Objective: The development of practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit (ICU) setting for the purpose of guiding clinical practice.

Participants: A task force of more than 40 experts in disciplines related to the use of analgesic and sedative agents in the ICU was convened from the membership of the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM).

Evidence: The task force members provided the personal experience and determined the published literature (MEDLINE articles, textbooks, pharmacopeias, etc.) from which consensus would be sought. Published literature was reviewed and classified into one of four predetermined categories, according to study design and scientific value.

Consensus Process: The task force met several times as a whole, and numerous times in smaller groups by teleconference, over a 1-yr period to identify the pertinent literature and arrive at consensus recommendations for the whole task force to discuss. Consideration was given to the relationship between the weight of scientific information and the experts' viewpoints. Over the next year, draft documents were composed by a task force steering committee and debated by the task force members until consensus was reached by nominal group process. The task force draft was then reviewed, assessed, and edited by the Board of Regents of the ACCM. After steering committee approval, the draft document was reviewed and approved by the SCCM Council.

Data Synthesis: To facilitate rapid communication of the six recommendations contained within the complete and unabridged practice parameter document, an executive summary was prepared for publication by the ACCM Board of Regents, and this executive summary was approved by the task force steering committee and the SCCM Executive Council.
Conclusions: A consensus of experts provided six recommendations with supporting data for intravenous analgesia and sedation in the ICU setting: a) morphine sulfate is the preferred analgesic agent for critically ill patients; b) fentanyl is the preferred analgesic agent for critically ill patients with hemodynamic instability, for patients manifesting symptoms of histamine release with morphine, or morphine allergy; c) hydromorphone can serve as an acceptable alternative to morphine; d) midazolam or propofol are the preferred agents only for the short-term (<24 hrs) treatment of anxiety in the critically ill adult; e) lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult; f) haloperidol is the preferred agent for the treatment of delirium in the critically ill adult. This executive summary selectively presents supporting information and is not intended as a substitute for the complete document. (Crit Care Med 1995; 23:1596–1600)

Key Words: analgesia; sedation; intensive care unit; morphine sulfate; fentanyl; hydromorphone; midazolam; propofol; lorazepam; haloperidol

The American College of Critical Care Medicine of the Society of Critical Care Medicine has developed practice parameters to assist healthcare providers in prescribing sedation and analgesia in the intensive care unit (ICU) setting. These practice parameters are limited to adult patients requiring sustained analgesia/sedation of longer than several hours duration, and do not consider one-time therapy, nonsystemic analgesic therapies such as epidural techniques, or patients who are <12 yrs of age. To assist the practitioner in determining the relative scientific authority of the cited references in the unabridged document, each reference is categorized as listed in Table 1. The unabridged document makes six specific recommendations, and each recommendation has been assigned a "rating level" (Table 1) that reflects the weight of scientific evidence, expert opinion, and clinical practice experience upon which the recommendation was based.

This executive summary is not intended to be, and must not be used as, a substitute or replacement for the unabridged practice parameters document. Rather, this executive summary is intended to facilitate communication of the document’s six specific recommendations and the fundamental information upon which these recommendations were based.

Table 1. Rating systems for citations and recommendations

<table>
<thead>
<tr>
<th>Rating System for Recommendations</th>
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<tbody>
<tr>
<td>(a), Randomized, prospective, controlled investigations</td>
</tr>
<tr>
<td>(b), Nonrandomized, concurrent, or historical cohort investigations</td>
</tr>
<tr>
<td>(c), Peer-reviewed state-of-the-art articles, review articles, editorials, or substantial case series</td>
</tr>
<tr>
<td>(d), Nonpeer-reviewed published opinions, such as textbook statements or official organizational publications</td>
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</table>

| Level 1: Convincingly justifiable on scientific evidence alone |
| Level 2: Reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion |
Adequate scientific evidence is lacking but widely supported by available data and expert critical care opinion.

**ANALGESIA**

Analgesia connotes the absence of sensibility to pain or noxious stimuli in the conscious patient. Pain has consequences in the critically ill patient that can lead to clinically significant physiologic responses such as tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism (1). ICU patients commonly experience pain from pathology as well as from diagnostic and therapeutic procedures, for which intravenous opiates are the mainstay of analgesic therapy. The opiates are central nervous system µ opioid receptor agonists that invoke analgesia, sedation, respiratory depression, constipation, urinary retention, nausea, and confusion. Opiates have little, if any, amnestic properties.

Some critically ill patients receive inadequate analgesia due to unwarranted concerns about inducing opiate addiction. More commonly, inadequate analgesia in the ICU results from attempting to avoid certain side effects of opiate analgesics that are prominent in the ICU population, such as: a) respiratory depression in spontaneously breathing patients and in patients receiving partial ventilator support; b) hypotension, which is most likely to occur in patients with hypovolemia; and c) gastric retention and ileus, which are common in critically ill patients and enhanced by opiates. Despite these legitimate concerns, adequate analgesia must remain a primary goal in the care of the critically ill.

**ANALGESIC AGENTS RECOMMENDED FOR ROUTINE USE IN THE INTENSIVE CARE UNIT**

**Recommendation 1—Level 2: Morphine Sulfate Is the Preferred Analgesic Agent for Critically Ill Patients.** In the United States, morphine sulfate is the most frequently used intravenous analgesic agent in the ICU, mainly because of low cost, potency, analgesic efficacy, and euphoric effect. Morphine has a half-life of 1.5 to 2 hrs after intravenous administration in normal subjects. In the ICU patient, distribution volume and protein binding may be abnormal, resulting in either an exaggerated or diminished response. Morphine may induce histamine release, causing hypotension and other adverse effects.

Morphine sulfate should be administered intravenously and titrated to effect. Therapy should generally start at a loading dose of 0.05 mg/kg, administered over 5 to 15 mins. Most adults require 4 to 6 mg/hr after receiving an adequate loading dose. With bolus therapy, redosing should be accomplished every 1 to 2 hrs; with continuous infusion therapy, one or more loading doses are required.

**Recommendation 2—Level 2: Fentanyl Is the Preferred Analgesic Agent for Critically Ill Patients With Hemodynamic Instability, for Patients Manifesting Symptoms of Histamine Release With Morphine, or Morphine Allergy.** Fentanyl (Sublimaze®, Janssen Pharmaceutica, Titusville, NJ) is a synthetic opiate with greater potency and lipophilic properties than morphine, resulting in a faster onset of action. Fentanyl does not cause histamine release, which may explain the reduced frequency of hypotension compared with morphine. Intravenous fentanyl has a relatively short half-life of 30 to 60 mins due to rapid redistribution to peripheral compartments (2). However, prolonged administration leads to accumulation in peripheral compartments that results in a progressive increase in half-life to 9 to 16 hrs (3). Fentanyl has little euphoric effect, no active metabolites, and does not cross-react in patients with morphine allergy.

Fentanyl should be administered by continuous intravenous infusion. Most patients will be adequately treated with 1 to 2 µg/kg/hr. One or more loading doses of 1 to 2 µg/kg are generally required when therapy is initiated.

**Recommendation 3—Level 3: Hydromorphone Can Serve as an Acceptable Alternative to Morphine.** Hydromorphone (Dilaudid®, Knoll Pharmaceutical, Whippany, NJ) is a semisynthetic
morphine derivative with more potent analgesic/sedative properties than morphine and significantly less euphoria. The dosage should be initiated at 0.5 mg and titrated by 0.5 mg increments, with most patients requiring 1 to 2 mg every 1 to 2 hrs.

**ANALGESIC AGENTS NOT RECOMMENDED FOR THE CRITICALLY ILL**

*Meperidine* (Demerol®, Sanofi Winthrop Pharmaceuticals, New York, NY) has an active metabolite, normeperidine, that may accumulate and produce central nervous system excitation (4). *Opiate agonist-antagonists* (nalbuphine, butorphanol, buprenorphine) are available for the relief of mild-to-moderate pain and may reverse other opiate agents. Agonist-antagonists are not recommended for routine use in critically ill patients (5). *Nonsteroidal anti-inflammatory drugs* have no analgesic advantages over opiates and have potential risks of gastrointestinal bleeding, bleeding secondary to platelet inhibition, and the development of renal insufficiency (6).

**SEDATION**

Sedation (calming or allaying excitement) is indicated in the ICU setting for the primary treatment of anxiety (psychophysiologic response to the anticipation of real or imagined danger) and agitation (excitement accompanied by motor restlessness). The prototype intravenous sedative agent is *diazepam* (Valium®, Roche Laboratories, Nutley, NJ, and others), a long-acting lipophilic benzodiazepine that rapidly penetrates the central nervous system, allowing for the sedative effect to be seen within 2 to 3 mins and peak effect within 3 to 5 mins. All parenteral benzodiazepines reliably cause anterograde amnesia (inability to form new memory) and have no analgesic activity. The effects of a single diazepam dose abates rapidly as the drug redistributes to peripheral tissues, while a more sustained effect is achieved with repeated administration due to the saturation of peripheral compartments and central nervous system binding sites (7). Diazepam is no longer recommended for routine use in the ICU for the following reasons: a) pain and thrombophlebitis are common when administered by peripheral vein injection; b) a scheduled intermittent dosing regimen may lead to excessive sedation unless an objective monitor of the level of sedation is utilized before each dose; and c) dilution is required for continuous infusion, which demands large volumes of fluid administration.

**SEDATIVE AGENTS RECOMMENDED FOR ROUTINE USE IN THE INTENSIVE CARE UNIT**

**Recommendation 4—Level 2:** Midazolam or Propofol Are the Preferred Agents Only for the Short-Term (<24 Hrs) Treatment of Anxiety in the Critically Ill Adult. The greater cost of these drugs is balanced by the rapidity with which their pharmacologic effects abate with short-term therapy.

*Midazolam* (Versed®, Roche Laboratories) is a short-acting, water-soluble benzodiazepine that becomes a lipophilic compound in the blood and that rapidly penetrates the central nervous system to produce an onset of sedation (2 to 2.5 mins) similar to diazepam. Midazolam is similar to diazepam in all respects, except for its brief duration of clinical effect due to rapid redistribution, a factor that favors continuous infusion for maintaining sedation in the critically ill. Long-term administration results in a prolongation of the clinical effects of the drug. A maintenance midazolam dosage of 0.03 mg/kg/hr serves well as a starting point, with dosage titrated to effect over time. One or more bolus loading doses (0.03 mg/kg) are generally required when therapy is initiated.

*Propofol* (Diprivan®, Stuart Pharmaceuticals, Wilmington, DE) is an intravenous, general anesthetic agent that has sedative, hypnotic, anxiolytic, and anterograde amnestic properties at subanesthetic dosages. When propofol is utilized in subanesthetic dosages, it produces anxiolysis and possesses some anterograde amnestic effects. When propofol infusion is compared with midazolam infusion in critically ill patients, the two drugs are equally effective sedative agents (8). The onset of action after a single subanesthetic intravenous dose of propofol is rapid (1 to 2 mins) and its effect is brief (10 to 15 mins) due to its rapid central nervous system penetration and subsequent redistribution. For these reasons, propofol is administered only by continuous infusion when used for sedation. Long-term infusions result in accumulation within lipid stores, resulting in a prolonged elimination phase with a half-life of up to 300 to 700 mins. However, subtherapeutic plasma concentrations are maintained after discontinuation of the drug by rapid clearance mechanisms. Propofol is administered at an initial infusion rate of 0.5 mg/kg/hr and titrated rapidly upward in increments of 0.5 mg/kg every 5 to 10 mins, according to clinical response. Typical
maintenance dosages are 0.5 to 3.0 mg/kg/hr. Propofol should be administered via a central vein.

**Recommendation 5—Level 2: Lorazepam Is the Preferred Agent for the Prolonged Treatment of Anxiety in the Critically Ill Adult.** Lorazepam (Ativan®, Wyeth-Ayerst Laboratories, Philadelphia, PA, and others) is an intermediate-acting benzodiazepine that is less lipophilic than diazepam, which decreases its potential for peripheral accumulation (9). Compared with midazolam, lorazepam is longer acting, causes less hypotension, causes an equally effective anterograde amnesia, is lower in cost, and with prolonged administration produces more rapid awakening (10). Lorazepam is most conveniently administered by intermittent intravenous bolus injection, but continuous intravenous infusion is an equally acceptable method of administration. The usual starting dosage is 0.044 mg/kg every 2 to 4 hrs, as needed, but this requirement is highly variable. One or more loading doses are generally required with continuous infusion therapy. Because lorazepam has a slightly delayed onset of action, a single dose of midazolam or diazepam may be utilized to initiate sedative therapy when rapid sedation is required.

**Recommendation 6—Level 1: Haloperidol Is the Preferred Agent for the Treatment of Delirium in the Critically Ill Adult.** Delirium is a state of reduced ability to appropriately respond to external stimuli, usually manifested as disorganized thinking (rambling, incoherent/irrelevant speech), decreased level of consciousness, altered sensory perception, disorientation, and/or altered level of psychomotor activity. Delirium is frequent in the ICU and is often incorrectly termed "ICU psychosis." Administration of opiates or benzodiazepines as initial therapy for delirium may cause a **paradoxical worsening of symptoms** because of the further alteration in sensory perception produced by these agents.

*Haloperidol* (Haldol®, McNeil Pharmaceutical, Raritan, NJ) is a butyrophenone neuroleptic drug with proven efficacy in the treatment of delirium in the critically ill (11). Although haloperidol has not been approved by the U.S. Food and Drug Administration for intravenous administration, this route of administration has been reported to be safe and effective (12) and is preferred in the critically ill patient to maximize bioavailability and predictability (11). Clinical effects are observed within 30 to 60 mins after intravenous administration and may last 4 to 8 hrs. Haloperidol may cause QT prolongation on the electrocardiogram (13) and should be used with caution in conjunction with other drugs that may prolong the QT interval. The usual starting dosage is 2 to 10 mg administered intravenously and the dosage is repeated every 2 to 4 hrs.

**AGENTS NOT RECOMMENDED FOR ROUTINE SEDATION OF THE CRITICALLY ILL**

*Etomidate* (Amidate®, Abbott Laboratories, Abbott Park, IL) is an intravenous anesthetic/hypnotic agent with minimal cardiovascular- and respiratory-depressant effects that is often used in the ICU to provide anesthesia for short procedures. Long-term use for sedation has been associated with adrenocortical suppression and increased mortality. *Ketamine* (Ketalar®, Parke-Davis, Morris Plains, NJ) is an intravenous anesthetic/analgesic agent that is utilized in the ICU in conjunction with specific procedures, such as painful dressing changes. Ketamine may induce increases in blood pressure, heart rate, and intracranial pressure when used as a sedative agent. The **barbiturate agents** thiopental (Pentothal®, Abbott Laboratories) and pentobarbital (Nembutal®, Abbott Laboratories) are used in the ICU population primarily to control intracranial pressure or as anticonvulsants. Utilizing subanesthetic doses, the barbiturates are effective sedative agents but lack amnestic and analgesic properties, and produce myocardial depression and vasodilation that commonly result in tachycardia and hypotension. *Chlorpromazine* (Thorazine®, SmithKline Beecham, Pittsburgh, PA) and *droperidol* (Inapsine®, Janssen Pharmaceutica) are neuroleptic agents that have been evaluated for the treatment of restlessness and delirium. Insufficient experience exists to recommend either of these agents in critically ill patients.

**REFERENCES**


*For an explanation of these annotations, see Table 1.