What Sedasys Is … And What It’s Not

Randy Hickle, MD
Anesthesiologist
Background of CAPS

• 20 years ago, a moment of insight
  • Assessment of pain outside the care of anesthesiologists

• 16 years ago
  • Started an engineering company, Scott Laboratories
    • To provide a set of tools and training to enable non-anesthesiologist physicians to more safely and effectively manage fear and pain during medical procedures
  • Developed research breadboards
  • Clinical trials, UCSF, University of Louisville
    • Dan Sessler, MD
    • Anthony Doufas, MD
    • Talmage Egan, MD
    • Steve Shafer, MD
  • What are the best sedative and analgesic drugs?
Four Questions

- Who?
- Why?
- How?
- What?
General Anesthesia

Deep Sedation

Moderate Sedation

Minimal Sedation

Home Use
Moderate Sedation, Not Much Prior Research

• What are the effects and side effects
  • Careful titration, dose governors
• What are the best monitors to detect drug effects and side effects?
Peer Reviewed Publications

- **An Exploration of Remifentanil-Propofol Combinations that Lead to a Loss of Response to Esophageal Instrumentation, a Loss of Responsiveness, and/or Onset of Intolerable Ventilatory Depression.** Anesth Analg; 2011:113:490-9

- **A Simulation Study of Common Propofol and Propofol-Opioid Dosing Regimens for Upper Endoscopy.** Anesthesiology; 2012:117:252

Peer Reviewed Publications (continued)

- **Automated responsiveness test (ART) predicts loss of consciousness and adverse physiologic responses during propofol conscious sedation.** Anesthesiology 2001; 94 (4): 585-592

- **Automated responsiveness test and bispectral index monitoring during propofol and propofol/N2O sedation.** ACTA Anaesthesiologica Scandinvica; 2003; 47 (8): 951-957

- **A new system to target the effect-site during propofol sedation.** ACTA Anaesthesiologica Scandinvica; 2003; 47 (8): 944-950
• *Induction speed is not a determinant of propofol pharmacodynamics.*
  Anesthesiology; 2004; 101 (5): 1112-1121

• *Influence of administration rate on propofol plasma - Effect site equilibration.*
  Anesthesiology 2007; 107 (3): 386-396

• *Automated Responsiveness Monitor to Titrate Propofol Sedation.*
  Anesthesia and Analgesia; 2009; 109 (3): 778-786
Peer Reviewed Publications (continued)

- *Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study* Daniel J. Pambianco, MD, John J. Vargo, MD, MPH, Ronald E. Pruitt, MD, Robert Hardi, MD, James F. Martin, PhD; Gastrointestinal Endoscopy; Volume 73, Issue 4, April 2011, Pages 765–772

- *An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy;* Daniel J. Pambianco, MD, FACG, Christopher J. Whitten, MD, Annelies Moerman, MD, Michel M. Struys, MD, PhD, James F. Martin, PhD Gastrointestinal Endoscopy Volume 68, Issue 3, September 2008, Pages 542–547
Search for a Partner

- Glaxo
- Borroughs-Welcome
- Baxter
- Ohmeda
- Datex-Finland
- Dragerworks-Germany
- Nihon Kohden-Japan
- Hewlett Packard
- Becton Dickenson
- Johnson & Johnson
Anesthesia Advisory Panel

- Steve Shafer
- Talmage Egan
- Peter Glass
  - And 8 others
## History of Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Initial concept for the SEDASYS® System was acquired by Ethicon Endo-Surgery, (EES)</td>
</tr>
<tr>
<td>2001-5</td>
<td>Product was further developed with of Anesthesia Advisory Panel</td>
</tr>
<tr>
<td>2005</td>
<td>Device granted FDA IDE (Investigational Device Exemption) for feasibility studies</td>
</tr>
<tr>
<td>2007</td>
<td>Pivotal trial began</td>
</tr>
<tr>
<td>2008</td>
<td>Premarket Approval (PMA) application submitted to FDA</td>
</tr>
<tr>
<td>2009</td>
<td>FDA Advisory panel voted 8-2 in favor of approval</td>
</tr>
<tr>
<td>2009</td>
<td>SEDASYS® System received Canada, European and Australian regulatory approvals</td>
</tr>
<tr>
<td>2010</td>
<td>Not-approvable/denial by FDA, appeal by EES</td>
</tr>
<tr>
<td>2011</td>
<td>PMA application reopened</td>
</tr>
<tr>
<td>2012</td>
<td>Approvable letter issued by FDA</td>
</tr>
<tr>
<td>2013</td>
<td>SEDASYS® System receives FDA Premarket Approval</td>
</tr>
</tbody>
</table>
Computer-Assisted Personalized Sedation

The Clinical Team

Patient Monitoring Compliant with ASA Guidelines for Sedation

The SEDASYS System

Pulse Oximetry Capnography Electrocardiogram Blood Pressure Responsiveness

Integrated Patient Monitoring and Drug Delivery via Dosing Limits, Patient Alarms, and Responsive Oxygen Delivery

Propofol Dosing Oxygen Delivery

Computer Controlled Drug Delivery
Procedure Room Unit: Main Monitoring Screen
Drug Delivery Algorithm

Propofol label
- Initiate sedation with up to 0.5 mg/kg over 3 to 5 minutes
- Most patients require 25 to 75 μg/kg/min to maintain sedation

SEDASYS® System
- User enters rate targeting moderate sedation
- System calculates loading dose (LD=0.5*[MR/75]*W)
- Loading dose delivered over 3 minutes

Incremental loading dose for infusion rate change

PRN to treat transient discomfort
- 0.25 mg/kg (1.7 cc / 70 kg pt)
Dosing Limits

- Maximum initial maintenance rate = 75 μg/kg/min
- 3-minute maintenance rate increase lockout-timer
- 90-second PRN dose lockout-timer
- Maintenance rate increases limited by patient responsiveness
- Maintenance rate reduction if responsiveness lost during loading dose
Responsive Oxygen Delivery

- Delivered to patient’s nose and mouth
- Automatically started upon detection of respiration
- Automatically increased as patient’s $\text{SpO}_2$ decreases
- SEDASYS System will not deliver propofol without supplemental oxygen delivery
Patient Alarms

Red Alarms
- Hypoxemia, apnea, bradycardia, hypotension
- Stops propofol delivery and instructs patient to breath
  - Significant hypoxemia and prolonged apnea

Yellow Alarms
- Hypoxemia and apnea
- Reduces propofol infusion and instructs patient to breath
Pivotal Study Design

- 1,000 subjects
  - 496 SEDASYS System (SDS)
  - 504 Current Standard of Care (CSC)
- Routine colonoscopy (721) or EGD (279) procedures
- 8 sites
  - 4 ambulatory surgery centers
  - 3 ambulatory endoscopy units
  - 1 academic center
- Randomized, non-blinded
Defining a Clinically Important Safety Endpoint

- Death / major morbidity is so rare that it is not used in any prospective study of sedation risk.
- The mechanism of injury is insufficient oxygen delivery to the brain and heart.
- Apnea and hypoventilation are responsible for insufficient oxygen delivery.
  - Most studies have not employed capnometry, so it is not an accepted “standard” for safety assessment.
- Pulse oximetry is the standard:
  - Convenient, continuous, and ubiquitous.
  - Linked directly to mechanism of injury.
Primary Endpoint

- Area-under-the-curve of oxygen desaturation

\[ AUC_{Desat} = \text{Area}_1 + \text{Area}_2 \]
**Secondary Endpoints**

- Clinician satisfaction
- Patient satisfaction
- Level of sedation

### MOAA/S

<table>
<thead>
<tr>
<th>MOAA/S</th>
<th>Definition</th>
<th>Level of Sedation (ASA Continuum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
<td>Minimal</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Responds after name called loudly or repeatedly</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>Purposeful response to mild prodding or shaking</td>
<td>Moderate</td>
</tr>
<tr>
<td>1</td>
<td>Responds to trapezius squeeze</td>
<td>Deep</td>
</tr>
<tr>
<td>0</td>
<td>No response to trapezius squeeze</td>
<td>General Anesthesia</td>
</tr>
</tbody>
</table>
## Drug Dosing

<table>
<thead>
<tr>
<th>SEDASYS System</th>
<th>Colonoscopy</th>
<th>EGD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propofol (mg)</strong></td>
<td>106 ± 57</td>
<td>70 ± 37</td>
</tr>
<tr>
<td><strong>Fentanyl (µg)</strong></td>
<td>74 ± 23</td>
<td>66 ± 22</td>
</tr>
</tbody>
</table>

![Bar chart showing Procedure Maintenance Rate (µg/kg/min)](chart.png)

Mean = 50 µg/kg/min
Measures of Oxygen Desaturation

P-values < 0.001
Primary Endpoint: $\text{AUC}_{\text{Desat}}$

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>SEDASYS System (N=482)</th>
<th>Current Standard of Care (N=486)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{\text{Desat}}$ (seconds•%)</td>
<td>24 ± 143</td>
<td>88 ± 443</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Values were analyzed using an analysis of variance with factors for group and study site; $\alpha=0.05$ significance level.
## Secondary Endpoints: Satisfaction

<table>
<thead>
<tr>
<th>Secondary Endpoint: Physician Satisfaction</th>
<th>SEDASYS System (N=490)</th>
<th>Current Standard of Care (N=491)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSSI (0 to 100)</td>
<td>92 ± 11</td>
<td>76 ± 17</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoint: Patient Satisfaction</th>
<th>SEDASYS System (N=393)</th>
<th>Current Standard of Care (N=397)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSSI (0 to 100)</td>
<td>92 ± 12</td>
<td>90 ± 13</td>
<td>0.007</td>
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</table>

Values were analyzed using an analysis of variance with factors for group; Tukey multiplicity adjusted \( \alpha=0.0253 \) significance level.
Secondary Endpoints: Level of Sedation

![Graph showing percent of MOAA/S measures for different levels of sedation]
### Adverse Events

<table>
<thead>
<tr>
<th>Subjects with:</th>
<th>SEDASYS System (N=496)</th>
<th>Current Standard of Care (N=504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more AEs</td>
<td>28 (6%)</td>
<td>44 (9%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>Rescue intervention</td>
<td>0</td>
<td>1**</td>
</tr>
<tr>
<td>* Severe abdominal pain requiring hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>** Bag-mask ventilation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiorespiratory AEs</th>
<th>SEDASYS System (N=496)</th>
<th>Current Standard of Care (N=504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oxygen desaturation</td>
<td>1</td>
<td>27 (5%)</td>
</tr>
</tbody>
</table>
Experience: Data From Use In Other Countries Use

- Works as intended
- Must let the dosing algorithm work
- Bias toward under-sedation
Alarm Timeout
Recommendation for an ASA Guidance

Whenever an alarm signals during CAPS
With heightened vigilance, the Sedation Care Team should SADMIM

- **STOP**: the conduct of the medical procedure*
- **ASSESS**: the patient, equipment, and environment to determine the likely root cause
- **DISCUSS**: Involve the whole team to consider the differential diagnosis and therapeutic alternatives
- **MANAGE**: the patient’s condition
- **INTERVENE**: to correct the root cause
- **MONITOR**: for resolution of the condition

* if doing so does not immediately and significantly compromise patient safety
The Oddest Transaction
The Collective Blind Eye
Medical Specialties That Induce Procedural Pain
Often Treated With Moderate (or Immoderate Sedation)

- Emergency Medicine
- Family Medicine
- Internal Medicine
- Critical Care Medicine
- Gastroenterology
- OB & GYN
- Ophthalmology
- Orthopaedic Surgery
- Otolaryngology
- Pediatrics
- Dermatology
- Dentistry

- Oral Surgery
- Physical Medicine & Rehab
- Plastic Surgery
- Radiology
- Urology
- Sports Medicine
- Cardiology
- Hematology & Oncology
- Nephrology
- Pulmonary Medicine
- Rheumatology
- Neonatology
It’s Not A Rare and Unfortunate Event
It’s 100,000,000 Procedures Per Year
With A Bias Toward Under-treatment

- Emergency Medicine
- Family Medicine
- Internal Medicine
- Critical Care Medicine
- Gastroenterology
- OB & GYN
- Ophthalmology
- Orthopaedic Surgery
- Otolaryngology
- Pediatrics
- Dermatology
- Dentistry
- Oral Surgery
- Physical Medicine & Rehab
- Plastic Surgery
- Radiology
- Urology
- Sports Medicine
- Cardiology
- Hematology & Oncology
- Nephrology
- Pulmonary Medicine
- Rheumatology
- Neonatology
Where’s the Focus?

• 2 Million  Vs.  • 100 Million
Because We Got Good At It

Good For Us
Coordination of care across the continuum from date surgery is scheduled through 90 days after discharge

- Large increased scope of practice for anesthesiology
- Unfunded

CMMS Conditions of Participation (§482.52)

- A hospital, which furnishes anesthesia services must provide these services under the direction of a doctor. The service is responsible for all anesthesia, including moderate sedation, administered in the hospital
- Unfunded