<td>• Hypoactivity(^1)</td>
</tr>
<tr>
<td>• Hyperactivity(^1)</td>
<td></td>
</tr>
<tr>
<td>• Minimal amnesia(^2)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) McGaffigan PA. *Crit Care Nursing*. 2002; Feb Suppl:29-36.  
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\(^2,3\).

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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\(^1\)
- Visual Analog Scale (VAS)\(^1\)
- Pain questionnaire\(^1\)
  - Qualitative aspects\(^1\)
- Sympathetic response to pain\(^1\)

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 Anxiety²
- The Hospital Anxiety and Depression Scale³
- Linear Analog Anxiety Scale⁴
- Surrogate markers of stress response⁵
- 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\(^1\)
- One group (n = 84) was tracked after guidelines were implemented\(^1\)
- Length of hospital and ICU stay and duration of mechanical ventilation were all shorter in the guidelines group\(^1\)
- Institution of the guidelines led to a decline in mean drug costs across all drug classes studied\(^1\)

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\(^1\)

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

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Analgesia(^1)</td>
<td>- Respiratory depression(^1,2)</td>
</tr>
<tr>
<td>- Sedation(^1)</td>
<td>- Hypotension(^1,2)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypnotic agent with antipsychotic properties&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Dysphoria&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>- For treatment of delirium in critically ill adults&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Adverse CV effects include QT interval prolongation, extrapyramidal symptoms, neuroleptic malignant syndrome (rare)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Does not cause respiratory depression&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Metabolism altered by drug-drug interactions&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup>Harvey MA. *Am J Crit Care*. 1996;5:7-16.  
### Benzodiazepines

#### Lorazepam

<table>
<thead>
<tr>
<th>Clinical Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sedation, anxiolysis, and amnesia(^1)</td>
<td>• Slower onset of action than midazolam(^2,3)</td>
</tr>
<tr>
<td>• Commonly used for long-term sedation(^2)</td>
<td>• Metabolic Acidosis (propylene glycol toxicity)(^4,5)</td>
</tr>
<tr>
<td></td>
<td>• Retrograde and anterograde amnesia can exceed desirability(^6)</td>
</tr>
<tr>
<td></td>
<td>• Delirium(^7)</td>
</tr>
</tbody>
</table>

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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\(^4\)

## Propofol

### Clinical Effects
- Sedation
- Hypnosis
- Anxiolysis
- Muscle relaxation
- ↓ ICP
- ↓ Cerebral metabolic rate
- Antiemetic

### Adverse Effects
- Respiratory depression (exacerbated by opioids)
- Hypotension
- Decreased myocardial contractility
- Preservative issues
- Potential for infection
- Tolerance
- Propofol infusion syndrome
- ↑ Serum triglycerides

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### Clinical Effects
- Antihypertensive$^{1,2}$
- Analgesia$^1$
- Anxiolysis$^1$
- Sedation$^1$
- ↓ Shivering$^1$

### Adverse Effects
- Bradycardia$^1$
- Dry mouth$^1$
- Hypotension$^3$

---

α₂ Agonists: Dexmedetomidine

**Clinical Effects**
- Antihypertensive¹,²
- Sedative¹,²
- Analgesic¹,²
- ↓ Shivering³
- Anxiolytic effects⁴
- Patient rousability⁴
- Potentiates effects of opioids, sedatives, and anesthetics²
- Decreased sympathetic activity⁵

**Adverse Effects**
- Bradycardia⁶
- Hypotension⁶
- Dry mouth²
- Vasoconstriction with rapid infusion or at high doses²
- Nausea²

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Key Components of the Ascending Arousal System

Key Projections to the Ascending Arousal System

“Switch” Mechanisms of Alertness and Sleep

a

VLPO  eVLPO

ORX

LC  TMN  Raphe

Awake

On

b

VLPO  eVLPO

ORX

LC  TMN  Raphe

Sleep

Off

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
- Sedation
- Anxiolysis
- Bradycardia
- Vagomimetic action
- Decrease Tachycardia
- Blocks cardioaccelerator nerve
- **α₂B** CNS-based thermoregulatory inhibition
- Anti-shivering
- **α₂B** Cerebral vessels and peripheral vasculature
- Vasoconstriction
- Vasodilation
- **α₂A** Peripheral smooth-muscle cells
- **α₂B** Dorsal horn of the spinal cord
- Analgesia
- 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></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analgesic Properties</strong></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Promote arousability during sedation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Facilitate ventilation during weaning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>No respiratory depression</strong></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Control delirium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

## Comparison of Adverse 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>Prolonged weaning¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression¹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Hypotension¹-³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Constipation¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Deliriogenic</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia¹</td>
<td></td>
<td></td>
<td></td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Bradycardia¹</td>
<td></td>
<td></td>
<td></td>
<td>Fentanyl</td>
<td>X</td>
</tr>
</tbody>
</table>

*Excluding remifentanil

³Maze 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
  - As a function of sedative and analgesic dose administration during the previous 24 hours
• Lorazepam was an independent risk factor for daily transition to delirium

<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(^1)</td>
<td>2.0-5.5</td>
<td>8.6-23</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Fentanyl(^1)</td>
<td>6.9-36.0</td>
<td>8.6-15.0</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Diazepam(^1)</td>
<td>21-120</td>
<td>0.4-0.9</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Midazolam(^1)</td>
<td>3.4-11</td>
<td>4.3-6.6</td>
<td>Hepatic/renal insufficiency</td>
</tr>
<tr>
<td>Lorazepam(^1)</td>
<td>10-15</td>
<td>1.2-4.1</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Propofol(^1)</td>
<td>6.3-32</td>
<td>17-31</td>
<td>–</td>
</tr>
<tr>
<td>Clonidine(^2)</td>
<td>6-23</td>
<td>1.9-4.3</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Dexmedetomidine(^3)</td>
<td>2</td>
<td>0.32-0.64 mL/hr/kg</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Haloperidol(^4)</td>
<td>28-38</td>
<td>10-13</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Aripiprazole(^4,5)</td>
<td>75</td>
<td>3.45-4.5 L/h</td>
<td>Hepatic insufficiency</td>
</tr>
<tr>
<td>Olanzapine(^4)</td>
<td>7</td>
<td>7.5</td>
<td>--</td>
</tr>
<tr>
<td>Ziprasidone(^4)</td>
<td>7</td>
<td>7.5</td>
<td>Hepatic insufficiency</td>
</tr>
</tbody>
</table>

*Healthy patients: no renal or hepatic disease.

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4. Prescribing information for respective drugs;  
Dexmedetomidine
Arousability From Sedation During Dexmedetomidine Infusion

- 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 tests¹.
- Patients receiving either infusion of dexmedetomidine could be completely aroused by a mild stimulus¹.

Comparison of Dexmedetomidine With Propofol

- 20 adult ICU patients were randomized to either dexmedetomidine or propofol¹
  - Dexmedetomidine; 10-minute 2.5 mcg/kg/h loading dose, 0.2-2.5 mcg/kg/h maintenance dose¹
  - Propofol; ≤1 mg/kg 10-minute loading dose (if required), 1-3 mg/kg/h maintenance dose¹
- Additional analgesia, if necessary, was provided by alfentanil¹
- Depth of sedation was measured with RSS and BIS¹
- Dexmedetomidine and propofol produced an equivalent depth of sedation¹

Predictable Effects on Heart Rate and Arterial Pressure

- Significantly lower heart rates in the dexmedetomidine group during intubation ($P=0.034$) but not after sedative discontinuation ($P=0.15$)
  - Predictable 10% decrease with plateau
- No significant differences in systolic and diastolic blood pressures ($P=0.60$)
- Attenuates postoperative tachycardia

Note: Reductions from baseline shown.

Postoperative Effects of Dexmedetomidine

Improved postoperative pain and greater sedation with dexmedetomidine compared with propofol

* $P<.05$ difference over time compared with baseline
† $P<.05$ 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 pneumonectomy\(^1\)

- 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 monitored\(^1\)

Reduction of Postoperative Requirement for Opioids With Dexmedetomidine

The requirement for supplemental ED fentanyl analgesia was significantly greater in the placebo group.

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

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.

* P<.025 MAC versus Regional

Injury and Liability Associated With Monitored Anesthesia Care (Cont’d)

- 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\(^1\)
- High ICU costs may be due to mechanical ventilation (MV) and/or delirium\(^1,2\)
- Sedatives have the potential to prolong MV and may increase healthcare costs\(^3,4\)
- Incorporation of a daily sedation interruption policy into a medical ICU guideline can significantly reduce ICU stays and days of MV\(^5\)

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

- Small sample sizes\(^1\)
- Results not applicable to other clinical sites\(^1\)
- Too few have been conducted to date\(^1\)
- Most do not evaluate total cost\(^1,2\)

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M+P</th>
<th>D+M+P</th>
<th>P-Value</th>
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<tbody>
<tr>
<td></td>
<td>n = 9996</td>
<td>n = 356</td>
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</tr>
<tr>
<td>Age, y (mean [SD])</td>
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<td>61.0 (11.1)</td>
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<td>1.6%</td>
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<td>0%</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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</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

$106K
$89K

P<.05

Pharmacoeconomic Analysis
Departmental Treatment Charges

ICU/CCU

- $17.7K (M+P), p < .0001
- $2.8K (D+M+P)

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

Operating Room

- $17.3K (M+P), p < .0001
- $12.8K (D+M+P)

Pharmacy

- $12.7K (M+P), p < .0001
- $16.7K (D+M+P)

Anesthesia

- $2.5K (M+P), p < .0001
- $3.4K (D+M+P)

Reductions in ICU and OR charges offset increases in other areas

Pharmacoeconomic Analysis  
Reduced Hospitalization and Mortality

Mean Length of Stay  
- M+P: 9.4 days  
- D+M+P: 8.8 days  
*P < .0001*

Mean Days in ICU/CCU  
- M+P: 5.3 days  
- D+M+P: 1.4 days  
*P < .0001*

Mortality Rate  
- M+P: 3.0%  
- D+M+P: 1.0%  
*P = .0142*

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

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

Mean Total Charges

Mean Length of Stay

Mortality Rate

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\(^1\)

Pharmacoeconomic Analysis
Study Conclusions

- Dexmedetomidine was added to standard sedative regimens (midazolam + propofol) under actual practice conditions¹
- 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 regimens¹
  - Addition of dexmedetomidine to the standard of care was associated with significant reductions in total LOS, stay in ICU/CCU, and mortality¹
  - Significantly lower total treatment charges¹

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

Mean heart rates were similar between groups throughout the study period\textsuperscript{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\textsuperscript{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

# Significantly different ($P<.05$) from dexmedetomidine group.
* Significantly different ($P<.05$) from baseline.

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
  - $O_2$ 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 perfusion
  - Jugular bulb oxygenation
  - Cerebral oxygen extraction/supply
  - Heart rate

Pediatric Applications
Use of Dexmedetomidine in MRI

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

Quality of MRI

- 1 = no motion
- 2 = minor movement
- 3 = major movement necessitating another scan

* $P<.001$ 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]\(^1\)

*\(P=.01\) compared with midazolam

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\(^3\)

\(^3\)Ramsay MA. Semin Anesth.2006;25:51-56.
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

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

- **N**
  - **Dexmedetomidine infusion rate < 0.7 mcg/kg/hr**
  - Assess pain and implement supplemental opioid protocol as needed
  - **Y**
    - Increase dexmedetomidine infusion rate < 0.1 mcg/kg/hr
    - Implement supplemental agitation protocol (dexmedetomidine < 2.0 mcg/kg/hr) if patient demonstrates agitation on assessment (**SAS > 4**)

- **Y**
  - 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.

Transitioning Long-Term Sedation to Dexmedetomidine

- Titrate propofol every hour with orders not to increase

- Administer dexmedetomidine infusion, 0.4 mcg/kg/hr

- If extreme agitation occurs, add benzodiazepine (synergistic with dexmedetomidine)

- Titrate dexmedetomidine according to HR and BP with allowed increases of 0.2 mcg/kg/hr

- If patient is agitated on waking, administer more benzodiazepine (requirement is less with dexmedetomidine on board)

- Increase dose of dexmedetomidine in PM to optimize natural sleep and circadian rhythm

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

Neurosurgery Anesthesia Protocol

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

Titratre dexmedetomidine after extubation to patient comfort (usually 0.2 – 0.5 mcg/kg/h)

Use supplemental opioid

Courtesy of M. Ramsay, MD.
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

Y: Obstruction of airway by adipose tissue?

Y: Awake fiberoptic intubation

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: Obstructive sleep apnea?
- O2 Desaturation Risk?
  - ↓ Lung Volumes
  - Functional residual capacity
  - Expiratory reserve
  - Forced vital capacity

Y: Proceed to Intraoperative Procedure

N: Proceed to Intraoperative Procedure

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

Brief Procedure

Y
Laparoscopic gastric bypass or gastric banding

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

Administer Dexmedetomidine Loading Dose
0.5 to 0.75 mcg/kg and monitor for transient hypertension

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
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