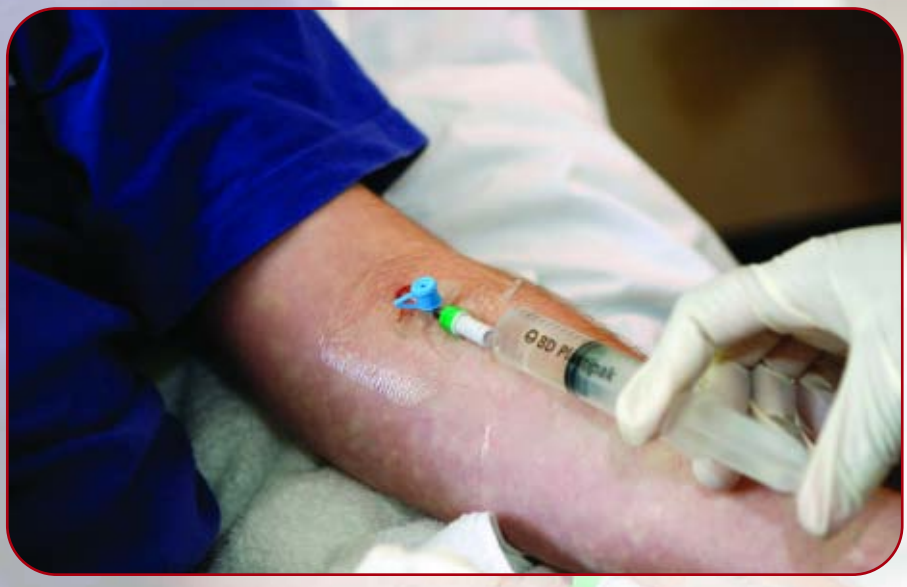
November 2009

Sedation and Analgesia Techniques:

Who? What? When? Where? And How?

The Changing State of the Art & Science



FACULTY

Thomas K. Henthorn, MD (Chair)
Professor and Chair
University of Colorado Denver
Department of Anesthesiology
Aurora, CO

Keith A. Candiotti, MD
Vice Chairman for Clinical Research
Chief, Division of Perioperative Medicine
Associate Professor of Anesthesiology, Internal Medicine
University of Miami Department of Anesthesiology, Perioperative Medicine and Pain Management
Miami, FL

Talmage D. Egan, MD
Professor of Anesthesiology
Adjunct Professor of Pharmaceutics and Bioengineering
K.C. Wong Presidential Endowed Chair
University of Utah School of Medicine
Salt Lake City, UT

Rafael A. Ortega, MD (Course Co-Director)
Professor of Anesthesia
Vice Chairman of Academic Affairs
Boston University School of Medicine
Boston, MA

Pamela Badger, RN, CRC (Course Co-Director)
Coordinator for Clinical Research and Quality Improvement
Department of Anesthesia
Boston Medical Center
Boston, MA

CME/CE Activity

Release Date: November 30, 2009
Expiration Date: November 29, 2010

Sponsored by
Boston University School of Medicine

Supported by
an educational grant from Eisai Pharmaceuticals

Produced by
HAYMARKET MEDICAL EDUCATION

NEEDS ASSESSMENT

Moderate sedation is a state of sedation/analgesia in which the patient is able to respond purposefully to verbal or tactile stimulation; this approach may combine elements of local/regional anesthesia and IV medications—and provides faster recovery than general anesthesia.[1]

Key issues in the administration of moderate sedation/analgesia include:

- Determining the proper dosage for a specific level of sedation in spite of the wide variability in patient drug response.
- Understanding the pharmacokinetics, incremental dosing, and synergistic effects of various agents, and recognizing and responding promptly to any adverse drug effects.
- Preventing oversedation, which may lead to respiratory depression or airway obstruction. Oversedation is the primary morbidity associated with sedation/analgesia, one that can be minimized through appropriate use of monitoring and early resuscitation.[2]

The choices of agents to use in procedures requiring sedation are expanding. Fospropofol disodium was approved by the United States Food and Drug Administration (FDA) in December 2008 for use in monitored anesthesia care in adults undergoing diagnostic or therapeutic procedures. In clinical trials, fospropofol was found to provide safe and effective sedation for patients undergoing flexible bronchoscopy, colonoscopy, and other procedures.[3]

Dexmedetomidine is an alpha$_2$-adrenergic agonist with hypnotic, sedative, sympatholytic, and analgesic properties that reduces anesthetic and opioid requirements. Because dexmedetomidine does not generally cause respiratory depression, and patients can be easily aroused, it may be used for sedation and analgesia for various procedures, including awake tracheal intubation.[4] It was originally approved in 1999 for continuous IV sedation of intubated and mechanically ventilated patients in the intensive care setting for up to 24 hours.[4] In October 2008, dexmedetomidine received an additional indication from the FDA for use in non-intubated patients who require sedation prior to or during surgery and other procedures.

Additional technologies being studied include computer-assisted personalized sedation (CAPS) and patient-controlled analgesia/sedation. One form of CAPS currently seeking FDA approval is designed to help deliver minimal to moderate sedation with propofol during endoscopy, monitoring six sedation parameters. The device has been reported to work well when operated by an endoscopist/nurse team during colonoscopy and other such procedures.[5]

One of the controversial issues with the use of propofol and now fospropofol for sedation is which health professionals should provide and monitor sedation during diagnostic and therapeutic procedures, and what qualifications are necessary.[6] The American Society of Anesthesiologists states that the provider of moderate sedation "must be prepared and qualified to convert to general anesthesia when necessary."[7]

In contrast, a joint statement by three gastroenterologic societies states that moderate sedation can be performed safely on "average-risk" patients in "diagnostic and uncomplicated therapeutic endoscopy and colonoscopy" without the routine assistance of an anesthesiologist or an anesthetist.[8] Similarly, the Society of Gastroenterology Nurses and Associates has stated: "Registered nurses trained and experienced in gastroenterology nursing and endoscopy can administer and maintain moderate sedation and analgesia (conscious sedation) by the order of a physician."[9]

As new, more efficient methods of sedation develop and gain acceptance, it is increasingly important for clinicians who are involved in providing or monitoring sedation to keep abreast of the scientific advances that are occurring in the field.

REFERENCES

1. Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. *Aliment Pharmacol Ther.* 2008;27:597-608.
2. Hug CC. MAC should stand for Maximum Anesthesia Caution, not Minimal Anesthesiology Care. *Anesthesiology*. 2006;104:221-223.
3. Silvestri GA, et al. A phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in patients undergoing flexible bronchoscopy. *Chest*. 2009;135:41-47.
4. Hashiguchi K, et al. Dexmedetomidine for sedation during upper gastrointestinal endoscopy. *Dig Endosc*. 2008;20:78-183.
5. Pambianco DJ, et al. An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. *Gastrointest Endosc*. 2008;68:542-547.
6. Carollo DS, et al. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol*. 2008;21:457-461.
7. American Society of Anesthesiologists. Position on monitored anesthesia care. Last updated September 2, 2008. www.asahq.org/publicationsAndServices/standards/23.pdf.
8. American College of Gastroenterology, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy. Three gastroenterology specialty groups issue joint statement on sedation in endoscopy. March 8, 2004. www.gi.org/physicians/nataffairs/trisociety.asp.
9. Society of Gastroenterology Nurses and Associates. Statement on the use of sedation and analgesia in the gastrointestinal endoscopy setting, 2007. www.sgna.org/Resources/statements/statement2.cfm.

TARGET AUDIENCE

Anesthesiologists and nurse anesthetists

LEARNING OBJECTIVES

At the conclusion of this program, clinicians should be better able to:

- Define the concept of sedation and analgesia techniques and the spectrum of clinical scenarios to which they apply
- Describe specific practical applications of sedation and analgesia techniques in diagnostic and therapeutic procedures, focusing on those that require moderate sedation
- Cite the latest safety and efficacy data on agents and combinations of agents used to achieve sedation/analgesia during diagnostic and therapeutic procedures
- Identify emerging agents and/or technologies used to achieve and monitor sedation/analgesia
- Summarize current guidelines on the appropriate use of sedation and analgesia techniques and the respective roles of health professionals performing the procedure and monitoring the patient.

ACCREDITATION STATEMENT

Boston University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Boston University School of Medicine designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This program is approved by the American Association of Nurse Anesthetists for 1 CE credit; Code# 32228; Expiration Date: 11/29/10. To receive credit, nurses must pass the post-test with a score of 80% or better.

Program Code: E.SAMBAHAY09.
Release Date: November 30, 2009. Expiration Date: November 29, 2010

DISCLOSURE POLICY

Boston University School of Medicine asks all individuals involved in the development and presentation of Continuing Medical Education (CME) activities to disclose all relationships with commercial interests. This information is disclosed to CME activity participants. Boston University School of Medicine has procedures to resolve apparent conflicts of interest. In addition, faculty members are asked to disclose when any discussion of unapproved use of pharmaceuticals and devices is being discussed.

DISCLOSURE STATEMENTS

Thomas K. Henthorn, MD (Chair), is a consultant to Schering-Plough Corporation.

Keith A. Candiotti, MD, receives grant/research support from Eisai Pharmaceuticals, Hospira, Pfizer Inc., Cadence, Stryker, and Schering-Plough Corporation. He is a consultant for Eisai Pharmaceuticals, Hospira, Pfizer Inc., Cadence, and Schering-Plough Corporation and is on the speakers' bureaus for Eisai Pharmaceuticals, Hospira, and Pfizer Inc.

Talmage D. Egan, MD, has received research support from Theravance and Daewon Pharmaceutical. He has served as a consultant to Johnson & Johnson, MGI Pharma, and Labopharm and is a minor shareholder for Scott Labs.

Rafael A. Ortega, MD (Course Co-Director), has nothing to disclose.

Pamela Badger, RN, CRC (Course Co-Director), has nothing to disclose.

Elizabeth Gifford-Drury, Boston University School of Medicine, Continuing Medical Education, has nothing to disclose.

The Haymarket Medical Education staff has nothing to disclose.

DISCLOSURE OF OFF-LABEL USE

Unlabeled/investigational uses of commercial products are discussed in this activity and will be so noted during the presentation.

DISCLAIMER

THESE MATERIALS AND ALL OTHER MATERIALS PROVIDED IN CONJUNCTION WITH CONTINUING MEDICAL EDUCATION ACTIVITIES ARE INTENDED SOLELY FOR PURPOSES OF SUPPLEMENTING CONTINUING MEDICAL EDUCATION PROGRAMS FOR QUALIFIED HEALTH CARE PROFESSIONALS. ANYONE USING THE MATERIALS ASSUMES FULL RESPONSIBILITY AND ALL RISK FOR THEIR APPROPRIATE USE. TRUSTEES OF BOSTON UNIVERSITY MAKES NO WARRANTIES OR REPRESENTATIONS WHATSOEVER REGARDING THE ACCURACY, COMPLETENESS, CURRENTNESS, NONINFRINGEMENT, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE OF THE MATERIALS. IN NO EVENT WILL TRUSTEES OF BOSTON UNIVERSITY BE LIABLE TO ANYONE FOR ANY DECISION MADE OR ACTION TAKEN IN RELIANCE ON THE MATERIALS. IN NO EVENT SHOULD THE INFORMATION IN THE MATERIALS BE USED AS A SUBSTITUTE FOR PROFESSIONAL CARE.

THIS ACTIVITY HAS BEEN PLANNED TO BE WELL BALANCED, OBJECTIVE, AND SCIENTIFICALLY RIGOROUS. INFORMATION AND OPINIONS OFFERED BY PRESENTERS REPRESENT THEIR VIEWPOINTS. CONCLUSIONS DRAWN BY THE AUDIENCE SHOULD BE DERIVED FROM CAREFUL CONSIDERATION OF ALL AVAILABLE SCIENTIFIC INFORMATION.

25 Philips Parkway, Suite 105, Montvale, NJ 07645
201-799-4800 **www.mycme.com**

Cover photo and photo, page 4: Photo Researchers, Inc.

Sedation and Analgesia Techniques:

Who? What? When? Where? And How?
The Changing State of the Art & Science

FACULTY

Thomas K. Henthorn, MD (Chair)
Professor and Chair
University of Colorado Denver
Department of Anesthesiology
Aurora, CO

Keith A. Candiotti, MD
Vice Chairman for Clinical Research
Chief, Division of Perioperative Medicine
Associate Professor of Anesthesiology, Internal Medicine
University of Miami Department of Anesthesiology, Perioperative Medicine and Pain Management
Miami, FL

Talmage D. Egan, MD
Professor of Anesthesiology
Adjunct Professor of Pharmaceutics and Bioengineering
K.C. Wong Presidential Endowed Chair
University of Utah School of Medicine
Salt Lake City, UT

Rafael A. Ortega, MD (Course Co-Director)
Professor of Anesthesia
Vice Chairman of Academic Affairs
Boston University School of Medicine
Boston, MA

Pamela Badger, RN, CRC (Course Co-Director)
Coordinator for Clinical Research and Quality Improvement
Department of Anesthesia
Boston Medical Center
Boston, MA

PUBLISHING STAFF

David Azevedo
Writer

Suzanne Bujara
Senior Project Editor

Lynne Callea
Program Director

Debbie Walsh
Program Manager

Nick Zittell
VP, Director of Editorial Services

Jeff Gherman
Sandra Clayton
Art Directors

TABLE of CONTENTS

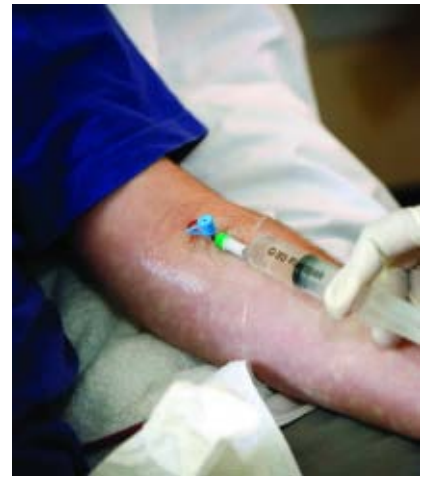
Sedation and Analgesia Techniques:
Who? What? When? Where? And How? The Changing State of the Art & Science

Sedation and Analgesia Techniques: Who? What? When? Where? And How? The Changing State of the Art & Science is a monograph based on material presented at a satellite symposium to anesthesiologists on May 15, 2009, in Scottsdale, Arizona. This monograph is intended for anesthesiologists and nurse anesthetists.

Providing sedation and analgesia for ambulatory procedures is as much art as science.[1] There is an array of pharmacologic choices, and varied patient responses to those choices depending on medical history, preferences, and expectations. Thus, a one-regimen-fits-all approach is not feasible. The clinician's challenge is to formulate a plan that will accomplish the goals of procedural sedation: effectively reduce the stress and discomfort associated with diagnostic and therapeutic procedures, allow successful completion of the procedures, and permit the patient to return to normal activities promptly.

The field has become increasingly important as the number of ambulatory surgical centers and the procedures they accommodate expand rapidly. A recent report found that outpatient surgery visits in the United States mushroomed 67% from 1996 to 2006, to 34.7 million.[2]

Many of those procedures do not require general anesthesia. For example, approximately 98% of the more than 20 million endoscopic diagnostic and therapeutic procedures in the United States annually are performed with sedation techniques.[3]



Procedures that routinely use sedation include colonoscopy, bronchoscopy, endoscopic ultrasound (EUS), esophagastroduodenoscopy (EGD), and endoscopic retrograde cholangiopancreatography (ERCP). Sedation is also employed in a host of oral and maxillofacial procedures, most commonly tooth extraction. In addition, it is used in plastic surgery, biopsies, cataract surgery, and other medical procedures.

The American Society of Anesthesiologists (ASA) depicts the various levels of sedation as a continuum, a concept that emphasizes the tendency of patients to move fluidly from one level to the next.[4] Individual patient response to sedation agents can vary significantly depending on a host of factors. Practitioners must be aware of and ready for patients to move from one sedation level to another, particularly a deeper, unintended level during a procedure.[5,6] Therefore, practitioners delivering sedation must be trained and skilled in rescue techniques, including appropriate use of reversal agents, managing airways, and providing advanced cardiac life support.[6]

ASA guidelines detail four levels of sedation (***Table 1***)[4]:

Minimal sedation/anxiolysis refers to a state during which patients respond normally to verbal commands; cognitive function and coordination may be impaired; ventilatory and cardiovascular functions are unaffected.

Moderate sedation/analgesia (formerly called conscious sedation) is a depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation (reflex withdrawal from a painful stimulus is not considered a purposeful response). No

interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep sedation/analgesia is a depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.[4]

For the overwhelming majority of endoscopic and many oral procedures, moderate sedation provides sufficient comfort, anxiolysis, and pain relief.[5,7] Moderate sedation is thought to be safer than deep sedation[7] and meets the patient's desire for a rapid recovery and return to everyday activities. Because many moderate-sedation regimens are administered by non-anesthesiologists, including gastroenterologists, trained nurses, emergency physicians, and oral and maxillofacial surgeons, this approach is widely used in the United States. As detailed later, the issue of non-anesthesiologists delivering some forms of moderate sedation is highly controversial.

Clinicians who administer sedation must strike a balance between under- and oversedation. If patients are undersedated, they can experience adverse effects such as agitation, hypertension, tachycardia, myocardial ischemia, and wound dehiscence. The patient also may injure himself or clinical staff.

Table 1. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (2004)

	Minimal Sedation (Anxiolysis)	Moderate Sedation/ Analgesia (Conscious Sedation)	Deep Sedation/ Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful* response to verbal or tactile stimulation	Purposeful* response following repeated or painful stimulation	Unarousable, even with painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous Ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular Function	Unaffected	Usually maintained	Usually maintained	May be impaired

*Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.
American Society of Anesthesiologists. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia, 2004.

In contrast, an oversedated patient may suffer from loss of airway, hypotension, desaturation, ischemia, and delayed recovery. Of the two problems, oversedation generally poses greater risk and consequences.

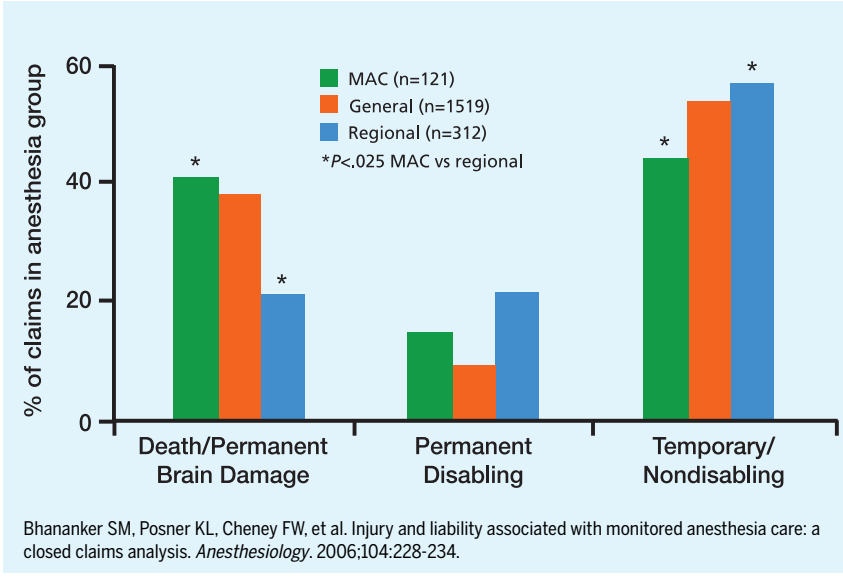
In 2006, Bhananker et al identified the risks involved by reporting on liability claims from the ASA's Closed Claims Database that were related to monitored anesthesia care (MAC).[8] The ASA defines MAC as "a physician service which is clearly distinct from moderate sedation due to the expectations and qualifications of the provider who must be able to utilize all anesthesia resources to support life and to provide patient comfort and safety during a diagnostic or therapeutic procedure."[9]

The study revealed that respiratory depression caused by oversedation was a major factor in MAC injuries, representing the specific damaging mechanism named in 21% of claims.[8] Of note, 18% of MAC claims were for hypoxic injuries. This is in contrast with hypoxic injury during general and regional anesthesia, which accounted for only 2% of claims.[8] While there were fewer claims related to MAC than for general anesthesia, approximately 41% of all claims related to either were for death or permanent brain damage (***Figure 1***).[8] It is notable that some drugs commonly used in MAC are also utilized in moderate sedation—midazolam, fentanyl, and propofol—and can cause respiratory depression, particularly when combined.

The study emphasized a telling point: MAC, even when targeting moderate sedation, needs to be approached with the same care and attention as general and regional anesthesia.[8]

GETTING STARTED

The process of administering procedural sedation begins with an evaluation of the patient, including medical history and physical examination. The examiner should be especially alert for indicators of



Bhananker SM, Posner KL, Cheney FW, et al. Injury and liability associated with monitored anesthesia care: a closed claims analysis. *Anesthesiology*. 2006;104:228-234.

Figure 1. Severity of injury in monitored anesthesia care (MAC), general, and regional anesthesia claims. The proportion of claims for death (14%) and permanent brain damage (7%) was reduced in regional anesthesia compared with MAC (33% death and 8% brain damage). In contrast, the severity of injury was similar between MAC claims and those associated with general anesthesia (27% death and 10% brain damage).

potentially increased risk for adverse outcomes from sedation, such as: significant cardiac or pulmonary disease; neurologic or seizure disorders; stridor, snoring, or sleep apnea; adverse reactions to sedation or anesthesia; current medications, drug and food allergies; and alcohol or drug abuse.[6] The ASA's physical status classification (P1-P5) is typically used to designate a patient's overall health (***Table 2***). Those designated ASA I-III can be appropriate for routine sedation with approved drugs, while ASA IV and V patients may require reduced dosing and other special considerations, including use of an anesthesiologist or nurse anesthetist to administer the sedation.[6]

During the procedure, sedated patients are given supplemented oxygen and must be carefully monitored. Typical monitoring includes the electrocardiogram, and blood pressure measurement, oxygenation with pulse oximetry, and, less frequently, capnography (although capnography is a routine monitor when anesthesia practitioners provide sedation).[6]

Additionally, a patient's level of consciousness should be assessed as soon as sedation is administered and throughout the procedure. A common assessment tool is the Modified Observer's Assessment of Alertness and Sedation, which rates the patient's responsiveness to various stimuli such as prodding, shaking, and calling of the patient's name.[6] Bispectral index (BIS) monitoring, a noninvasive measure of consciousness level, has been used, but its efficacy in procedural sedation has not yet been well established.[6]

One of the significant challenges in procedural sedation is determining proper dosage and titration. As noted, individual patients respond differently to the same dose of the same sedative—up to a fivefold difference to a given agent.[5] Clinicians must understand the pharmacokinetics and interactions of various agents. Many sedation drugs are used in combination, and the effects are typically synergistic not additive, requiring clinicians to understand the various properties of those combinations.[5] For example, even a low dose of an opioid can substantially reduce the amount of benzodiazepine or propofol needed to maintain proper sedation during endoscopy.[5]

Most regimens begin with an initial bolus of a sedative or opioid, followed by ongoing titration of one or more agents during the procedure. Practitioners delivering sedation must have knowledge of an individual agent's onset and peak effect properties, being careful to distinguish between the two.[5] Evaluating a patient's sedation level before a drug's peak effect is reached can lead to administering more sedative than necessary to maintain the

Table 2. ASA Physical Status Classification System

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
Source: http://www.asahq.org/clinical/physicalstatus.htm. Accessed July 30, 2009.	

Table 3. Pharmacologic Profile of Drugs Used for Endoscopic Sedation

				Dosing for endoscopic sedation*			
Drug	Onset of action (min)	Peak effect (min)	Duration of effect (min)	Initial dose	Maximum dose	Pharmacologic antagonist	Significant adverse effects
Dexmedetomidine (µg)	<5	15	Unknown	1/kg	200	None	Hypotension, bradycardia
Diazepam (mg)	2-3	3-5	360	5-10	20	Flumazenil	Respiratory depression, chemical phlebitis
Diphenhydramine (mg)	2-3	60-90	>240	25-50	400	None	Dizziness, prolonged sedation
Fentanyl (µg)	1-2	3-5	30-60	50-100	200	Naloxone	Respiratory depression, vomiting
Fospropofol (mg)	2-4	8-12	2-16	6.5/kg	577.5	None	Respiratory depression, hypoxemia, loss of purposeful responsiveness, hypotension
Ketamine (mg)	<1	1	10-15	0.5/kg	Titrate to effect	None	Emergence reaction, apnea, laryngospasm
Meperidine (mg)	3-6	5-7	60-180	25-50	150	Naloxone	Respiratory depression, pruritus, vomiting, interaction with MAOI
Midazolam (mg)	1-2	3-4	15-80	1-2	6	Flumazenil	Respiratory depression, disinhibition
Promethazine (mg)	2-5	Unknown	>120	12.5-25	100	None	Hypotension, respiratory depression, extrapyramidal effects
Propofol (mg)	<1	1-2	4-8	10-40	400	None	Respiratory depression, cardiovascular instability

*For healthy individual <60 years of age.
Cohen LB, DeLegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology*. 2007;133:675-701.

desired level and result in adverse effects brought on by oversedation.

AVAILABLE AGENTS

The landscape of agents used in ambulatory sedation has changed significantly in recent years. Current staples include a benzodiazepine (most commonly midazolam and diazepam) with an opioid (often fentanyl or remifentanil), and propofol with or without a benzodiazepine and/or an opioid. Newer agents such as dexmedetomidine and fospropofol are attracting more attention. Ketamine, a rapid-acting agent usually employed for general anesthesia, has been used in low doses for moderate sedation and has been paired with low-dose propofol (*Table 3*).

Each agent and combination has particular advantages and drawbacks in the ambulatory setting:

Opioids are primarily associated with analgesia, though they can be used as

Table 4. Physician Ratings of Propofol vs. Midazolam and Meperidine

Questionnaire item	Mean Score
Safer and smoother titration	3.4
More relaxed ambience	3.6
Procedure is faster	3.8
Better memory at discharge	3.8
More rapid discharge	4.0
Quicker to get started	4.0
Better patient tolerance	4.0
Better reputation in the community	4.0
More procedures in a fixed-bed recovery area	4.0

Scores: 1 = very strongly disagree; 2 = somewhat disagree; 3 = very strongly agree; 4 = agree completely.
Walker JA, et al. *Am J Gastroenterol.* 2003;98:1744-1750.

adjunctive therapy when additional sedation is required.[10]

Fentanyl and meperidine are used as adjunctive analgesic therapy with propofol and benzodiazepines. Fentanyl is more potent than meperidine, and has a more rapid onset and shorter duration of action.[11] Both drugs have the potential to significantly depress respiratory function, particularly at higher doses.[10]

Remifentanil, a short-acting opioid, has been paired with a benzodiazepine in outpatient oral surgery. A recent study concluded that remifentanil with midazolam was safe and reliable during extraction of third molars.[12] In another study, remifentanil produced significantly lower peak heart rate and systolic blood pressure levels as adjunct therapy in third molar extraction compared with meperidine.[13] Remifentanil has also proven safe and effective in colonoscopy when combined with midazolam or propofol.[14]

In addition to depressing respiratory function, other adverse effects of opioids are hypotension when combined with benzodiazepines, bradycardia, dysphoria, nausea, and vomiting.[10,11] Opioids' effects can be reversed by naloxone.

Midazolam is a water-soluble agent that causes sedation, anxiolysis, and amnesia. Its peak effect is slower than that of diazepam's, and it is the shortest-acting benzodiazepine available.[15] Its typical half-life of 2 hours in healthy adults can be prolonged in patients aged >50 years.

A much more potent agent than diazepam, midazolam is typically paired with fentanyl or meperidine and has also been combined with propofol. A benzodiazepine with an opioid was the preferred regimen for three-fourths of surveyed endoscopists, and midazolam is considered the most widely used sedative for endoscopy.[3]

In one nationwide survey, 85% of endoscopists reported using midazolam; fewer than 10% used diazepam.[7] A recent meta-analysis found that midazolam was preferable to diazepam because of faster onset of action, shorter duration of action, and a lower proportion of patients with memory of the procedure.[7] The study's pooled data show that a higher percentage of patients are satisfied with and would repeat sedation with midazolam vs. diazepam.[7]

Overall, the meta-analysis reported an adequate or better level of sedation with midazolam and an opioid in 94% of cases. Approximately 88% of physicians and 89% of patients were satisfied with the sedation experience, and 82% of patients would be willing to repeat the procedure with the same sedation.[7]

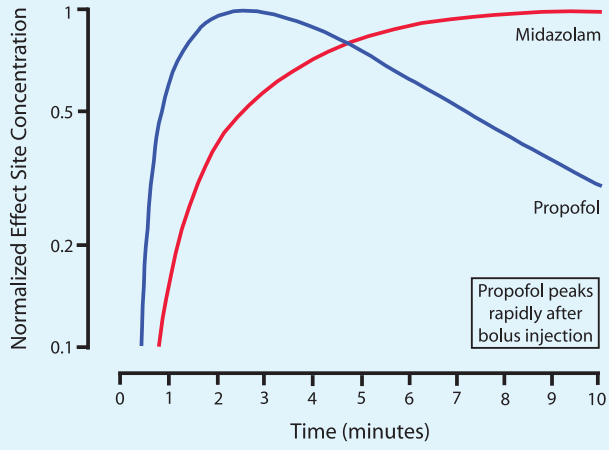
One study of various elective endoscopic procedures using midazolam and meperidine found that unintended deep sedation occurred for 68% of patients, including 85% undergoing ERCP, 80% undergoing EUS, 60% undergoing EGD, and 45% undergoing colonoscopy.[16]

The synergistic effect of combining midazolam with an opioid reduces the amount of midazolam needed, but it also has the potential to cause significant respiratory depression and airway obstruction.[7]

Common adverse effects of midazolam include anterograde amnesia, prolonged recovery after long-term or high-dose use, hypoxemia, hypotension, and, as noted, respiratory depression when paired with an opioid.[11,15,17]

The reversal agent for benzodiazepines is flumazenil.

Propofol was approved by the FDA in 1989 for general anesthesia and is used widely in intensive care units for sedation of mechanically ventilated patients.[6] Propofol is an important sedative agent in ambulatory sedation.[6] About one-fourth of endoscopists report using propofol for sedation for outpatient procedures, most commonly in collaboration with an anesthesiologist.[3] Compared with benzodiazepines and opioids, the agent is associated with faster onset of action, more rapid recovery to full consciousness, minimal residual sedative effects, and higher patient satisfaction.[18,19] One study found a clear preference for propofol vs. midazolam and meperidine among surveyed gastroenterologists (***Table 4***).[20]



Adapted from Johnson KB, Egan TD. Principles of pharmacokinetics and pharmacodynamics: applied clinical pharmacology for the practitioner. In: Longnecker DE, Brown DL, Newman MF, et al, eds. *Anesthesiology*. New York, NY: McGraw Hill; 2008.

Figure 2. A Simulation of the Time to Peak Effect Site Concentrations of Propofol and Midazolam After Bolus Injection

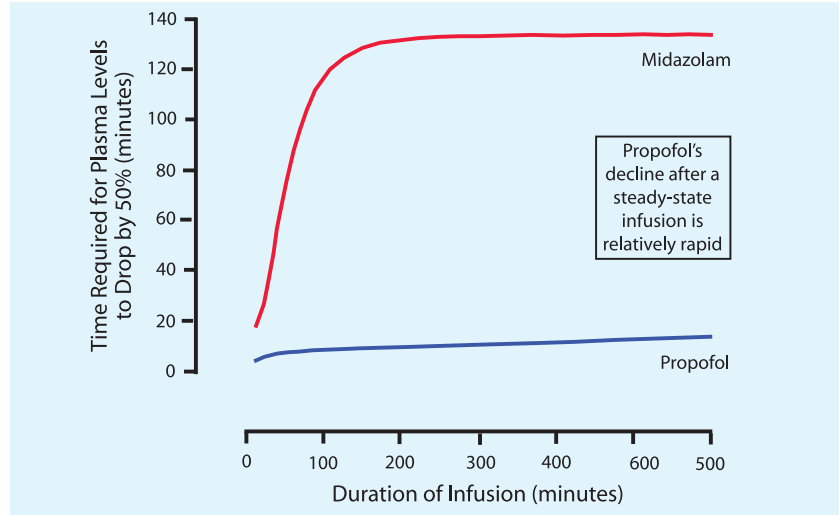
Propofol causes sedation, hypnosis, and anxiolysis.[11] When used alone, propofol can be associated with coughing and pain-withdrawal movements that interrupt the procedure[5] and can lead to administration of more propofol that pushes the patient into deep sedation. For this reason, propofol is typically used with fentanyl or meperidine to block the coughing and to add analgesia.

Propofol has also been combined with midazolam, though results have been inconsistent. One study concluded that oral midazolam combined with IV propofol reduced the amount of propofol needed and also reduced patient anxiety before ERCP;[21] another showed that midazolam reduced the amount of propofol needed during EGD or ERCP but otherwise had no effect;[22] and a third study reported that premedication with midazolam did not reduce the amount of propofol needed during EUS.[23] Recently, a report noted that adding midazolam to propofol for colonoscopy did not result in more cognitive impairment vs. propofol alone but did improve the ease of colonoscopy without increasing the rate of complications or recovery times.[24]

Many favor what is called "balanced propofol sedation." This regimen begins with low doses of midazolam and an opioid, then propofol is titrated to establish moderate sedation.[25,26] The advantages of this approach include maintaining a reversible agent (for midazolam and the opioid) and simplifying the administration of propofol, which is given less often and in smaller doses, lessening the risk of deep sedation. In a study of 100 cases using this technique, deep sedation was recorded in only 2% of assessments and never for longer than 2 minutes.[26]

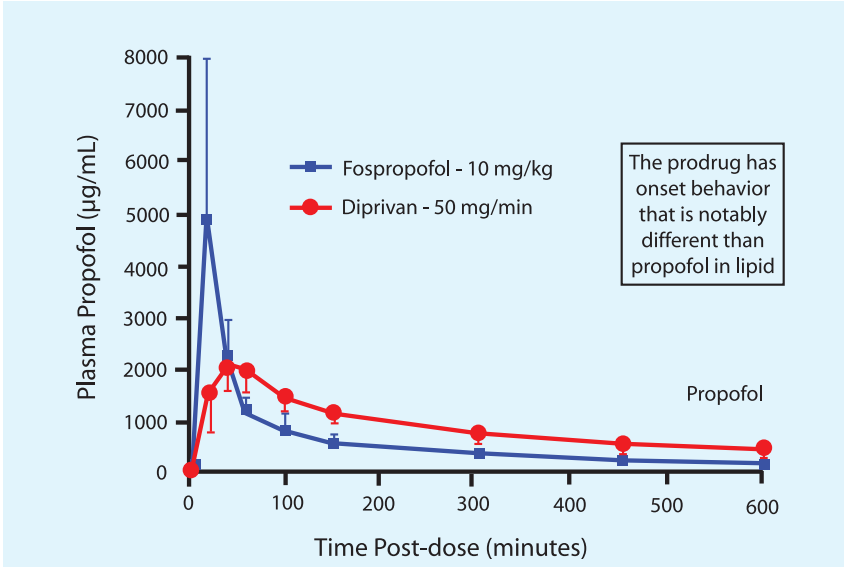
A major issue with propofol has been how it is formulated. Propofol cannot be easily dissolved in water, and thus miscibility can be achieved only in lipophilic substances. The current formulation includes propofol in a combination of soybean oil, glycerol, and egg lecithin.[27] The lipid component can support growth of microorganisms. In the United States, disodium edetate (EDTA) or metabisulfite is added to retard such growth.

Propofol's formulation can contribute to unwanted effects such as pain on injection, allergic reactions, microbial growth, alteration of a patient's lipid profile, and what has become known as "propofol infusion syndrome," which is characterized by cardiac failure, acidosis,



Adapted from Johnson KB, Egan TD. Principles of pharmacokinetics and pharmacodynamics: applied clinical pharmacology for the practitioner. In: Longnecker DE, Brown DL, Newman MF, et al, eds. *Anesthesiology*. New York, NY: McGraw Hill; 2008.

Figure 3. A Simulation of the Time Required to Achieve a 50% Decrease in Concentration After Stopping Continuous Infusions (ie, the context sensitive half-time)



Shah A, Fechner J, Struys M, Mistry B. Differential PK/PD of propofol after intravenous fospropofol and Diprivan in healthy subjects. *Anesthesiology*. 2007;107:A46.

Figure 4. Fospropofol Pharmacokinetics

and rhabdomyolysis. A recent spot-check survey of anesthesia professionals found that pain on injection was rated by 79% of respondents as the biggest of problems presented by propofol.[28]

The Centers for Disease Control and Prevention (CDC) first documented propofol infection risk in seven hospitals between 1990 and 1999, eliciting calls for strict aseptic techniques when handling the agent.[29] With awareness of the risk and the addition of ethylenediaminetetraacetic acid (EDTA) as an antimicrobial, this risk was presumably decreased. However, in June 2007, the FDA issued an alert noting "several clusters of patients who have experienced chills, fever, and body aches shortly after receiving propofol." The agency emphasized compliance with strict handling protocols.[30]

As with many sedative agents, propofol causes respiratory depression, which is exacerbated by opioids. Propofol has also been associated with hypotension and has been found to cause hypertriglyceridemia if given in sufficient quantities (usually over a prolonged period in the ICU).[11,27]

Propofol's kinetics include rapid onset and offset (***Figures 2 and 3***). Rapid onset can be an advantage allowing for a more rapid establishment of the sedated state. It can also be a disadvantage because patients can enter quickly into deeper-than-intended sedation if the clinician administering the drug is not experienced and well-trained. That risk led the US Food and Drug Administration to include labeling that restricts use of propofol in sedation to anesthesiology professionals.[27] Rapid offset leads to shorter recovery times, and propofol has a favorable profile regarding nausea and vomiting.[31,32]

Propofol has no reversal agent; this is often considered a disadvantage of propofol.

Fospropofol, a prodrug of propofol, was approved for use in MAC in December 2008. The body's alkaline phosphatases completely and rapidly metabolize fospropofol into propofol, formaldehyde, and phosphate. Like propofol, fospropofol causes sedation, hypnosis, and anxiolysis, and has antiemetic effects.[19]

Although it converts to propofol, fospropofol behaves differently than propofol in terms of pharmacokinetics (***Figure 4***). Fospropofol's peak propofol plasma concentration is achieved later and at a lower level than propofol delivered in a lipid formulation. In one study, for example, propofol (administered 50 mg/min) peaked in only 4 minutes, while fospropofol (administered 10 mg/kg/IV bolus) took 8 minutes. Fospropofol also has a longer duration of clinical effect.[33]

Adverse effects also differ. Unlike propofol formulations, fospropofol disodium is water-based, eliminating the problem of injection pain that often accompanies the administration of propofol. Theoretically, fospropofol carries a reduced risk for infection compared with propofol because there is no lipid solution in which bacteria can grow. There are no controlled studies confirming this, however. Also, fospropofol's aqueous solution does not affect a patient's serum triglycerides with prolonged infusions.[19]

On the other hand, the phosphate group released when fospropofol is metabolized does cause brief but potentially intense perineal paresthesias not experienced with propofol. Other adverse effects are similar to those of propofol and include respiratory depression (exacerbated by opioids), hypotension, and hypoxemia.[34]

Fospropofol carries the same labeling as propofol, calling for administration by clinicians trained in general anesthesia who have no other involvement in the procedure.[34]

As with propofol, there is no reversal agent.

Dexmedetomidine is an alpha$_2$-adrenoreceptor agonist that combines analgesic, sedative, and anxiolytic properties without significantly depressing respiration and allows patients to remain arousable.[35,36] It was approved in 1999 for seda-

tion in intubated and mechanically ventilated ICU patients. In October 2008, the FDA added approval for use in non-intubated patients prior to and/or during surgical and other procedures.

The approval for the new indication was based on a Phase 3 clinical trial by Candiotti and colleagues.[37] The study looked at 326 patients undergoing various elective procedures that called for MAC. Both the placebo arm and dexmedetomidine arms (at loading doses of 0.5 or 1 mcg/kg) received midazolam to titrate to adequate sedation, and fentanyl was given when needed for pain. The placebo arm roughly approximated a typical midazolam-fentanyl combination sedation approach.

The dexmedetomidine arms used significantly less midazolam and fentanyl to maintain sedation than the midazolam-fentanyl arm. The midazolam-fentanyl group saw 12.7% of patients experience respiratory depression, defined as 0_2 saturation <90% and a respiratory rate <8. The two dexmedetomidine arms had respiratory depression rates of 3.7% and 2.3% for the lower and higher doses, respectively.

Other advantages for dexmedetomidine vs. midazolam-fentanyl in the study included: significantly fewer patients required postoperative analgesics; anxiety scores were significantly lower; and patient satisfaction measured by the Iowa Satisfaction with Anesthesia Scale was significantly higher.

Other studies have found dexmedetomidine safe and effective for procedures in plastic surgery, ophthalmology, orthopedics, and vascular surgery as well as for upper gastroscopy and breast biopsies.[38-40]

It has also been studied in dental procedures. Üstün and colleagues compared dexmedetomidine with midazolam during sedation for third molar surgery. They found dexmedetomidine a "reliable and safe method, with additional analgesic effect providing a satisfactory sedation level without any serious side effects during impacted third molar surgery.[41]

Adverse effects with an incidence of >2% include hypotension, bradycardia, and dry mouth, and were found by one study to be significant. In that study, Jalowiecki et al halted their efforts to evaluate dexmedetomidine in colonoscopy because of adverse events. The study was designed to compare dexmedetomidine alone to midazolam-meperidine and to on-demand fentanyl. The dexmedetomidine group experienced prolonged recovery times and profound hypotension and bradycardia.[42] Intensive medical interventions were needed in 3 of 19 patients receiving dexmedetomidine.[42]

Ketamine is used most often in general anesthesia and has been combined with propofol in various settings. The two agents are combined in one syringe or given in separate syringes. The concept is to pair the two agents at doses lower than those required if using either drug alone, and therefore minimize the adverse effects associated with each.

Ketamine and propofol have been studied in pediatrics,[43] cosmetic surgery,[44] emergency departments (EDs),[45,46] and in hard-to-sedate cases, with mixed results.[47] For example, Willman and Andolfatto found that ketamine-propofol was safe and effective for painful ED procedures, elicited few adverse events, and produced rapid recovery times and highly satisfied patients and staff.[45] On the other hand, Slavik and Zed declared that "combination propofol and ketamine has not demonstrated superior clinical efficacy compared with propofol alone for procedural sedation and analgesia."[48]

PROPOFOL ADMINISTRATION

The administration of propofol outside the operating room has generated considerable controversy. The FDA mandated product labeling on both propofol and fospropofol that the drugs "should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure."[27,34]

The American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy issued a joint statement in 2004 disagreeing with the FDA's recommendation and offering their own:

- There are data to support the use of propofol by adequately trained non-anesthesiologists. Large case series indicate that with adequate training, physician-supervised nurse administration of propofol can be done safely and effectively.
- The routine assistance of an anesthesiologist/anesthetist for average-risk patients undergoing standard upper and lower endoscopic procedures is not warranted.[49]

Concerned that propofol's rapid action could move patients quickly through moderate sedation, deep sedation, and general anesthesia, and noting that the drug has no reversal agent, the ASA and the American Association of Nurse Anesthetists then issued a joint statement declaring that failure to adhere to the packaging recommendations "could put patients at increased risk of significant injury or death."[50]

Advocates for only anesthesiology-trained clinicians using propofol express concerns that administration by other specialists may lead to avoidable adverse events. Deep sedation using propofol is a technically complex task, they argue, with a substantial learning curve and is beyond the expertise of practitioners without formal anesthesiology training.

Despite such arguments, it is generally conceded that use of propofol by non-anesthesiologists is commonplace. A recent study in *Annals of Emergency Medicine* noted 28 published studies showing the safety and efficacy of

propofol use in nearly 4,000 ED patients.[51] Authors argued that "a residency-trained emergency physician possesses the ideal skill set for deep sedation" and concluded that "deep sedation using propofol is rapidly evolving into an essential emergency physician skill."

A more controversial issue is nurse-administered propofol sedation (NAPS) for various endoscopic procedures, most commonly colonoscopy. A number of studies have investigated the safety and efficacy of propofol, including one that looked at more than 9,000 endoscopic cases in an Oregon ambulatory surgery center.[20,52,53] That study reported that only 7 patients suffered respiratory compromise, 3 experienced prolonged apnea accompanied by hypoxemia due to oversedation, and none required endotracheal intubation, laryngeal mask airway or rescue by an anesthesiologist.[20]

On the other hand, another study involved more complex procedures such as ERCPs and a significant number of ASA class III and IV patients.[54] Out of more than 9,500 cases where propofol was delivered by a non-anesthesiologist physician, there were 135 adverse events, including 117 from oversedation, 4 deaths (3 from oversedation), 40 patients who needed assisted ventilation, 9 who needed endotracheal intubation, and 28 who needed monitoring in the ICU.[54]

Most recently, Rex and colleagues reported on 646,000 cases of endoscopist-directed propofol (EDP) sedation worldwide, including 223,000 in published studies. Of those EDP cases, investigators reported 11 endotracheal intubations, no permanent neurologic injuries, and 4 deaths. They concluded that the safety record of EDP was comparable to that of published data on general anesthesia by anesthesiologists and better than that of endoscopist-delivered benzodiazepines and opioids.[55]

The controversy over who is qualified to administer propofol is far from settled and promises to be a topic of great interest and debate.

ON THE HORIZON

Because propofol is effective in patients yet problematic in its delivery, researchers are trying to develop improved formulations, including those using new lipid-type approaches. Other efforts have focused on cyclodextrin-based formulations that attempt to make propofol water soluble and thus minimize the injection pain associated with lipid delivery systems.

Unfortunately, in at least one lab the cyclodextrin-based formulation actually *increased* injection pain.[28] Other approaches have included microemulsion formulation, which in one study produced efficacy and safety results similar to a lipid emulsion,[56] and micellar solution, or nanotechnology, which aims to manifest propofol's natural antimicrobial activity.[57]

Delivering propofol more efficiently is also the subject of emerging solutions. The most common device used in the United States to deliver propofol is a calculator pump. The user determines the appropriate infusion rate based on various criteria, then programs the pump to deliver a constant flow of the medication throughout the procedure.[58]

New systems take a different tack. One such system is target-controlled infusion (TCI). Under TCI, the user sets a target concentration based on knowledge of the drug's therapeutic window. The TCI computer, using the drug's pharmacokinetic model, then calculates the proper dosage to maintain that target concentration, and the pump delivers a time-varying infusion. The user can adjust the target concentration based on patient response. The TCI pump displays the patient's predicted drug concentration in addition to the infusion rate.[6,28,59]

Studies have evaluated TCI for endoscopy and found the technique safe and effective for propofol alone and propofol plus midazolam.[23,60]

TCI systems are not approved for use in the United States but are used regularly in other parts of the world.[59] Advocates hope they will be available in the United States within a few years.

A similar technologic approach is computer-assisted personalized sedation (CAPS), which uses computerization to personalize drug delivery based on an individual patient's physiology.

In May 2009, an FDA advisory committee recommended approval of a CAPS device named Sedasys® (Sedasys® is a trademark of Ethicon Endo-Surgery). The device integrates delivery of propofol and oxygen with patient monitoring of pulse oximetry, capnometry, ECG, noninvasive blood pressure, and patient responsiveness.[61] It can automatically detect oxygen saturation and apnea and aims to regulate propofol infusion to avoid oversedation. Sedasys® is designed for physician/nurse teams.[62]

A feasibility study published in 2008 reported on the use of Sedasys® with colonoscopy and EGD procedures.[61] Desired sedation was achieved with about one-third of propofol dosages used in the NAPS trial.[20] Postprocedure recovery was shortened to <30 seconds, leading to high satisfaction from both subjects and clinicians.

Results from a larger study that compared Sedasys® with a regimen of midazolam and an opioid were presented to the FDA. That study found that patients who received sedation from Sedasys® experienced fewer and less significant episodes of oxygen desaturation.

A new development that could impact computerized propofol delivery is the successful measurement of propofol in expired gas. This method uses mass spectrometry to measure exhaled propofol concentration in parts per billion in real

time. At least two studies have compared plasma and exhaled propofol concentrations and found that the expired gas measurement could be successfully used for real-time propofol monitoring.[63,64]

One innovative technologic approach allows patient-controlled sedation (PCS). A recent study compared PCS with propofol and remifentanil to PCS with midazolam and fentanyl for colonoscopy. Investigators found that the propofol/remifentanil group yielded better results, including shorter recovery time.[65]

An older study looked at PCS with propofol and alfentanil vs. traditionally delivered diazepam and meperidine.[66] Patients in the PCS group recovered significantly faster (median 5 minutes vs. 35 minutes; $P < .0001$) but reported significantly higher pain scores.

PCS has also been studied in oral surgeries and been found effective with propofol,[67] midazolam,[12] and midazolam and remifentanil.[12]

CONCLUSION

Sedation and analgesia techniques make up a fast-moving field with new agents and new combinations of existing agents aimed at making patients safer and more comfortable during diagnostic and therapeutic procedures. New developments—both pharmacologic and technologic—are also targeted at giving clinicians more choice of regimens and easier and more effective use of medications.

Patients are increasingly expecting safe, pain- and anxiety-free outpatient procedures with little recovery time, even for relatively complicated procedures. To successfully meet that demand in the future will require new agents and combinations of agents, new delivery mechanisms, and new sedation strategies. The future promises to hold more innovations that will provide clinicians with added tools and tactics to satisfy patients' high expectations.

REFERENCES

1. Zuccaro G Jr. Sedation and analgesia for GI endoscopy. *Gastrointest Endosc*. 2006;63:95-96.
2. Cullen KA, Hall MJ, Golosinskiy A. *Ambulatory Surgery in the United States, 2006*. National health statistics reports; no 11. Revised. Hyattsville, MD: National Center for Health Statistics. 2009.
3. Cohen LB, Wecsler BA, Gaetano JN. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol*. 2006;101:967-974.
4. American Society of Anesthesiologists. Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia, 2004. www.asahq.org/publicationsAndServices/standards/20.pdf. Accessed July 22, 2009.
5. Rex DK. Review article: moderate sedation for endoscopy: sedation regimens for non-anaesthesiologists. *Aliment Pharmacol Ther.* 2006;24:163-171.
6. Cohen LB, DeLegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology.* 2007;133:675-701.
7. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc*. 2008;67:910-923.
8. Bhananker SM, Posner KL, Cheney FW, et al. Injury and liability associated with monitored anesthesia care: a closed claims analysis. *Anesthesiology*. 2006;104:228-234.
9. American Society of Anesthesiologists' Economics Committee Position on Monitored Anesthesia Care. http://www.asahq.org/publicationsAndServices/standards/23.pdf. Accessed July 22, 2009.
10. Wagner BK, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet*. 1997;33:426-453.
11. Harvey MA. Managing agitation in critically ill patients. *Am J Crit Care*. 1996;5:7-16.
12. Garip H, Gürkan Y, Toker K, Göker K. A comparison of midazolam and midazolam with remifentanil for patient-controlled sedation during operations on third molars. *Br J Oral Maxillofac Surg*. 2007;45:212-216.
13. Ganzberg S, Pape RA, Beck FM. Remifentanil for use during conscious sedation in outpatient oral surgery. *J Oral Maxillofac Surg.* 2002;60:244-250.
14. Fanti L, Agostoni M, Gemma M, et al. Remifentanil vs. meperidine for patient-controlled analgesia during colonoscopy: a randomized double-blind trial. *Am J Gastroenterol.* 2009;104:1119-1124.
15. Blanchard AR. Sedation and analgesia in intensive care. *Postgrad Med*. 2002;111:59-74.
16. Patel S, Vargo JJ, Khandwala F, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol*. 2005;100:2689-2695.
17. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med*. 1998;26:947-956.
18. Sipe BW, Rex DK, Latinovich D. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc.* 2002;55:815-825.
19. Levitzky BE, Vargo JJ. Fospropofol disodium injection for the sedation of patients undergoing colonoscopy. *Ther Clin Risk Manag.* 2008;4:733-738.
20. Walker JA, McIntyre RD, Schleinitz PF. Nurse-administered propofol sedation without anesthesia specialists in 9152 endoscopic cases in an ambulatory surgery center. *Am J Gastroenterol.* 2003;98:1744-1750.
21. Paspatis GA, Manolaraki MM, Vardas E. Deep sedation for endoscopic retrograde cholangiopancreatography: intravenous propofol alone versus intravenous propofol with oral midazolam premedication. *Endoscopy.* 2008;40:308-313.
22. Seifert H, Schmitt TH, Gültekin T, et al. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. *Aliment Pharmacol Ther.* 2000;14:1207-1214.
23. Fanti L, Agostoni M, Arcidiacono PG, et al. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: propofol alone versus midazolam plus propofol. A prospective double-blind randomised controlled trial. *Dig Liver Dis*. 2007;39:81-86.
24. Padmanabhan U, Leslie K, Eer AS, et al. Early cognitive impairment after sedation for colonoscopy: the effect of adding midazolam and/or fentanyl to propofol. *Anesth Analg.* 2009;109:1448-1455.
25. Rex DK, Deenadayalu V, Eid E. Gastroenterologist-directed propofol: an update. *Gastrointest Endosc Clin N Am*. 2008;18:717-725.
26. Cohen LB, Hightower CD, Wood DA, et al. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc.* 2004;59:795-803.
27. Diprivan (propofol). Prescribing information. Wilmington, DE: AstraZeneca Pharmaceuticals; 2004.

28. Egan TD. Presentation: Advances in propofol formulation and delivery: new drugs, new machines. May 15, 2009; Scottsdale, AZ.
29. Bennett SN, McNeil MM, Bland LA, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med*. 1995;333:147-154.
30. US Food and Drug Administration. FDA Alert: Propofol (marketed as Diprivan and as generic products). June 2007. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109357.htm. Accessed July 23, 2009.
31. Apfel CC, Bacher A, Biedler A, et al. Eine faktorielle studie von 6 interventionen zur vermeidung von übelkeit und erbrechen nach narkosen (article in German). *Anaesthesist*. 2005;54:201-209.
32. Steinbacher DM. Propofol: a sedative-hypnotic anesthetic agent for use in ambulatory procedures. *Anesth Prog*. 2001;48:66-71.
33. Shah A, Fechner J, Struys M, Mistry B. Differential PK/PD of propofol after intravenous fospropofol and Diprivan in healthy subjects. *Anesthesiology*. 2007;107:A46.
34. Lusedra (fosproprofol disodium). Prescribing information. Woodcliff Lake, NJ: Eisai Corporation of North America; 2008.
35. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth*. 2001;87:684-690.
36. Shehabi Y, Ruettimann U, Adamson H. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med*. 2004;30:2188-2196.
37. Candiotti K, Bekker A, Feldman M, et al. Safety and efficacy of dexmedetomidine for sedation during MAC anesthesia: a multicenter trial. *Anesthesiology*. 2008;109:A1202.
38. Demiraran Y, Korkut E, Tamer A, et al. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. *Can J Gastroenterol*. 2007;21:25-29.
39. Hashiguchi K, Matsunaga H, Higuchi H, Miura S. Dexmedetomidine for sedation during upper gastrointestinal endoscopy. *Dig Endosc*. 2008;20:178-183.
40. Busick T, Kussman M, Scheidt T, Tobias JD. Preliminary experience with dexmedetomidine for monitored anesthesia care during ENT surgical procedures. *Am J Ther*. 2008;15:520-527.
41. Üstün Y, Gündüz M, Erdogan O, Benlidayi ME. Dexmedetomidine versus midazolam in outpatient third molar surgery. *J Oral Maxillofac Surg*. 2006;64:1353-1358.
42. Jalowiecki P, Rudner R, Gonciarz M, et al. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *Anesthesiology*. 2005;103:269-273.
43. Tosun Z, Esmaoglu A, Coruh A. Propofol-ketamine vs propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. *Paediatr Anaesth*. 2008;18:43-47.
44. Friedberg BL. Propofol ketamine anesthesia for cosmetic surgery in the office suite. *Anesthesiol Clin*. 2003;41:39-50.
45. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;49:23-30.
46. Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. *Ann Pharmacother*. 2007;41:485-492.
47. Varadarajulu S, Eloubeidi MA, Tamhane A, Wilcox CM. Prospective randomized trial evaluating ketamine for advanced endoscopic procedures in difficult to sedate patients. *Aliment Pharmacol Ther*. 2007;25:987-997.
48. Slavik VC, Zed PJ. Combination ketamine and propofol for procedural sedation and analgesia. *Pharmacotherapy*. 2007;27:1588-1598.
49. American College of Gastroenterology, American Gastroenterological Association, American Society for Gastrointestinal Endoscopy. Three gastroenterology specialty groups issue joint statement on sedation in endoscopy. March 8, 2004. www.gi.org/physicians/nataffairs/trisociety.asp. Accessed January 25, 2009.
50. American Association of Nurse Anesthetists-American Society of Anesthesiologists Joint Statement Regarding Propofol Administration. April 14, 2004. http://www.aana.com. Accessed January 25, 2009.
51. Green SM, Krauss BK. Barriers to propofol use in emergency medicine. *Ann Emerg Med*. 2008;52;392-398.
52. DeWitt J, McGreevy K, Sherman S, Imperiale TF. Nurse-administered propofol sedation compared with midazolam and meperidine for EUS: a prospective, randomized trial. *Gastrointest Endosc*. 2008;68:499-509.
53. Fatima H, DeWitt J, LeBlanc J, et al. Nurse-administered propofol sedation for upper endoscopic ultrasonography. *Am J Gastroenterol*. 2008;103:1649-1656.
54. Wehrmann T, Riphaus A. Sedation with propofol for interventional endoscopic procedures: a risk factor analysis. *Scand J Gastroenterol*. 2008;43:368-374.
55. Rex DK, Deenadayalu VP, Eid E. Endoscopist directed administration of propofol: a world-wide safety experience. *Gastroenterology*. 2009;137:1229-1237.
56. Kim KM, Choi BM, Park SW, et al. Pharmacokinetics and pharmacodynamics of propofol microemulsion and lipid emulsion after an intravenous bolus and variable rate infusion. *Anesthesiology*. 2007;106:924-934.
57. Ravenelle F, Gori S, Le Garrec D, et al. Novel lipid and preservative-free propofol formulation: properties and pharmacodynamics. *Pharm Res*. 2008;25:313-319.
58. Egan TD. Target-controlled drug delivery. *Anesthesiology*. 2003;99:1214-1219.
59. Egan TD, Shafer SL. Target-controlled infusions for intravenous anesthetics: surfing USA not! *Anesthesiology*. 2003;99:1039-1041.
60. Fanti L, Agostoni M, Casati A. Target-controlled propofol infusion during monitored anesthesia in patients undergoing ERCP. *Gastrointest Endosc*. 2004;60:361-366.
61. Pambianco DJ, Whitten CJ, Moerman A, et al. An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. *Gastrointest Endosc*. 2008;68:542-547.
62. FDA advisory panel recommends approval of the Sedasys® system. May 28, 2009. Ethicon Endo-Surgery. http://www.ethiconendo.com/dtcf/pages/press_room_32.htm. Accessed July 23, 2009.
63. Takita A, Masui K, Kazama T. On-line monitoring of end-tidal propofol concentration in anesthetized patients. *Anethesiology*. 2007;106:659-664.
64. Grossherr M, Hengstenberg A, Meier T. Propofol concentration in exhaled air and arterial plasma in mechanically ventilated patients undergoing cardiac surgery. *Br J Anaesth*. 2009;102:608-613.
65. Mandel JE, Tanner JW, Lichtenstein GR, et al. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanil versus midazolam/fentanyl for colonoscopy. *Anesth Analg*. 2008;106:434-439.
66. Bright E, Roseveare C, Dalgleish D, et al. Patient-controlled sedation for colonoscopy: a randomized trial comparing patient-controlled administration of propofol and alfentanil with physician-administered midazolam and pethidine. *Endoscopy*. 2003;35:683-687.
67. Rodrigo C, Irwin MG, Yan BS, Wong MH. Patient-controlled sedation with propofol in minor oral surgery. *J Oral Maxillofac Surg*. 2004;62:52-56.

CME/CE POST-TEST

On page 16, please darken the circle with the correct answer to each question.

1. **What is the percentage of endoscopic diagnostic and therapeutic procedures in the United States performed with sedation rather than general anesthesia?**
   a. 50%
   b. 75%
   c. 85%
   d. 98%

2. **The level of sedation that includes a state in which a patient is not easily aroused but responds purposefully to repeated or painful stimulation is**
   a. Minimal
   b. Moderate
   c. Deep
   d. General anesthesia

3. **Which of the following indicates increased risk of adverse outcomes from sedation?**
   a. Diabetes
   b. Family history of sedation problems
   c. Snoring
   d. Mild dyslipidemia

4. **Three-quarters of surveyed endoscopists favored which sedation regimen?**
   a. Benzodiazepine with an opioid
   b. Benzodiazepine alone
   c. Propofol alone
   d. Dexmedetomidine with a benzodiazepine

5. **Which of the following is a common effect of midzolam?**
   a. Coughing
   b. Anterograde amnesia
   c. Dry mouth
   d. Bradycardia

6. **Coughing and pain-withdrawal movements that impede a procedure can be associated with which agent(s)?**
   a. Benzodiazepine with opioid
   b. Propofol with opioid
   c. Propofol alone
   d. Dexmedetomidine alone

7. **Brief but intense perineal paresthesias can result from the use of which agent(s)?**
   a. Fospropofol alone
   b. Midazolam with fentanyl
   c. Fentanyl alone
   d. Propofol with any opioid

8. **In the Phase 3 study by Candiotti et al, which adverse effect was significantly more present in the midazolam-fentanyl group than in the dexmedetomidine arms?**
   a. Increased anxiety
   b. Respiratory depression
   c. Bradycardia
   d. Hypotension

9. **Which of the following drugs have/has no reversal agents?**
   a. Meperidine and midazolam
   b. Propofol and fospropofol
   c. Diazepam
   d. Fentanyl

10. **What is the one reason researchers are investigating micellar solution (nanotechnology) for propofol delivery?**
    a. To increase the speed of onset
    b. To reduce injection pain
    c. To release propofol's natural antimicrobial activity
    d. To allow non-anesthesiologists to administer propofol more safely

PROGRAM EVALUATION AND ANSWER SHEET

Please read the monograph and take the test. Fill in the answer sheet and submit it to BUSM CME before November 29, 2010. CME credit will be awarded if a score of 70% or better is achieved. To receive CE credit, nurses must pass the post-test with a score of 80% or better. Submit the answer sheet via mail or fax to: Boston University School of Medicine, Continuing Medical Education, E.SAMBAHAY09, 72 East Concord St., A305, Boston, MA 02118. Fax 617-638-4905. Your certificate will be mailed to you in 4-6 weeks. To participate online and receive your certificate instantly, go to www.bucmetest.com. Enter E.SAMBAHAY09 in the Test Code Search Field. For questions, please contact BUSM CME at 617-638-4605.

Please type or print clearly

First name _____ Middle initial _____ Last name _____ Degree _____ Specialty _____

Mailing address _____

City _____ State _____ ZIP + 4-digit code _____

Phone _____ Fax _____ E-mail address _____

The amount of time I spent on this activity was _____ (max of 1 hour).

Exam Answer Form

Darken the circle with the correct answer to each question in the CME/CE activity.

1.	(A)	(B)	(C)	(D)	5.	(A)	(B)	(C)	(D)	9.	(A)	(B)	(C)	(D)
2.	(A)	(B)	(C)	(D)	6.	(A)	(B)	(C)	(D)	10.	(A)	(B)	(C)	(D)
3.	(A)	(B)	(C)	(D)	7.	(A)	(B)	(C)	(D)					
4.	(A)	(B)	(C)	(D)	8.	(A)	(B)	(C)	(D)					

Program Evaluation

1. How would you rate this activity overall?
(5 = excellent, 1 = poor; please circle one)
5 4 3 2 1

2. Do you feel each of the learning objectives listed on page 2 was met?

Objective 1	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 2	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 3	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 4	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 5	❑ Yes	❑ Partially	❑ No	❑ N/A

3. In your opinion, did you perceive any commercial bias?
❑ Yes ❑ No If yes, please specify: _____

4. Please rate the content of this activity.
(5 = excellent, 1 = poor; please circle one)
4a. Timely, up to date? 5 4 3 2 1
4b. Relevant to your practice? 5 4 3 2 1

5. Do you feel that the information in this activity was based on the best evidence available? ❑ Yes ❑ No
If no, please explain: _____

6. Do you intend to make changes in your practice as a result of this activity? ❑ Yes ❑ No
If yes, please explain: _____

7. Please make suggestions for future programs.

Boston University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
Boston University School of Medicine designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This program is approved by the American Association of Nurse Anesthestists for 1 CE credit.