

American Society for Pain Management Nursing Guidelines on Monitoring for Opioid-Induced Sedation and Respiratory Depression

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■ ABSTRACT:

As the complexity of analgesic therapies increases, priorities of care must be established to balance aggressive pain management with measures to prevent or minimize adverse events and to ensure high quality and safe care. Opioid analgesia remains the primary pharmacologic intervention for managing pain in hospitalized patients. Unintended advancing sedation and respiratory depression are two of the most serious opioid-related adverse events. Multiple factors, including opioid dosage, route of administration, duration of therapy, patient-specific factors, and desired goals of therapy, can influence the occurrence of these adverse events. Furthermore, there is an urgent need to educate all members of the health care team about the dangers and potential attributes of administration of sedating medications concomitant with opioid analgesia and the importance of initiating rational multimodal analgesic plans to help avoid adverse events. Nurses play an important role in: 1) identifying patients at risk for unintended advancing sedation and respiratory depression from opioid therapy; 2) implementing plans of care to assess and monitor patients; and 3) intervening to prevent the worsening of adverse events. Despite the frequency of opioid-induced sedation, there are no universally accepted guidelines to direct effective and safe assessment and monitoring practices for patients receiving opioid analgesia.

Moreover, there is a paucity of information and no consensus about the benefits of technology-supported monitoring, such as pulse oximetry (measuring oxygen saturation) and capnography (measuring end-tidal carbon dioxide), in hospitalized patients receiving opioids for pain therapy. To date, there have not been any randomized clinical trials to establish the value of technologic monitoring in preventing adverse respiratory events. Additionally, the use of technology-supported monitoring is costly, with far-reaching implications for hospital and nursing practices. As a result, there are considerable variations in screening for risk and monitoring practices. All of these factors prompted the American Society for Pain Management Nursing to approve the formation of an expert consensus panel to examine the scientific basis and state of practice for assessment and monitoring practices for adult hospitalized patients receiving opioid analgesics for pain control and to propose recommendations for patient care, education, and systems-level changes that promote quality care and patient safety.

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BACKGROUND

Effective pain management is a priority of care and a patient right (Joint Commission, 2010). Advances in pain science justify the need for more aggressive pain therapies to reduce pain severity and the likelihood for both short- and long-term consequences of unrelieved pain (Basbaum, Bautista, Scherrer, & Julius, 2009; Carr & Goudas, 1999; Latremoliere & Woolf, 2009; Woolf & Salter, 2000). Multimodal analgesia, which combines analgesics with variable pharmacodynamics to target multiple underlying mechanisms of pain, is evolving as an acceptable approach to pain treatment for both acute and chronic (persistent) pain (Pasero, 2003; Pasero, Quinn, Portenoy, McCaffery, & Rizo, 2011; Polomano, Dunwoody, Krenzischek, & Rathmell, 2008; Polomano, Rathmell, Krenzischek, & Dunwoody, 2008). As the complexity of analgesic therapies increases, priorities must be established to balance aggressive pain treatment with measures to prevent or minimize adverse events and ensure high-quality and safe care. Appropriate assessment and monitoring of patients are essential components of care; however, these practices are not clearly defined to promote optimal patient outcomes.

Opioid analgesia remains the primary pharmacologic intervention for managing pain in hospitalized patients; however, as with any medication, opioids can cause adverse effects. Unintended advancing sedation and respiratory depression are among the most serious. A study conducted in the United Kingdom ranked opioids second in the classes of medications contributing to adverse-event reporting for hospitalized patients, and sedation and respiratory depression were among the most commonly reported adverse effects (Davies, Green, Taylor, Williamson, Mottram, & Pirmohamed, 2009). In a report from the Joint Commission, opioid-related events resulting in death or permanent loss of

function accounted for 0.25% of all events reviewed between 2004 through the third quarter of 2010; 58% were the result of improper monitoring (The Joint Commission, 2010). Opioid-induced adverse events in postoperative patients significantly increase length of hospital stay and cost of hospitalization (Oderda, Said, Evans, Stoddard, Lloyd, Jackson, Samore, 2007). According to the Institute for Safe Medication Practices, opioid-induced adverse events may be on the rise as clinicians treat pain more aggressively in response to the Joint Commission pain standards (Smetzer & Cohen, 2003).

Opioid-induced respiratory depression is a decrease in the effectiveness of an individual's ventilatory function after opioid administration. Sedation generally precedes significant respiratory depression (Abou Hammoud, Simon, Urien, Riou, Lechat, & Aubrun 2009; Taylor, Voytovich, & Kozol, 2003). Opioid-induced sedation occurs on a continuum ranging from full consciousness to complete loss of consciousness and respiratory arrest. Unintended advancing sedation occurs at increasingly higher levels along the continuum of sedation, impairing both arousal mechanisms and content processing (Young-McCaughan & Miaskowski, 2001a). Monitoring is the act of purposeful and systematic serial assessments of the level of sedation and respiratory status (quality, character, rate, and effectiveness).

Precise estimates for the incidences of unintended advancing sedation and respiratory depression from opioids administered for pain management in hospitalized patients are highly variable. Multiple factors, such as opioid class, dose, formulation, route of administration, duration of therapy, concomitant medication administration, and patient-specific characteristics, can influence the occurrence of these adverse effects. Differences in study designs, sample populations, methods of administration, and definitions of sedation and respiratory depression

used in research also contribute to the variability in the incidences of opioid-induced sedation and respiratory depression reported in the literature.

Sedation is a common and expected adverse effect of opioids, particularly at the start and generally during the first 24 hours of opioid therapy (possibly longer for transdermal fentanyl) and with increases in opioid dose (Pasero et al., 2011). Although respiratory depression is less common than sedation, it is frequently the most serious of the opioid-induced adverse effects. A meta-analysis compiled data from 116 studies and reported an incidence of respiratory depression (defined by respiratory rate of <10 breaths per minute) among 29,607 postoperative patients receiving opioid-containing pain management regimens of 1.1% (95% confidence interval [CI] 0.7%–1.7%) (Cashman & Dolin, 2004). These estimates must be cautiously interpreted owing to variations in the incidence of respiratory depression associated with different opioid regimens.

An extensive review of the medical records over a 8-year period (2000–2008) of patients with sudden-onset life-threatening critical respiratory events during opioid analgesia therapy (including intravenous [IV] patient-controlled analgesia [PCA] and patient-controlled epidural analgesia [PCEA]) for postoperative pain revealed an incidence of 3.6 per 10,000 adult patients (0.038%) (Ramachandran, Haider, Saran, Mathis, Morris, & O'Reilly, 2011). Patients identified in that study required rescue by naloxone, endotracheal intubation, or cardiopulmonary resuscitation. Deep levels of sedation were associated with mortality, which led the researchers to emphasize the importance of systematic sedation assessment during opioid administration.

A comprehensive review of multiple studies that used a variety of definitions for respiratory depression and methods of opioid administration determined an overall incidence of <0.5% (Dahan, Aarts, & Smith, 2010). Some of the variance in incidence may be associated with mode of delivery. For example, a review of the literature from 1990 to 2004 reported frequencies of respiratory depression ranging from 0.19% to 5.2% in patients receiving IV PCA (Hagle, Lehr, Brubakken, & Shippee, 2004). Interestingly, an observational study of 53 patients reported that those who received opioids via IV PCA after surgery experienced sedation levels similar to those who received opioids for “conscious sedation” during colonoscopy (Taylor et al., 2003). The literature is inconsistent regarding the risk associated with the use of background infusions (basal rates) during IV PCA therapy. Higher rates of respiratory depression were reported in early studies when a basal rate was administered with IV PCA (Fleming & Coombes, 1992; Schug & Torrie, 1993);

however, more recent research has shown similar (Guler, Unlugenc, Gundogan, Ozalevli, Balcioglu, & Topcuoglu, 2004) or lower (Overdyk, Carter, Maddox, Callura, Herrin, & Henriquez, 2007) rates of sedation and respiratory depression in patients who received basal rates compared with those who did not.

Despite the frequency of opioid-induced sedation and the potentially devastating outcomes of undetected respiratory depression, there are no universally accepted guidelines to direct effective and safe assessment and monitoring practices. As a result, there are considerable variations in monitoring practices.

Guidelines and recommendations for monitoring patients receiving neuraxial analgesia (American Society of Anesthesiologists [ASA], 2009) provide specific direction regarding the extent of monitoring in patients receiving various types of neuraxial analgesia but do not address other opioid-based therapies. In a 2006 publication, the Anesthesia Patient Safety Foundation urged health care professionals to “give consideration to the potential safety value of continuous monitoring of oxygenation (pulse oximetry) and ventilation in patients receiving PCA or neuraxial opioids in the postoperative period” (p. 66). Although this opinion is helpful in offering a general recommendation, it does not provide specific guidance as to which patients might benefit most from monitoring technology during these therapies. Furthermore, the value of technology-supported monitoring, such as pulse-oximetry (measuring oxygen saturation [SpO₂]) and capnography (measuring end-tidal carbon dioxide [ETCO₂]), in preventing mortality secondary to respiratory depression in hospitalized patients receiving opioids for pain therapy has not been firmly established by research. The use of technology-supported monitoring is costly, with far-reaching implications for already-stressed hospital budgets that must plan for the capital expense of monitoring equipment and the education of staff to properly use the equipment. The effect of mechanical monitoring on the efficiency and quality of nursing care is unknown and raises concerns regarding alarm fatigue and desensitization and nursing liability for interpreting and communicating respiratory trends.

Additionally, there is a lack of evidence to inform the best practices for deciding the type and frequency of nursing assessments. Nurses are ideally suited by virtue of their 24-hour presence and close proximity to the patient to develop and implement clinical practice guidelines for assessment and monitoring of patients during opioid administration for pain management. They play a critical role in: 1) the identification of patients at risk; 2) the development and implementation of plans of care to assess and monitor patients; and 3) the execution of interventions to prevent

serious adverse events secondary to unintended advancing sedation and respiratory depression from opioid therapy. All of these factors prompted the American Society for Pain Management Nursing (ASPMN) Board of Directors to approve the formation of an expert consensus panel to examine the scientific basis and state of practice for assessment and monitoring of adult hospitalized patients receiving opioid analgesics for pain management.

ASPMN Expert Consensus Panel

In 2007, the ASPMN Board of Directors approved the formation of an expert panel to develop recommendations for assessment and monitoring of adult hospitalized patients in noncritical care settings who are at risk for sedation and respiratory depression from opioids administered for pain management. These recommendations were to be based on the strength of existing evidence and expert consensus of the panel members. Specifically, this expert panel of ASPMN members was charged to: 1) perform an extensive review of the literature and a scientific appraisal of research and evidence-based guidelines; 2) conduct a nation-wide survey of ASPMN members to examine current practices for monitoring hospitalized patients receiving opioid analgesics for pain control; and 3) compile a comprehensive document outlining the processes and outcomes of the scientific review with recommendations for monitoring practices.

Under the leadership of Donna Jarzyna, MS, RN-BC, CNS-BC nine ASPMN members were invited to participate. Each was selected on the basis of qualifications that included academic preparation, having a master's or doctorate degree in nursing, expertise in clinical practice, education or research, and evidence of nationally recognized scholarship and accomplishments. Members of the ASPMN Expert Consensus Panel convened in April 2008 to formulate a strategic plan and timeline for completing the required work to the final submission of a report to ASPMN Board of Directors.

METHODOLOGY

For this review, the definition of "monitoring" is the practice of using nurse observations of sedation and respiration including but not limited to the use of sedation assessment scales and technologies to collect serial measurements to anticipate and recognize unintended advancing sedation or respiratory depression. There was early agreement among panel members that the search and appraisal of scientific literature and formulation of recommendations

should focus primarily on adult hospitalized medical-surgical populations receiving opioid analgesics for acute pain (e.g., postsurgical pain, trauma pain, and acute pain from medical conditions). Consequently, the contents of this report and recommendations put forth by the expert panel may not be applicable to patients with chronic pain or those at the end of life. Several steps were taken to ensure the integrity of the decision-making processes for compiling literature, appraising the quality of studies and state of the science, and summarizing pertinent findings to support recommendations made by the expert panel.

Step 1: Panel members independently searched various electronic databases (Medline, PubMed, Cumulative Index to Nursing and Allied Health Literature [CINAHL], and Cochrane Library) for relevant publications (data-based articles, case reports, clinical reviews, commentaries, and editorials) on opioid-induced sedation and respiratory depression. More than 50 citations were initially posted on the ASPMN Blackboard (a communication tool for task force members) for review, and frequent telephone conferences were held to discuss the readings.

Step 2: To facilitate literature appraisal skills and determine levels of agreement among panel members, 17 articles of varying quality were selected and each panel member independently rated at least three of the articles on the scope of content, overall quality, adequacy of references, evidence of research synthesis, confirmation or disconfirmation of existing evidence and research, and relevance to practice. Rating criteria were specifically designed for this exercise. When possible for ratings, agreement was measured among raters using the Cohen's kappa statistic. Percent agreement ranged from 0.72 to 1.00 across all articles, demonstrating a high degree of concordance among raters.

Step 3: Based on an evaluation of published literature, the expert panel reached consensus regarding four categories for compiling evidence relevant to opioid-induced sedation and respiratory depression. These were: Individual Patient Risks, Iatrogenic Risks, Pharmacology, and Monitoring. Subgroups were then formed with each panel member assigned to one of these groups. The focus of the literature review was determined, and decision rules for electronic literature searches were established. Search strategies for retrieving relevant literature included identifying meta-analyses, systematic reviews, randomized controlled trials (RCTs), clinical trials, prospective observational studies, retrospective reviews, and secondary analyses. Clinical review articles, commentaries, and editorials were considered if published in influential journals and authored by recognized leaders in pain management. Panelists were in agreement that it would be virtually impossible to retrieve, review, and evaluate all opioid-related efficacy studies.

TABLE 1.

American Society of Anesthesiologists (ASA) Evidence Categories

Category A: Supportive literature. Randomized controlled trials report statistically significant ($p < .01$) differences between clinical interventions for a specified clinical outcome.

Level 1: The literature contains multiple randomized controlled trials, and the aggregated findings are supported by meta-analysis.

Level 2: The literature contains multiple randomized controlled trials, but there is an insufficient number of studies to conduct a viable meta-analysis for the purpose of this advisory.

Level 3: The literature contains a single randomized controlled trial.

Category B: Suggestive literature. Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: The literature contains observational comparisons (e.g., cohort, case-control research designs) of two or more clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome.

Level 2: The literature contains noncomparative observational studies with associative (e.g., relative risk, correlation) or descriptive statistics.

Level 3: The literature contains case reports.

Category C: Equivocal literature. The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: Meta-analysis did not find significant differences among groups or conditions.

Level 2: There is an insufficient number of studies to conduct meta-analysis, and 1) randomized controlled trials have not found significant differences among groups or conditions, or 2) randomized controlled trials report inconsistent findings.

Level 3: Observational studies report inconsistent findings or do not permit inference of beneficial or harmful relationships.

Category D: Insufficient evidence from literature. The lack of scientific evidence in the literature is described by the following terms.

Silent: No identified studies address the specified relationships among interventions and outcomes.

Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes. The literature either does not meet the criteria for content as defined in the 'Focus' of the Advisory or does not permit a clear interpretation of findings owing to methodologic concerns (e.g., confounding in study design or implementation).

Opinion-Based Evidence: All opinion-based evidence relevant to each topic (e.g., survey data, open forum testimony, internet-based comments, letters, editorials) is considered in the development of this advisory. However, only the findings obtained from formal surveys are reported.

Category A: Expert opinion.

Category B: Membership opinion.

Category C: Informal opinion. Open-forum testimony, internet-based comments, letters, and editorials are all informally evaluated and discussed during the development of the advisory. When warranted, the task force may add educational information or cautionary notes based on this information.

Step 4: To obtain opinion-based data, the panel developed an ASPMN membership survey to conduct a practice analysis of assessment and monitoring practices for opioid-induced sedation and respiratory depression. The on-line survey was launched with the ASPMN membership in January 2009 and closed at the end of February 2009. Survey results will be reviewed in a separate upcoming publication.

Step 5: Given the multiple grading systems available for appraising the strength of evidence, the panel decided to use the ASA evidence categories as outlined in Table 1. This evidence-rating system had been used by the ASA task force for their report on fires in the operating room (Caplan, Barker, Connis, et al., 2008) and subsequently for the Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration (Horlocker, Burton, Connis, Hughes, Nickinovich, et al., 2009). Findings from meta-analyses, systematic reviews, RCTs, clinical trials, and non-experimental studies (observational cohort studies and case reports) were evaluated, summarized, and assigned a scientific rating with the ASA evidence categories. Panel members in subgroups made initial scientific ratings of research and then conveyed their findings to the rest of the panelists during telephone conferences and face-to-face meetings at the annual 2009 and 2010 ASPMN conferences. Disagreements as to the quality of evidence were resolved through reevaluation of studies and consensus building. By September 2010, the expert panel had summarized the strength of evidence and formulated preliminary recommendations. Scientific ratings within each subgroup category are reported for some, but not all, of the literature retrieved, reviewed, and reported. Results from isolated studies and information from clinical reviews are cited throughout this report to support scientific summaries and recommendations put forth by the expert panel. A glossary of terms is provided in Appendix A (available online at www.painmanagementnursing.org).

Interpreting Scientific Ratings

When it was possible, scientific ratings according to the ASA evidence categories were assigned to specific literature content areas for each of the category sections for compiling evidence relevant to opioid-induced sedation and respiratory depression: Individual Risks, Iatrogenic Risks, and Pharmacology. It is important to note that the strength of scientific evidence reported for specific categories for research is based on the evaluation of evidence for adverse events and monitoring practices, not the efficacy or effectiveness of treatment interventions. The last section of this report summarizes the literature related to monitoring. It was not possible for panel members to assign evidence ratings for relevant research in that area.

Recommendations by the ASPMN Expert Consensus Panel for Monitoring of Opioid-Induced Sedation and Respiratory Depression

Recommendations put forth at this time are compiled from scientific literature (e.g., meta-analyses, systematic reviews, RCTs, and quasi- and nonexperimental studies), state of the practice, published evidence-based guidelines, and consensus-based opinions of the ASPMN Expert Consensus Panel. These recommendations should be carefully evaluated and interpreted for their applicability to patient populations and practice settings in the context of institutional policies and procedures, state boards of nursing scope of practice, regulations and mandates, existing standards promulgated by other professional organizations, advances in technology, and new scientific information. All recommendations have been subjected to an extensive external peer review process and public commentary to ensure their accuracy, completeness, and relevance to practice. The names and affiliations for external reviewers are provided in Appendix B (available online at www.painmanagementnursing.org).

Recommendations were developed within each of the four categories (Individual Risks, Iatrogenic Risks, Pharmacology, and Monitoring) based on appraisal and grading of the scientific evidence and applications to practice. To assist with prioritizing the strength and importance of the recommendations, the ASPMN Consensus Panel used procedures and criteria described in the Methodologies and Policies from the ACCF/AHA Task Force on Practice Guidelines (American College of Cardiology Foundation and American Heart Association, 2010). The ACCF/AHA process for writing recommendations includes the assignment of the recommendation to a classification representing its strength. The strength of the recommendations is based on the strength of the scientific evidence and the benefit/risk ratio assigned by the expert panel members using their knowledge and clinical experience. Recommendations were written using terms that denote the strength of evidence, consensus, or opinion as determined by the ASPMN panel experts. The classifications include (American College of Cardiology Foundation and American Heart Association, 2010):

- Class I.** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective: *Benefit >>> Risk.*
- Class II.** Conditions for which there is conflicting evidence and/or a divergence of opinion about

the usefulness/efficacy of a procedure or treatment.

Class IIa. Weight of evidence/opinion is in favor of usefulness/efficacy: *Benefit* >> *Risk*.

Class IIb. Usefulness/efficacy is less well established by evidence/opinion: *Benefit* \geq *Risk*.

Class III. Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful: *Risk* \geq *Benefit*.

STATEMENT OF CONDITIONS

This report is aligned with ASPMN's mission and goals to promote optimal nursing care for people affected by pain through best nursing practices, education, standards, advocacy, and research. (<http://aspmn.org/>) The ASPMN Expert Consensus Panel on Monitoring for Opioid-Induced Sedation and Respiratory Depression recommendations serve as a guide for developing and implementing safe and effective plans of care, facilitating systems-level changes to support safe and effective patient care, and applying scientifically derived and consensus-based statements as the foundations for practice. Recommendations for patient monitoring practices, education, health care systems processes, policies, and procedures put forth at the time of this publication were compiled to reflect the best available evidence and consensus among panel members and were made without pharmaceutical or industry influence. All recommendation statements have been subjected to an extensive external peer review process to ensure their accuracy, completeness, and relevance to practice.

INDIVIDUAL RISKS

Definition

Individual risks are defined as factors that predispose a person to unintended opioid-induced advancing sedation and respiratory depression. These factors include but are not limited to age, anatomic anomalies, physical characteristics, primary and comorbid medical conditions, psychologic states, and functional status. Identification of patients at risk for adverse events when opioid analgesics are administered for pain management is a critical consideration when developing plans of care to ensure patient safety.

Search Strategies

An extensive review of relevant literature was performed in Medline. Figure 1 shows the number of abstracts, the categories related to risk assessment, and

the final primary citations retained for the purposes of this report. From two systematic reviews, secondary references were identified that did not appear in the database search (Gross, Bachenberg, Benumof, Caplan, Connis, & American Society of Anesthesiologists Task Force on Perioperative Management, 2006; Smetana, Lawrence, Cornell, & American College of Physicians, 2006).

Patient Risk Factors

There is insufficient evidence on the individual characteristics that predispose patients to opioid-induced respiratory depression to provide guidelines for clinical practice (Fig. 2; category D: Insufficient Evidence). Given that preexisting conditions and other patient characteristics are fixed, most studies addressing patient-specific risks involved case-controlled or cohort samples. The highest level of evidence for research examining individual risks for opioid-induced sedation and respiratory depression was category B evidence: Observational Cohort Studies. After compiling the available evidence, two main categories emerged: 1) risk factors for sleep-disordered breathing; and 2) risk factors for postoperative pulmonary complications. Because these categories are physiologically similar, they served as the basis for compiling a summary for the strength of evidence in defining populations most at risk for opioid-induced sedation and respiratory depression.

Risk Factors for Sleep-Disordered Breathing (Category B-1 Evidence). Respiration is most

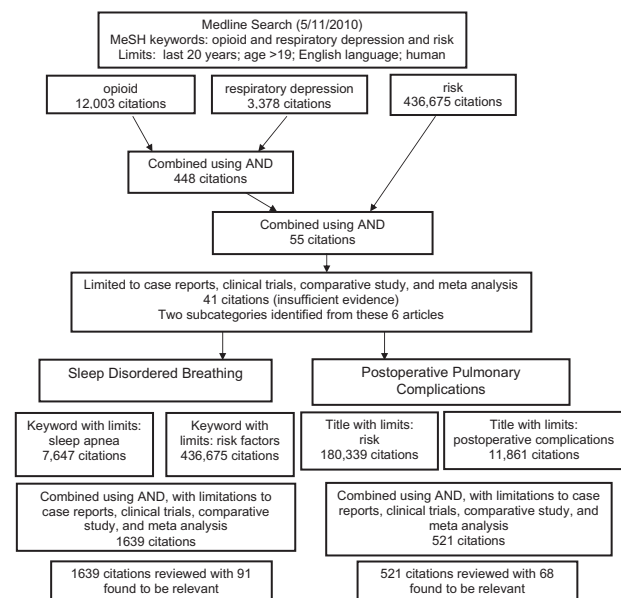


FIGURE 1. ■ Search strategy for individual risk factors.

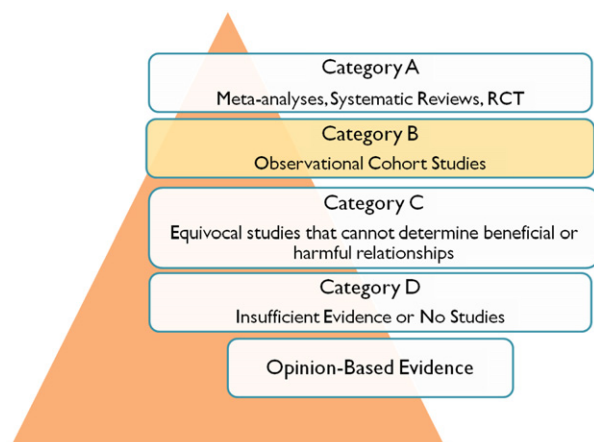


FIGURE 2. ■ Levels of evidence for individual risk factors.

vulnerable during sleep and similarly with sedation, because the protective wake mechanism for airway support and respiratory drive is absent (Hudgel & Devadatta, 1984; Hudgel, Martin, Johnson, & Hill, 1984). Opioids work synergistically with this physiology to suppress respiration during sleep and periods of sedation. Opioids blunt the chemoreceptor response to rising carbon dioxide (CO_2) levels as well as suppress the respiratory centers in the brain.

Sleep-disordered breathing is a term encompassing obstructive sleep apnea (OSA), central sleep apnea (CSA), and upper airway resistance syndrome (American Academy of Sleep Medicine, 2005). The prevalence of OSA is estimated to range between 7% and 14% in adult men and between 2% and 7% in adult women (Bixler, Vgontzas, ten Have, Tyson, & Kales, 1998; Bixler, Vgontzas, Line, ten Have, Rein, et al., 2001). OSA disorder is characterized by recurrent absence of breath for periods of ≥ 10 seconds owing to collapse of the lower posterior pharynx. CSA disorder is the recurrent absence of breath for periods of ≥ 10 seconds owing to the temporary loss of ventilatory effort (White, 2005). Upper airway resistance syndrome is the term used for a lesser form of OSA where only partial airway collapse occurs and snoring is usually present (White, 2005).

Opioids, when given to patients with untreated sleep-disordered breathing increases the occurrence of advancing sedation and respiratory depression (Bernards, Knowlton, Schmidt, DePaso, Lee, et al., 2009; Blake, Yew, Donnan, & Williams, 2009; Mogri, Khan, Grant, & Mador, 2008; Mogri, Desai, Webster, Grant, & Mador, 2009; Ramachandran et al., 2011; Walker, Farney, Rhoneau, Boyle, Valentine, Cloward & Shilling, 2007; Wang, Teichtahl, Drummer, Goodman, Cherry, et al., 2005; Wang & Teichtahl, 2007; Webster, Choi, Desai, Webster, & Grant, 2008). Furthermore, there is evidence

that sleep-disordered breathing is associated with an increased risk of postoperative complications (Chung, Yuan, & Chung, 2008; Hwang, Shakir, Limann, Sison, Kalra, et al., 2008).

Predictors of OSA include obesity (waist-to-hip ratio >1 in adult men and >0.85 in adult women), male gender, age >55 years, body mass index (BMI) $>30 \text{ kg/m}^2$, snoring, witnessed episodes of apnea, excessive daytime sleepiness, and hypertension (BaHammam, Alrajeh, Al-Jahdali, & BinSaeed, 2008; Bixler et al., 2001; Flemons, Whitelaw, Brant, & Remmers, 1994; Genta, Marcondes, Danzi, & Lorenzi-Filho, 2008; Guilleminault & Bassiri, 2005; Hiestand, Britz, Goldman, & Phillips, 2006; Hora, Napolis, Daltro, Kodaira, Tufik, et al., 2007; Ibrahim, Almohammed, Allangawi, Sattar, Mobayed, et al., 2007; Li, Powell, Kushida, Riley, Adornato, & Guilleminault, 1999; Martinez-Rivera, Abad, Fiz, Rios, & Morera, 2008; Mihaere, Harris, Gander, Reid, Purdie, et al., 2009; Moreno, Carvalho, Lorenzi, Matuzaki, Prezotti, et al., 2004; Netzer, Stoohs, Netzer, Clark, & Strohl, 1999; Ohta, Okada, Kawakami, Suetsugu, & Kuriyama, 1993; Quintana-Gallego, Carmona-Beernal, Capote, Sanchez-Armengol, et al., 2004; Sharma, Vasudev, Sinha, Banga, Pandey, et al., 2006; Tan, Khoo, Low, Wong, Theng, et al., 1999; Young, Shahar, Nieto, Redline, Newman, et al., 2002). Physical anomalies in an adult that increase the likelihood of having OSA are cricoid space of $\leq 1.5 \text{ cm}$ (retrognathia), Mallampati class $>II$, and $>17.5 \text{ inch}$ neck circumference (Heuss, Schnieper, Drewe, Pflimlin, & Beglinger, 2003; Tsai, Remmers, Brant, Flemons, Davies, & MacCarthur, 2003). A useful tool developed specifically for risk assessment of sleep-disordered breathing and screening for OSA in the preoperative setting is the Stop-Bang questionnaire, which requires evaluation of snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck size, and gender. A review of this instrument along with others used for this purpose has been published elsewhere (Chung, Abrishami, & Khajehdehi, 2010).

Risk factors for the development of CSA include medical conditions that affect the cardiac and respiratory systems, medications that depress the central nervous system (CNS), and age >65 years (Rupprecht, Hutschenreuther, Brehm, Figulla, Witte & Schwab, 2008; Strassburg, Majunke, Notges, Ortak, Kothe, et al., 2008; Szollosi, Thompson, Krum, Kaye, & Naughton, 2008; Wang & Teichtahl, 2007). Additionally, CSA events may occur as a result of obstructive apnea events or at transitions between sleep stages (Wang & Teichtahl, 2007; Webster et al., 2008).

Risk Factors for Postoperative Pulmonary Complications (Category B-1 Evidence). Predictors of pulmonary complications during the

postoperative period can be grouped into four categories: 1) individual characteristics (i.e., age and general state of health); 2) presence of certain disease states; 3) type of anesthesia; and 4) type of surgical procedure (Arozullah, Daley, Henderson, & Khuri, 2000; Lai, Lai, Wang, Lee, Ling, et al., 2007; Reilly, McNeely, Doerner, Greenberg, Staiger, et al., 1999; Wolters, Wolf, Stutzer, & Schroder, 1996). Table 2 lists specific factors that may contribute to respiratory problems following surgery, and should be considered in determining a patient's risk.

Individual Characteristics (Category B-1 Evidence)

Age. There is limited but compelling evidence that older age (>65 years) is associated with a greater risk for opioid-induced adverse events, including respiratory depression. A reduction in total body water and fat-free mass, worsening tissue perfusion, reduced creatinine clearance, and numerous other changes that occur with aging can alter the pharmacokinetics and pharmacodynamics of medications and render older adults more sensitive to the effects of opioid

analgesics (Aubrun & Marmion, 2007; Aubrun & French Society of Anesthesia and Resuscitation, 2009; Mann, Pouzeratte, & Eledjam, 2003).

In a retrospective secondary analysis of outcomes data from a sample of >8,000 patients receiving short-term opioid therapy, the risk of respiratory depression increased substantially in individuals >60 years of age (Cepeda, Farrar, Baumgarten, Boston, Carr, & Strom, 2003). Odds ratios in this analysis revealed that patients between the ages of 61 and 70 years of age were 2.8 times more likely to develop respiratory depression; those 71-80 years old were 5.4 times more likely; and, those ≥ 80 years old had 8.7 times the risk. An evaluation of a small cohort of 62 postoperative patients also found that older age (≥ 65 years) was associated with respiratory depression (Taylor, Kirton, Staff, & Kozol, 2005).

Clearly, the combination of age with other risk factors must be considered when determining risk for respiratory depression with opioid therapy. An extensive review of the influence of age with coexisting chronic obstructive pulmonary disease (COPD) on respiratory depression documents the need for greater vigilance in

TABLE 2.
Risk Factors for Opioid-Induced Respiratory Depression

Patient may have one or more of the following to be considered high risk:

Age >55 years

Obesity (e.g., body mass index ≥ 30 kg/m²)

Untreated obstructive sleep apnea

History of snoring or witnessed apneas

Excessive daytime sleepiness

Retrognathia

Neck circumference >17.5"

Preexisting pulmonary/cardiac disease or dysfunction, e.g., chronic obstructive pulmonary disease, congestive heart failure

Major organ failure (albumin level <30 g/L and/or blood urea nitrogen >30 mg/dL)

Dependent functional status (unable to walk 4 blocks or 2 sets of stairs or requiring assistance with ambulation)

Smoker (>20 pack-years)

American Society of Anesthesiologists patient status classification 3-5

Increased opioid dose requirement

Opioid-naïve patients who require a high dose of opioid in short period of time, e.g., 10 mg IV morphine or equivalent in postanesthesia care unit (PACU)

Opioid-tolerant patients who are given a significant amount of opioid in addition to their usual amount, such as the patient who takes an opioid analgesic before surgery for persistent pain and receives several IV opioid bolus doses in the PACU followed by high-dose IV patient-controlled analgesia (PCA) for ongoing acute postoperative pain

First 24 hours of opioid therapy (e.g., first 24 hours after surgery is a high-risk period for surgical patients)

Pain is controlled after a period of poor control

Prolonged surgery (>2 hours)

Thoracic and other large incisions that may interfere with adequate ventilation

Concomitant administration of sedating agents, such as benzodiazepines or antihistamines

Large single-bolus techniques, e.g., single-injection neuraxial morphine

Continuous opioid infusion in opioid-naïve patients, e.g., IV PCA with basal rate

Naloxone administration: Patients who are given naloxone for clinically significant respiratory depression are at risk for repeated respiratory depression

monitoring older patients who are at greatest risk for serious consequences if respiratory function is compromised from anesthesia and postoperative analgesia (Gruber & Tschernko, 2003).

There is substantial evidence that patients aged >50 years are at added risk of pulmonary complications in the postoperative setting (Arozullah, Conde, & Lawrence, 2003; Arozullah, Khuri, Henderson, Daley, & Participants in the National Veterans Affairs Surgical Quality Improvement Program, 2001; Hulzebos, van Meeteren, de Bie, Dagnelie, & Helders, 2003; Johnson, Arozullah, Neumayer, Henderson, Hosokawa, & Kuri, 2007; Pereira, Fernandes, da Silva Ancao, de Araujo Pereres, Atallah, & Faresin, 1999; Sogame, Vidotto, Jardim, & Faresin, 2008). This finding compounds the possibility of an adverse opioid-induced respiratory event in older adults.

General State of Health. An individual's general state of health is inclusive of level of physical function as well as physiologic renal and hepatic function. A study of 600 community-based individuals undergoing perioperative evaluation reported that those who could not walk four blocks and climb two flights of stairs were 1.94 times more likely to develop a postoperative complication than those who could (Reilly et al., 1999). In another large cohort study ($n = 81,719$), patients who were partially dependent (required assistance with ambulation) were 1.5 times more likely to experience a postoperative complication, such as pneumonia, pulmonary edema, sepsis or cardiac arrest, than patients who were independent with activities of daily living (Arozullah et al., 2000; Reilly et al., 1999). This risk increased to 2.24 in patients who were totally dependent for function.

Optimal physiologic hepatic and renal function are critical for effective metabolism and excretion of anesthetic agents and medications. Patients with high preoperative blood urea nitrogen levels (>30 mg/dL) have been found to be 2.09 times more likely to experience a postoperative complication compared with patients with levels ≤ 20 (Arozullah et al., 2000). Nutritional status and hepatic function are also predictive of postoperative risk. Patients with albumin levels <30 g/L were 2.16 times more likely to experience a complication than those with albumin levels >40 g/L (Arozullah et al., 2000; Johnson et al., 2007).

Presence of Disease States

The ASA classification of general health status was introduced in 1941 and revised in 1963 (Table 3). The instrument is a surrogate representing the patient's underlying severity of illness and reflects both survival and health-related quality of life. It has been shown to

be more useful than history alone for predicting patient outcome (Rogers, Kenyon, Lowe, Grant, & Dempsey, 2005). There have been several studies to validate this instrument as a screening tool for predicting operative risk (Albarran, Simoens, van de Winkel, da Costa, & Thill, 2009; Brouquet, Cudennec, Benoist, Moulias, Beauchet, et al., 2010; Chida, Ono, Hoshikawa, & Kondo, 2008; Johnson et al., 2007; Peersman, Laskin, Davis, Peterson, & Richart, 2008; Sanjay, Jones, & Woodward, 2006; Skaga, Eken, Sovik, Jones, & Steen, 2007; Wolters et al., 1996). Operative risk, according to the developers of the ASA classification, is defined as any morbidity or mortality resulting from a surgical procedure. Patients who are classified as class IV are 4.26 times more likely to develop a postoperative cardiac or pulmonary complication than patients who are classified as class I (Wolters et al., 1996). Although this instrument is well validated in predicting operative risk, there is not strong evidence supporting its use as a sole tool for predicting risk of opioid-induced respiratory depression.

As already mentioned, the presence of pulmonary disease significantly raises the likelihood of pulmonary complications in the postoperative setting (Arozullah et al., 2000; Arozullah et al., 2003; Jensen & Yang, 2007; Kanat, Golcuk, Teke, & Golcuk, 2007; Lai et al., 2007; Mistiaen & Vissers, 2008; Ozdilekcan, Songur, Berktaş, Dinc, Ucgul, & Ok, 2004; Pereira et al., 1999; Sogame et al., 2008; Taylor et al., 2005). Patients with a history of COPD, characterized by functional disability, hospitalization in the past year, routine use of bronchodilator therapy, or an 1-minute forced expiratory volume $<75\%$ of predicted, were found to be 1.58 times more likely to experience postoperative respiratory failure than those with normal pulmonary function (Arozullah et al., 2000; Johnson et al., 2007).

History of heart failure also significantly increases the risk of postoperative pulmonary complications (Johnson et al., 2007; Mistiaen & Vissers, 2008; Reilly et al., 1999). Risk for developing a postoperative pulmonary complication, such as respiratory failure, pneumonia, or atelectasis, was increased in patients undergoing aortic valve replacement with a history of heart failure (4.7 times), previous pacemaker implant (4.4 times), or COPD (1.7 times) (Mistiaen & Vissers, 2008). Congestive heart failure, cardiac dysrhythmia, coronary artery disease, as well as postoperative acute renal failure, OSA, and hypertension were found to be significantly associated with sudden-onset, life-threatening critical respiratory events during opioid analgesia therapy for postoperative pain (Ramachandran, Haider, Saran, Mathis, Morris, & O'Reilly, 2011).

Current smoking or a history of smoking is another risk factor for postoperative pulmonary

TABLE 3.
American Society of Anesthesiologists Classification

Class I	Normal healthy
Class II	Patient with mild systemic disease
Class III	Patient with severe systemic disease
Class IV	Patient with severe systemic disease that is a threat to life
Class V	Morbid patient who is not expected to survive without the operation
Class VI	A declared brain-dead patient whose organs are being removed for donor purposes

complications (Brooks-Brunn, 2000; Johnson et al., 2007; McCulloch, Jensen, Girod, Tsue, & Weymuller, 1997; Pereira et al., 1999; Reilly et al., 1999). Smoking ≥ 20 pack-years more than doubles (2.13 \times) the risk of a serious perioperative pulmonary complication (Brooks-Brunn, 2000; Reilly et al., 1999; Scholes, Browning, Sztendur, & Denehy, 2009). An encouraging finding is that smoking cessation 3-8 weeks before surgery decreases the risk of postoperative complications (Mason, Subramanian, Nowicki, Grab, Murthy, et al., 2009; Tonnesen, Nielsen, Lauritzen, & Moller, 2009).

Type of Anesthesia

Major categories that have been studied for risk for postoperative pulmonary complications related to anesthesia include general anesthesia versus spinal anesthesia, length of surgery, and emergent surgery. Patients receiving general anesthesia are reported to be 1.9 times more likely to suffer postoperative pulmonary complications than patients undergoing spinal anesthesia (Arozullah et al., 2000; Johnson et al., 2007). The risk of pulmonary complications also increases as the duration of general anesthesia increases. One prospective study of 95 cancer patients undergoing surgery found that every additional hour of general anesthesia duration placed patients at 1.7 times higher risk for pulmonary complications, such as bronchospasm and atelectasis (Ozdilekcan et al., 2004). The most significant increase in risk occurs after 210 minutes of general anesthesia (Ozdilekcan et al., 2004; Pereira et al., 1999; Sogame et al., 2008). Patients undergoing emergency surgery were found to be 2.8 times more likely to experience postoperative respiratory failure (Arozullah et al., 2000).

Type of Surgical Procedure

The type of surgical procedure is an independent risk factor for postoperative respiratory failure. Patients who undergo abdominal aortic aneurysm repair are 11 times more likely to experience respiratory failure than patients who undergo surgery on the ears, nose, throat, mouth, lower abdomen, extremity, spine, or back (Arozullah et al., 2000; Johnson et al., 2007;

Reilly et al., 1999). Similar results were reported for patients undergoing thoracic surgery (5.9 times), peripheral vascular surgery (3.4 times), upper abdomen (3.3 times), neurosurgery (2.9 times), and neck (2.1 times) (Arozullah et al., 2000; Johnson et al., 2007; Reilly et al., 1999).

The location and size of incision can predict postoperative pulmonary complications. An incision that extends from above to below the umbilicus is more likely to be associated with postoperative pulmonary complications (Brooks-Brunn, 2000). Patients undergoing bariatric surgery are also at high risk of postoperative hypoxemia (Gallagher, Haines, Osterlund, Mullen, & Downs, 2010; Gallagher, Haines, Osterlund, Murr, & Downs, 2010).

Summary of Evidence

Evidence of individual characteristics that predispose patients to opioid-induced respiratory depression is insufficient (category D evidence: Insufficient Evidence) to provide guidelines for clinical practice. There is, however, sufficient evidence of individual risk for sleep-disordered breathing and pulmonary complications (e.g., atelectasis, pneumonia, and respiratory failure) in the postoperative setting, and opioid administration may increase the frequency or severity of these conditions. Therefore, the practice guidelines were developed from these two related bodies of evidence (Table 2). Although accepted pain guidelines (American Pain Society, 2008) state that opioid-naive individuals (i.e., those who are not taking regular daily doses of opioids) are at higher risk for opioid-induced respiratory depression than individuals who are opioid tolerant, no research comparing the two states for incidence of respiratory depression could be found. Consideration should be given to the severity and number of risk factors present.

Recommendation Statements

Recommendations for Identifying and Communicating Individual Risk for Opioid-Induced Respiratory Depression

1. Comprehensive preadmission, admission and preoperative therapy assessments *are recommended* to

identify and document existing conditions, disease states, and other factors that may place patients at risk for unintended advancing sedation and respiratory depression with opioid therapy. Class I

- A. Risk factors may include but are not limited to: age >55 years, preexisting pulmonary disease (e.g., COPD), known or suspected sleep-disordered breathing problems, anatomic oral or airway abnormalities, and comorbidities (systemic disease, renal or hepatic impairment), or presurgical or preprocedural ASA status >2.
 - B. Preoperative ASA Physical Status Classification System category status assigned by the anesthesia provider (anesthesiologist or certified registered nurse anesthetist) is an important factor in determining level of care following surgery.
 - C. Interpretation of evidence-based assessment criteria/tools can be useful in determining patient risk status (e.g., results of sleep studies, history of witnessed apneas, and the Stop-Bang questionnaire).
 - D. Develop medical record forms that include risk assessment criteria and/or information to facilitate documentation.
2. Nurses **should** communicate all pertinent information regarding patients' risk during shift report and across all transitions in care from pre-hospitalization to discharge to ensure that health care providers are informed of potential risks for unintended advancing sedation and respiratory depression with opioid therapy. Class I
 - A. Including information about a patient's potential risk for adverse effects from opioids during all levels of hand-offs of care helps to promote high-quality and safe patient care.
 - B. Nurses can act as advocates to also ensure that patients are informed and educated about any risk factors that they may have, actual problems with opioid therapy that they may have experienced during hospitalization, and current or future implications for specific interventions for respiratory care or diagnostic evaluations.
 3. It **is reasonable** that organizations develop and implement policies and procedures that define the scope of patient risk assessment practices, requirements for documentation, standards of care, and accountability of health care providers for ensuring safe patient care with opioid therapy. Class IIa
 4. Information obtained from patient assessments and available clinical information **should be used** to formulate individualized plans of care for the level, frequency, and intensity of patient monitoring of sedation and respiratory status during opioid therapy. Class I
 - A. Nurses must be aware of the seriousness of unintended advancing sedation and opioid-induced respiratory depression.
 - B. Individualized plans of care are essential to providing high-quality and safe patient care and

promoting optimal patient outcomes during hospitalization.

5. Mechanisms for oversight and surveillance of practice outcomes with patient risk assessment **can be effective** methods to ensure safe and optimal care of patients receiving opioid therapy. Class IIa

Recommendations for Education.

1. All nurses caring for patients receiving opioid therapy **should be** educated about individual risk factors for opioid-induced unintended advancing sedation and respiratory depression. Class I
 - A. Content for educational programs to prepare nurses for identifying risk factors and formulating effective plans of care for monitoring patients receiving opioids should include: pertinent information for health histories, pathophysiology and clinical features for risk factors, evidence-based assessment criteria and tools for assessing risks, and requirements for documentation and communication of risk factors.
 - B. Competency-based education should be considered to ensure learning and application of knowledge for risk assessment.
2. Education through attendance and participation at pain professional organization and society meetings, on-line and publication continuing education programs, and interprofessional organization-sponsored education and case-based learning **might be considered** to augment educational opportunities for nurses. Class IIb
3. Published evidence-based guidelines and standards from professional organizations addressing risk assessment for opioid-induced sedation and respiratory depression **should be** available as resources to guide practice. Class I

Implementation Strategies

1. Establish policies and procedures that define and guide practice for nurses and their responsibilities to assess, document, and communicate risk factors for opioid-induced sedation and respiratory depression.
2. Evaluate appropriate resources to assist nurses in conducting risk assessments for opioid-induced sedation and respiratory depression and facilitating documentation and communication.
3. Implement policies and procedures regarding the organization's position on the use of home equipment, such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), while in the hospital.
4. Implement practices to assure that all patients are assessed or evaluated for safe respiratory care (e.g., need for CPAP or BiPAP) given their risk status.

IATROGENIC RISKS

Definition

Iatrogenic risks are defined as pain therapy-related variables, environmental factors, and circumstances in the hospital workplace that may predispose a patient to increased risk for unintended advancing sedation or respiratory depression. Methods of opioid administration and nurse practice variables, such as staffing and communication, are of greatest concern.

Search Strategies

Three separate searches of Medline and PubMed databases were performed to identify relevant publications in the past 20 years. Searches were limited to adult human populations, publications in English, and clinical trials, RCTs, meta-analyses, guidelines, and reviews. Case reports were excluded from the search. Key search terms and MeSH keywords included: PCA, epidural, regional anesthesia, respiratory depression, opioid (opioid OR morphine OR hydromorphone OR fentanyl), naloxone, nurse education, nurse staffing, patient mortality, and failure to rescue. Figures 3-5 show the breakdown of the articles that were retrieved and examined. Searches were consolidated to include only those studies that related to adults in the acute noncritical care setting. A secondary search was conducted of studies that were found in the reference lists of the studies identified and reviewed from the initial search.

Owing to the lack of evidence, it was not possible to evaluate the association between opioid-induced sedation and respiratory depression and nursing practice, nursing staffing, and communication (e.g., nurse-to-nurse and interprofessional). Research, however, has demonstrated a relationship between optimal nurse-to-patient ratios and a decrease in "failure to rescue" rates (Aiken, Clarke, Cheung, Sloane, & Silber, 2003; Aiken, Clarke, Sloane, Lake, & Cheney, 2008, 2009; Aiken, Clarke, Sloane, Sochalski, & Silber, 2002; Friese, Lake, Aiken, Silber, Sochalski, 2008; Kutney-Lee & Aiken, 2008). This body of research serves as the basis for formulating recommendations on the minimal standards for nurse staffing and modifications in the workplace to sustain an environment for patient safety.

Iatrogenic Risks with Pain Treatment Modalities

Neuraxial Therapy. The term neuraxial pain therapy refers to the delivery of medications (e.g., opioids and local anesthetics) into the subarachnoid or epidural compartments. As mentioned earlier, the ASA Task Force on Neuraxial Opioids published evidence-based

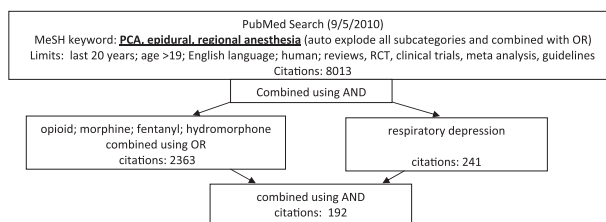


FIGURE 3. ■ Search strategy for iatrogenic risk - mode of delivery.

recommendations and guidelines for the care of patients receiving neuraxial therapy in 2009 (Horlocker, Burton, Connis, Hughes, Nickinovich, et al.) (category C-1 evidence). In that document, the ASA task force compared the risk of respiratory depression during neuraxial therapy with the risk during parenteral therapy (IV, intramuscular [IM], or subcutaneous) and found the risk to be similar for parenteral opioid administration, single-injection neuraxial opioid administration, and extended-release epidural morphine (EREM; category C-2 evidence). One meta-analysis of three RCTs indicated that EREM was much more likely to cause respiratory depression (odds ratio 5.80; 95% CI 1.05-31.93; $p = .04$) compared with IV PCA (Sumida, Lesley, Hanna, Murphy, Kumar, & Wu, 2009) (category A-1 evidence).

Although treatment efficacy appears to be similar between intracerebroventricular opioid administration and epidural opioid administration, the former was found to pose a higher risk for respiratory depression in cancer populations (Ballantyne & Carwood, 2005). Multiple RCTs have demonstrated that the risk for respiratory depression is less with continuous epidural opioid infusion than with parenteral opioid administration (Horlocker et al., 2009) (category A-1 evidence). The ASA Task Force provides guidelines for monitoring and recommends that the frequency of monitoring for all forms of neuraxial opioid delivery "should be dictated by the patient's overall clinical condition and concurrent medications" (Horlocker et al., 2009, p. 222). Thus far, the ASA guideline presents the most comprehensive review and grading of the strength of

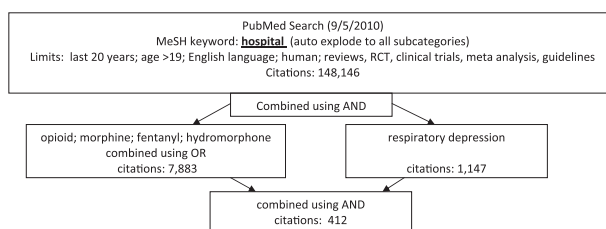


FIGURE 4. ■ Search strategy for iatrogenic risk - opioid and respiratory depression.

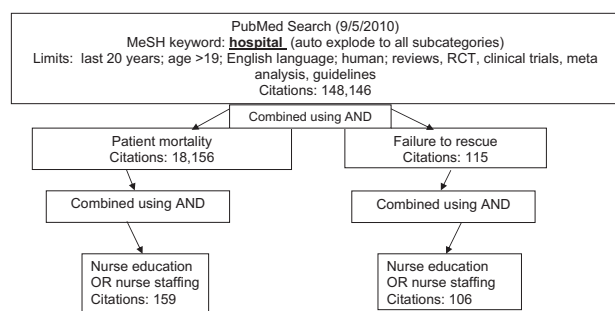


FIGURE 5. ■ Search strategy for iatrogenic risk - hospital and nurse.

evidence related to risks for respiratory depression with neuraxial therapies, and therefore it served as the basis for recommendations by the ASPMN Consensus Panel on Monitoring for Opioid-Induced Sedation and Respiratory Depression.

Supplemental Opioids with Peripheral Local Anesthetic Infusions (Category A-2 Evidence). To date, there are no compelling data to calculate the risk for respiratory depression associated with supplemental opioid administration in conjunction with local anesthetic delivery via continuous peripheral nerve block and continuous local wound infusions (Liu & Wu, 2007). However, data do suggest that there are clinical benefits in terms of pain control associated with administering supplemental opioids with these therapies (Liu & Wu, 2007).

Parenteral, Subcutaneous, and Patient-Controlled Analgesia (Category A-1 Evidence). Although there is a lack of evidence on the oral route of administration, there is strong evidence to document that the risk of respiratory depression is similar among other systemic routes and methods of opioid administration. A meta-analysis of 55 studies involving 2,023 patients receiving IV PCA and 1,838 patients managed with conventional parenteral “as-needed” opioid medication found the risk of adverse respiratory events to be similar between IV PCA and nurse-administered IV opioids on the patient’s request (Hudcova, McNichol, Quah, Lau, Carr, 2006). Another meta-analysis ($n = 165$) conducted by Cashman and Dolin (2004) found considerable variation among studies regarding how respiratory depression was defined. Nonetheless, those investigators quantified the incidence of respiratory depression for three analgesic methods of opioid administration: epidural analgesia, IV PCA, and intermittent IM injections. Estimates for the overall mean incidence of respiratory depression for these three methods were: 0.3% (95% CI 0.1%-1.3%) when defined by naloxone requirement; 1.1% (95% CI 0.7%-1.7%) when defined by hypoventilation; 3.3% (95% CI 1.4%-7.6%) when defined by hypercarbia; and

17.0% (95% CI 10.2%-26.9%) when defined by oxygen desaturation (Cashman & Dolin, 2004). The incidence of respiratory depression, as defined by hypoventilation and oxygen desaturation, following IM opioid administration was 0.8%-37.0%, which represented the widest range for incidence among the various methods. The ranges for incidence with IV PCA and epidural analgesia were 1.2%-11.5% and 1.1%-15.1%, respectively.

Factors associated with an increased risk for respiratory events during IV PCA include the use of a basal rate, rapid dose escalations, and patient-specific variables, such as older age, type of surgery, and unauthorized activation of the PCA device by staff or family (Fleming & Coombs, 2006; Sidebotham, Dijkhuizen, & Schug, 1997) (category B-2 evidence). In a retrospective case-controlled review, Rapp, Ready, and Nessly (1995) found an association between higher IV PCA consumption and increased sedation in opioid-tolerant patients.

A meta-analysis of 14 RCTs determined the risk for respiratory depression with a basal rate to be 4.68 times greater compared with IV PCA demand dosing without a basal rate (George, Lin, Hanna, Murphy, Kumar, Ko, & Wu, 2010). A two-step pharmacokinetic simulation study characterizing IV PCA morphine use patterns in ten postoperative patients compared PCA with no basal rate (control) and basal rates of 0.5 mg/h, 1 mg/h, and 2 mg/h and found that peak morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) increased as the basal infusion of morphine increased, with the peak effect-site concentration greatest at 8-24 hours after the start of the basal rate (Sam, MacKey, Lötsch, & Drover, 2010). The lowest peak was with no basal rate and highest was with 2 mg/h. Furthermore, the simulated morphine, M6G, and M3G effect-site pharmacokinetic profiles remained elevated after peak concentrations in the 2 mg/h group, indicating that this dose was associated with the highest risk for respiratory depression. This would be of particular concern in any patient (e.g., postoperative) whose pain trajectory was decreasing while the levels of opioid are sustained by a continuous opioid infusion. Caution should be exercised with the use of basal rates or continuous infusions, particularly with rapid dose escalation practices.

Coadministration of Antihistamines (Category D Evidence: Insufficient Evidence). Although case reports describe the addition of antihistamines to opioid regimens in the postoperative setting, the risk of excessive sedation and respiratory depression as well as constipation and urinary retention increases (Anwari & Iqbal, 2003). Unfortunately, this phenomenon has not been systematically investigated.

Coadministration of Benzodiazepines (Category D Evidence: Insufficient Evidence). The coadministration of benzodiazepines with opioid analgesia carries a significant risk for diminishing respiratory drive secondary to its potential to produce sedation. The evaluation of studies using benzodiazepines in the perioperative setting was beyond the scope of the present scientific review; however, the American Hospital Formulary Service (AHFS) Drug Information Manual (2009) warns that the CNS-depressant effect of benzodiazepines can result in diminished respiratory drive or apnea, particularly with IV administration. CNS depression may be additive and occur when benzodiazepines are used concomitantly with any other medications that produce CNS depression, including mu-opioid agonists and partial opioid agonists. Such combinations can lead to excessive sedation, which can result in partial airway obstruction (AHFS, 2009). In a retrospective cohort-controlled review of 10,511 patients undergoing surgery, Gordon and Pellino (2005) found 56 (0.53%) who received naloxone, and those who required naloxone took more CNS depressants than those in the cohort group. When type and amount of CNS depressant were evaluated, the authors found that nine patients in the naloxone group and three patients in the cohort group received benzodiazepines, which made benzodiazepines the only category of agent that approached significance.

Timing as a Predictor for Opioid-Induced Sedation and Respiratory Depression (Categories B-1 and B-2 Evidence). The risk of opioid-induced respiratory depression in postoperative patients is greatest in the first 24 hours after surgery (Ramachandran et al., 2011; Taylor et al., 2005; Thompson, J. S., Baxter, T. M., Allison, J. G., Johnson, F. E., Lee, K. K., Park, W. Y., 2003) and occurs more frequently between the hours of 2300 and 0700, when most patients are sleeping (Schmid-Mazzocchi, Hoffman, Happ, & Devita, 2008). The trajectory for the onset of sedation and respiratory depression after the administration of opioids is highly variable and dependent on patient-specific factors (e.g., sleep/wake state) and the opioid, route of delivery, and dose. Moreover, there are limited data defining the time periods for greatest risk of these adverse events. With IV PCA, for example, levels of sedation warranting concern have been observed within 4 hours after discharge from the postanesthesia care unit (PACU), and the risk for sedation may persist for 24 hours after surgery (Taylor et al., 2003; Taylor et al., 2005). A retrospective observational cohort study designed to identify risk factors for life-threatening critical respiratory events during analgesic therapy for postoperative pain found that 75% of the deaths and 81% of reversible critical respiratory events

occurred within the first 24 hours of opioid therapy and that, typically, the patients had received small doses of opioids, suggesting a role for opioid sensitivity in irreversible events leading to death (Ramachandran et al., 2011). Interpretations of the evidence on when patients are at greatest risk is complicated by various criteria for sedation and respiratory depression, use of sedation scales that have been validated only for assessment during purposeful or procedural sedation (moderate sedation), and timing and duration of assessments across studies of opioid-induced sedation and respiratory depression in hospitalized postoperative patients.

Patient environments that create patient stimulation that can alter arousal also influence the onset of sedation associated with analgesic therapies. Despite the additive effects of opioid analgesia and anesthetic agents in the immediate postoperative period, the rate of respiratory depression was found to be less in the PACU environment than later in the quieter and less stimulating environment of a general care unit (Shapiro, Zohar, Zaslansky, Hoppenstein, Shabat, & Fredman, 2005).

Shapiro et al. (2005) noted a direct correlation between intraoperative fentanyl administration and postoperative respiratory depression in a retrospective review of 1,524 patients receiving IV PCA morphine ($p = .03$) or neuraxial morphine ($p = .05$). The incidence of respiratory depression (defined as <10 breaths/min) occurred in 1.2% of cases in that study, and the time to respiratory depression ranged from 2 to 31 hours from initiation of IV PCA and from 2 to 12 hours from the last dose of neuraxial morphine. Neuraxial therapy with hydrophilic opioids and extended-release morphine may delay respiratory depression for up to 24 hours (Ballantyne, 2002).

A systematic review examined the timing, frequency, and method of pain assessment for nonsurgical populations in an attempt to identify safe practices; however, no evidence was found to link any of these variables to improvements in patient outcomes (Helfand & Freeman, 2009).

Communication (Category B-2 Evidence). Despite recommendations that institutions develop standards for hand-off communication among health care professionals (The Joint Commission, 2010), a limited number of studies have identified criteria and mechanisms of communication that ensure safe practices with transitions of care. A systematic review of hand-off communication identified 15 intervention studies (all of which were conducted without control groups) that demonstrated effective strategies for facilitating hand-off communication (Riesenberg, Leisch, & Cunningham, 2010). These strategies were placed into seven categories: communication skills, standardization strategies, technologic solutions,

environmental strategies, training and education, staff involvement, and leadership. In addition, the literature emphasizes structure and processes for complete, concise, and organized approaches to hand-off communication. Specifically, Sandlin (2007) recommends the Situation, Background, Assessment, and Recommendation (SBAR) method be used to facilitate effective dialogue for report when patients are admitted and discharged from the PACU. Others have also advocated for the SBAR method around transitions of care unrelated to pain management (Carroll, 2006; Haig, Sutton, & Whittington, 2006).

Staffing and Practice Environment (Category B-2 Evidence). There is insufficient evidence to establish specific staffing requirements or standards of practice environment that are universal in preventing opioid-induced adverse events in all settings. In general, staffing factors that decrease the incidence of failure to rescue or iatrogenic mortality and morbidity and/or increase satisfaction with pain management are: lower patient-to-nurse ratios, nursing staff holding bachelor's degrees or higher, higher numbers of RNs on the unit, and more experienced nurses (Aiken, Clarke, Cheung, Sloane, & Silber, 2003; Aiken, Clarke, Sloane, Lake, & Cheney, 2008, 2009; Aiken, Clarke, Sloane, Sochalski, & Silber, 2002; Friese, Lake, Aiken, Silber, Sochalski, 2008; Kutney-Lee & Aiken, 2008; Needleman, Buerhaus, Pankratz, Leibson, Stevens, & Harris, 2011; Schmid-Mazzoccoli et al., 2008; Smith et al., 2007; Thornlow, D. K., & Stukenborg, G., 2006).

Because of insufficient evidence on the topic of staffing related to outcomes of pain management, the ASPMN expert panel is encouraging the alignment of staffing practices with standards promulgated by professional organizations, and use of institution-specific policies and procedures and acuity measures to ensure safe staffing. It is recognized that state mandates for nurse-to-patient ratios take precedence in determining staffing practices. A recent survey of the American Society of PeriAnesthesia Nurses' (ASPAN) members identified that further investigations of safe staffing ratios are among the top priorities for national research agendas (Mamaril, Ross, Poole, Brady, & Clifford, 2009).

Practice environment issues that increase the incidence of adverse events are: units where high patient turnover occurs, settings where procedures are performed on rare occasions, patients placed on units where nurses are unfamiliar with patient care requirements after specific procedures, and nursing-practice environments with poor employee satisfaction and negative relationships with managers and physicians (Schmid-Mazzoccoli et al., 2008; Smith, Elting, Learn, Raut, & Mansfield, 2007; Needleman, Buerhaus, Pankratz, Leibson, Stevens, & Harris, 2011; Friese et al., 2008; Smith, Elting, Learn, Raut, & Mansfield, 2007).

Higher nurse satisfaction, and thus a potential for better outcomes, are associated with better staffing, educational preparation of nurses, opportunities for professional development, and quality management as well as effective managers and leadership and collegial nurse/physician relationships (Aiken et al., 2003; Kane, Shamiyan, Mueller, Duval, & Wilt, 2007; Seago, Williamson, & Atwood, 2006). No significant differences in patient outcomes were found when 8-hour and 12-hour shifts were compared in another study (Stone, Du, Cowek, Amsterdam, Helfrich, et al., 2007).

Pain Team/Service Oversight. There is a paucity of literature measuring the impact of involvement of pain experts in routine clinical care on the incidence and severity of opioid-induced adverse respiratory events. Moreover, there are various interpretations and a lack of consistent operational definitions for what constitutes pain teams, services, and experts. Future research must be done to more precisely evaluate the impact of care delivery by pain teams or services on patient outcomes (Silber, Kennedy, Even-Soshan, Chen, Koziol, et al., 2000; Story, Shelton, Poustie, Colin-Thome, McIntyre, & McNicol, 2006; Werner, Søholm, Rotbøll-Nielson, & Kehlet, 2002). Although system-wide interventions that involve pain-management teams have been shown to improve pain assessment and use of analgesics, there is no compelling evidence that they affect patient outcomes.

Summary of Evidence

Figure 6 represents the evidence categories for all aspects of iatrogenic risk. A comprehensive review of research and related literature has identified numerous variables that influence the risk for opioid-induced sedation and respiratory depression in hospitalized patients. Variables associated with negative outcomes are the use of basal infusion with PCA and/or unauthorized staff or family activation of the PCA dose pendant (PCA by proxy), rapid opioid dose escalation, coadministration of

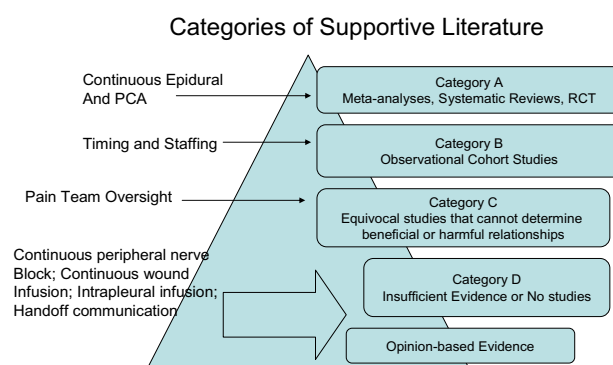


FIGURE 6. ■ Levels of evidence for iatrogenic risk factors.

antihistamines and benzodiazepines, lack of aggressive monitoring of patients at risk during the first 24 hours after surgery and between the hours of 2300 and 0700 (during sleep), and transferring patients to units where nurses are unfamiliar with specific nursing care required for a specific procedure, are less experienced, have less than bachelor's degrees, and/or are fewer in number of RNs. Further research is needed to establish if IV PCA or "as-needed" nurse-delivered opioid analgesia is better at preventing adverse events as well as timing of nursing assessments, the use of pain management teams, and type of communication procedures.

Recommendation Statements

Recommendations for Monitoring

1. Iatrogenic risk assessment and other patient risk factors **should be** considered when determining the intensity and frequency of monitoring for patients receiving opioid analgesia. Class I
2. The duration and intensity of monitoring **should be** continually reevaluated based on potential/actual iatrogenic risks and assessments of response to therapy. Class II

Recommendations for Staffing Practices

1. Safe staffing practices **should be** determined by state boards of nursing regulations and/or mandates, acuity classification systems or criteria, evidence-based staffing guidelines, and staffing guidelines promulgated by professional nursing organizations to adhere to defined standards of care. Class I
2. Consideration of patient complexity and risk for unintended advancing sedation and respiratory depression when determining patient assignment and staffing practices **can be effective** in ensuring quality and safe care. Class II
3. The use of technology **does not** replace the need for systematic nursing assessment and **should not** diminish staffing levels. Class III

Recommendations for Institutional Practice Policies and Procedures

1. Policies and procedures and guidelines **are recommended** to facilitate accurate and complete hand-off communication among all health care professionals during change of shift report and transitions of care. Class IIa
 - A. Effective communication among all health professionals should exist throughout the continuum of care during opioid therapy, because it is essential to the delivery of safe and effective care.
 - B. Documentation forms and tools can be useful in communicating patients' underlying conditions, comorbidities and risk factors, previous use and response to opioid therapy, opioid naïve or tolerant

status, anesthesia history, and current opioid therapy and response.

2. Institutions **should** establish procedures to ensure safe monitoring practices to help prevent opioid-induced adverse events. Class I
3. Institutions **should** establish mechanisms and outline specific directives in practice policies to ensure that unauthorized use of PCA devices or administration does not occur. Class I

Recommendations for Quality of Care

1. Quality improvement and surveillance programs **can be effective** in augmenting procedures for tracking, analyzing, and reporting adverse events related to unintended advancing sedation and respiratory depression from opioid therapy. Class IIa
 - A. Reporting structures and centralized data repositories should be maintained as best practices to monitor pain therapy adverse events, medication errors, and technology failures.
 - B. Tracking the use of reversal agents for opioids (e.g., naloxone) and benzodiazepines (e.g., flumazenil) and Code Blue or Rapid Response Team calls are beneficial in identifying and evaluating episodes of unintended advancing sedation and respiratory depression.
2. Medical record systems and forms **can be effective** in facilitating complete and accurate documentation of patient risks for complications (i.e., unintended advancing sedation and respiratory depression) and tracking ongoing responses to analgesic therapy. Class IIb
3. Institutions **are encouraged** to establish procedures to ensure the availability and consistency of a rapid response to opioid-induced respiratory emergencies 24 hours a day, 7 days a week. Class IIa
4. Quality improvement or performance methodologies, such as root cause analysis, peer reviews, and mortality and morbidity conferences, **are reasonable** approaches to examining sentinel or serious potential/actual events. Class IIa

Implementation Strategies

1. Educate nurses to recognize factors associated with a higher likelihood for adverse events from opioid therapies.
2. Implement population- and institution-specific practice policies and procedures and surveillance to ensure adequate monitoring, safe patient environments, and review of opioid-induced adverse events.
3. Use an interprofessional approach to design patient goals and expected outcomes of institutional efforts for achieving patient safety in opioid therapy.
4. Document and communicate risk for respiratory depression so that information is accessible across the continuum of care.
5. Track opioid-induced respiratory depression events through quality and safety programs such as Code

Blue or Rapid Response Team calls, naloxone administration, and safety events reporting systems.

6. Provide timely feedback to health care professionals regarding quality and patient safety outcomes.
7. Focus efforts for improving care around the four Ps: practice environment, practice policies, practice patterns, and practices for monitoring.
8. Incorporate theoretic and practical knowledge and competency-based learning for monitoring practices, and require education for new employees and ongoing education for existing staff.

PHARMACOLOGY

Definition

For the present review, pharmacology is defined as pharmacologic agents that are administered for the treatment of pain in the acute care setting.

Search Strategies

Medline and the Cochrane Collaboration databases were searched for relevant publications of research with limits for age (>19 years), English language, and human studies from 1990 to year end 2009. MeSH terms used included: opioid, opioid analgesics, morphine, hydromorphone, fentanyl, oxycodone, respiratory depression, sedation, opioid-induced sedation, opioid-induced respiratory depression, opioid-induced side effects, and opioid-induced adverse effects. The term "opioid analgesics" was combined with (AND) respiratory depression, sedation, side effects, adverse effects, acetaminophen, paracetamol, nonsteroidal antiinflammatory drugs (NSAIDs), nonselective NSAIDs, cyclooxygenase (COX) 2 selective NSAIDs, COX-2 inhibitors, anticonvulsants, gabapentin, pregabalin, antidepressants, ketamine, clonidine, and dexmedetomidine.

The search yielded 10,585 citations, which were consolidated to include only citations pertaining to opioid-related sedation or respiratory depression. Citations mentioning opioid adverse effects without reference to sedation or respiratory depression were eliminated, along with all titles that involved children. The review was eventually narrowed to 572 relevant citations that included research studies or clinical reviews. See Figure 7 for the evidence categories for pharmacology and Table 4 for a summary of the evidence for the pharmacologic agents reviewed.

Comparison of Opioid Analgesics (Category C-2 Evidence)

All mu-receptor opioid agonists (morphine-like opioids) can cause sedation and respiratory depression; however, there are a limited number of studies that compare

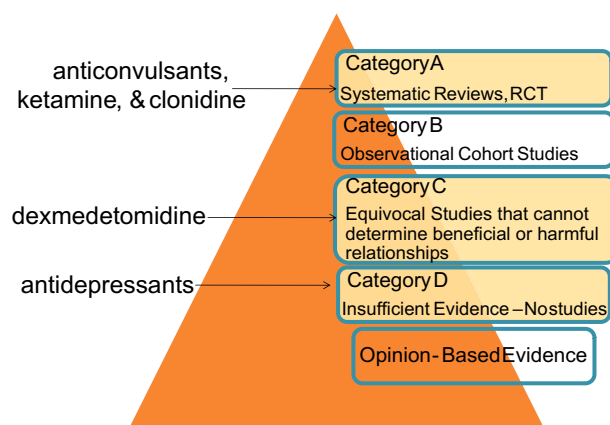


FIGURE 7. ■ Levels of evidence for pharmacological factors.

the incidence of opioid-induced sedation and respiratory depression between or among commonly administered opioid analgesics in the acute care setting. Research that does exist is equivocal regarding these adverse effects. One RCT comparing hydromorphone and morphine administered by a single equipotent IV bolus dose for severe acute pain found no differences in adverse effect profiles between the two medications (Chang, Bijur, Meyer, Kenny, Solorzano, & Gallagher, 2006). None of the patients in either group experienced respiratory rates <12 breaths/min and none required naloxone; however, there was one episode of oxygen desaturation in each group. Another RCT of equipotent doses of remifentanyl and fentanyl administered by IV infusion for postoperative pain reported three episodes of serious respiratory depression in patients who received remifentanyl and none in those who received fentanyl; however, the investigators could not rule out other causes for the episodes (Choi, Koo, Nam, Lee, Kim, et al., 2008). A retrospective review of medical records for patients receiving opioids showed no statistical differences in respiratory depression between morphine, hydromorphone, and fentanyl administered by IV PCA (Hutchison, Chon, Tucker, Gilder, Moss, & Daniel, 2006).

Summary of Classes of Analgesics and Individual Pharmacologic Agents

Acetaminophen (Category A-1 Evidence). Existing research does not show that coadministration of acetaminophen with opioid analgesics for acute pain appreciably reduces opioid-induced sedation and respiratory depression. A meta-analysis of seven RCTs published between 1996 and 2003 ($n = 491$) examined the opioid dose-sparing effects of oral and IV acetaminophen with IV PCA for postoperative pain control, and although acetaminophen was associated with an opioid

dose-sparing effect of 20% (mean -9 mg, 95% CI -15 to -3 mg; $p = .003$) in the first 24 hours, there were no significant effects on the incidence of opioid-related adverse outcomes (Remy, Marret, & Bonnet, 2005). Another meta-analysis of 52 RCTs ($n = 4893$) also observed that acetaminophen added to opioid treatment had no effect on the incidence of sedation and respiratory depression (Elia, Lysakowski, & Tramer, 2005). A systematic review of four meta-analyses involving 118 RCTs ($n = 10,031$) that evaluated postoperative analgesic techniques concluded that data were insufficient to evaluate the effect of acetaminophen alone on reducing any opioid-induced adverse effects (Liu & Wu, 2007a).

Nonsteroidal Antiinflammatory Drugs (Category A-1 Evidence). Well controlled studies are lacking to document the effects of nonselective and COX-2 selective NSAIDs on opioid-induced respiratory depression; however, several meta-analyses support the conclusion that nonselective NSAIDs added to opioid regimens for postoperative pain result in reduced incidence of opioid-induced sedation, likely as the result of diminished need for opioid. A meta-analysis of 52 RCTs ($n = 4,893$) concluded that nonselective NSAIDs added to postoperative opioid treatment resulted in reduced sedation; the effect on respiratory depression was not reported (Elia et al., 2005). Another meta-analysis of 22 RCTs ($n = 2,307$) showed that nonselective NSAIDs produced a 29% reduction in opioid-induced sedation but no significant reduction in respiratory depression (Marret, Kurdi, Zufferey, & Bonnet, 2005). A systematic review of four meta-analyses involving 118 RCTs ($n = 10,031$) that evaluated multimodal analgesics concluded that NSAIDs decrease opioid adverse effects, but reductions for each adverse effect and differences in effects between nonselective and COX-2 selective NSAIDs were not distinguishable (Liu & Wu, 2007a). A review of meta-analyses, systematic reviews, and RCTs from 2217 articles published between 1996 and 2006 reported that nonselective NSAIDs produce opioid dose-sparing effects and reduce opioid-induced sedation, but data were insufficient to evaluate the impact of COX-2 selective NSAIDs on opioid-induced adverse effects (Liu & Wu, 2007b). More recent RCTs have shown that the addition of an NSAID to postoperative IV PCA morphine regimens produced a significant opioid dose-sparing effect but no difference in opioid-induced adverse effects compared with placebo (Chen, Ko, Wen, Wu, Chou, Yien, & Kuo, 2009; Kroll, Meadows, Rock, & Pavliv, 2011).

Anticonvulsants (Category A-1 Evidence for Sedation). A single RCT reported no clinically significant differences in sedation levels among surgical

patients who were premedicated with gabapentin or placebo and given IV PCA morphine postoperatively (Menigaux, Adam, Guignard, Sessler, & Chauvin, 2005); however, a number of meta-analyses of RCTs reported that gabapentin added to postoperative opioid treatment increases sedation (Ho, Gan, & Habib, 2006; Hurley, Cohen, Williams, Rowlingson, & Wu, 2006; Mathiesen, Moiniche, & Dahl, 2007; Peng, Wijeyesundera, & Li, 2007; Tiippana, Hamunen, Kontinen, & Kalso, 2007).

More research is needed to evaluate the effect of perioperative gabapentin on opioid-induced respiratory depression. Although respiratory depression was included as an outcome in some studies on perioperative gabapentin use, specific measurement criteria and outcomes data were not always provided, which can lead to a potentially inaccurate assumption that no respiratory depression events occurred (Menigaux et al., 2005). Only two of 16 RCTs that were analyzed in a systematic review of gabapentin combined with opioids after surgery reported the incidence of respiratory depression (Ho et al., 2006). One of those RCTs found no cases of respiratory depression in patients who received gabapentin, compared with 3.9% of patients who received tramadol and 0.7% of those who received placebo (Pandey, Singhl, Kumar, Lakra, Ranjan, et al., 2005). Another RCT administered gabapentin before or after surgery and observed no respiratory depression regardless of the time of administration (Pandey et al., 2005).

Antidepressants (Category D Evidence: Insufficient Evidence). There are few RCTs that yield meaningful information about the effects of antidepressants on opioid-induced sedation and respiratory depression in patients with acute pain (Amr & Yousef, 2010). Existing research primarily focuses on the use of antidepressants in the treatment of chronic (persistent) pain, and although sedation can be a significant adverse effect for some antidepressant agents, there are no compelling data to indicate measurable effects of antidepressants on opioid-induced sedation and respiratory depression (Amr & Yousef, 2010).

Clonidine (Category C-2 for Sedation). Clonidine is added to postoperative pain treatment regimens in combination with a variety of agents given by various routes of administration for the purpose of enhancing anesthesia and analgesia. Only research that involved administration of clonidine in conjunction with opioids for postoperative pain relief was reviewed.

A single RCT, which provided IV PCA morphine after surgery, demonstrated that preoperative administration of 300 μ g intrathecal clonidine produced postoperative sedation levels similar to those produced by intrathecal bupivacaine or placebo, i.e.,

TABLE 4.
Pharmacologic Agents: Summary of Evidence

Drug/Drug Class	Level of Evidence	Comments
Morphine-like opioids (e.g., morphine, hydromorphone, fentanyl)	C2	Comparative studies are lacking; no conclusions can be drawn regarding differences in sedation and respiratory depression between opioids.
Acetaminophen	A1	Meta-analyses showed opioid dose-sparing effects but no impact on incidence of sedation and respiratory depression.
NSAIDs	A1 for sedation	Further research is needed to evaluate the effect of nonselective NSAIDs on respiratory depression; however, several meta-analyses support the conclusion that these agents reduce opioid-induced sedation. Further research is needed to evaluate the effect of COX-2 selective NSAIDs on sedation and respiratory depression.
Anticonvulsants	A1 for sedation	Several meta-analyses demonstrate that perioperative administration of anticonvulsants increases postoperative sedation. Further research is needed to evaluate the effect of anticonvulsants on the incidence of opioid-induced respiratory depression.
Antidepressants	D	Research is lacking to evaluate the effect of antidepressants on opioid-induced sedation and respiratory depression.
Clonidine	A1 for sedation	Clonidine produces sedation in a dose-dependent manner, and doses of >150 µg are noted in the literature to be associated with a high incidence of adverse effects, including excessive sedation. Numerous randomized controlled trials (RCTs) demonstrated no increase in sedation when clonidine in doses <150 µg are added to opioids. Further research is needed to fully evaluate the effect of clonidine on respiratory depression; however, one RCT reported no deterioration in the respiratory status of surgical patients with OSA when preoperative oral clonidine was added to the opioid treatment plan.
Ketamine	C2	Although a single RCT showed fewer patients had respiratory depression during IV patient-controlled analgesia using morphine with ketamine than without ketamine, several systematic reviews cited insufficient data to determine the impact of ketamine on sedation and respiratory depression.
Dexmedetomidine	C2	The literature is equivocal regarding the effect of dexmedetomidine on opioid-induced sedation and respiratory depression; one RCT showed a lower incidence, one showed a higher incidence, and others have shown no effect. Further research is needed.

all patients in the study were spontaneously awake or asleep but easily arousible (DeKock, Lavand'homme, & Waterloos, 2005); however, several investigators have reported that clonidine doses >150 µg are associated with excessive sedation (Forester & Rosenberg, 2004; McCartney, Duggan, & Apatu, 2007; Strelbel, Gurzeler, Schneider, Aeschbach, & Kindler, 2004). One RCT established a linear relationship between clonidine dose and the incidence and severity of sedation in patients who received a variety of doses of clonidine plus morphine and ropivacaine via PCEA after surgery (Huang, Lin, Huh, Sheen, Yeh, et al., 2007). Further support for a dose-related sedative effect was found in a small RCT (n = 8) that administered IV clonidine infusions to healthy volunteers and noted the highest sedation levels in those receiving the highest clonidine dose (Hall, Uhrich, & Ebert, 2001).

Most RCTs combining clonidine with an opioid regimen for postoperative pain used clonidine doses that were much lower than 150 µg and reported that these doses had no appreciable effects on increased sedation (Jeffs, Hall, & Morris, 2002; Mannion, Hayes, Loughnane, Murphy, & Shorten, 2005; Sites, Beach, Biggs, Rohan, Wiley, et al., 2003). Sedation levels were also not notably different when IV PCA was administered after a bupivacaine popliteal block with or without clonidine (YaDeau, LaSala, Paroli, Kahn, Jules-Elysee, et al., 2008). Similarly, no differences in sedation level were apparent among patients who received intra-articular clonidine in combination with bupivacaine with or without morphine in another RCT (Joshi, Reuben, Kilaru, Sklar, & Maciolek, 2000).

Respiratory depression is not considered to be an adverse effect of clonidine, and occurrences are rarely reported in the literature. One RCT of patients

with obstructive sleep apnea (OSA) administered oral clonidine or placebo the night before and again 2 hours before undergoing ear-nose-throat surgery, followed by as-needed opioid analgesia, and found no deterioration in respiratory status, no differences in apnea and desaturation index, and a higher minimum oxygen saturation in the patients who received clonidine (Pawlik, Hansen, Waldhauser, Selig, & Kuehnel, 2005).

Ketamine (Category C-2 Evidence). Respiratory depression is not associated with ketamine administration for analgesia. Sedation is much more likely to occur with ketamine and is typically dose dependent. A single RCT (n = 41) demonstrated that no patients who received IV PCA morphine plus ketamine had oxygen desaturation compared with four patients who received IV PCA morphine alone (Nesher, Ekstein, Paz, Marouani, Chazan, & Weingbroum, 2009). The opioid dose-sparing effects of ketamine are considered to be a benefit, and a Cochrane Collaboration review of 37 RCTs (n = 2,240) (Bell, Dahl, Moore, & Kalso, 2006), a systematic review of 37 RCTs (n = 2,385) (Subramaniam, Subramaniam, & Steinbrook, 2004), and another systematic review of 53 RCTs (n = 2,839) (Elia & Tramer, 2005) compiled convincing evidence to support that ketamine administration along with opioids does not increase the incidence of sedation and respiratory depression.

Dexmedetomidine (Category C-2 Evidence). Dexmedetomidine is used for purposeful sedation, which may account for a general lack of research on its effect on unwanted sedation when it is combined with opioids for pain management. It should be noted that dexmedetomidine is approved in the United States for inducing sedation in intensive care units (ICUs) only. When given concomitantly, dexmedetomidine has been found to reduce postoperative morphine consumption without altering levels of sedation before induction in the operative setting (Unlugenc, Gunduz, Guler, Yagmur, & Isik, 2005). Similar results were shown with a comparison of an intraoperative infusion of dexmedetomidine and placebo (Gurbet, Basagan-Mogol, Turker, Ugun, Kaya, & Ozcan 2006).

The adverse effect profile for dexmedetomidine does not typically include respiratory depression (Hsu, Cortinez, Robertson, Keifer, Sum-Ping, et al., 2004); however, patients given an IV infusion of dexmedetomidine and supplemental IV morphine after surgery in one RCT demonstrated lower oxygen saturation readings and higher sedation scores while in the PACU than those who received an IV infusion of acetaminophen and supplemental IV morphine after surgery (Gomez-Vasquez, Hernandez-Salazar, Hernandez-Jimenez, Perez-Sanchez, Zepeda-Lopez, & Salazar-Paramo, 2007). Another RCT

reported a lower incidence of respiratory depression in the PACU for patients who had a loading dose of dexmedetomidine followed by a dexmedetomidine infusion compared with a placebo loading dose followed by dexmedetomidine before major surgery (Candiotti, Bergese, Bokesch, Feldman, Wisemandle, et al., 2010). Other RCTs have shown no differences in sedation levels and incidence of respiratory depression postoperatively in patients who received IV PCA morphine with or without dexmedetomidine (Arain, Ruehlow, Ulrich, & Ebert, 2004; Lin et al., 2009).

Summary of Evidence

Table 4 summarizes all evidence categories for classes of analgesics and individual medications. Based on the evaluation of existing research, there is a lack of evidence comparing the effects of opioids administered for postoperative pain management on sedation and respiratory depression. Acetaminophen appears to produce opioid dose-sparing effects but no reduction in sedation and respiratory depression. The nonselective NSAIDs are associated with an opioid dose-sparing effect and reduced sedation scores, but further research is needed to evaluate their effect on respiratory depression. More research is also needed to examine the effects of COX-2 selective NSAIDs on opioid-induced adverse effects. There is compelling evidence that anticonvulsants increase sedation when added to an opioid postoperative pain treatment regimen; however, it is not clear that anticonvulsants have any effect on respiratory depression. A dose-dependent effect of clonidine (doses >150 µg) is associated with a higher incidence of adverse effects, including excessive sedation. The effects of clonidine on respiratory status have not been consistently reported. There are insufficient data to determine the degree to which certain antidepressants, ketamine, and dexmedetomidine affect opioid-induced sedation and respiratory depression, although it is important to note that these agents do have sedating properties.

Recommendation Statements

Recommendations for Analgesic Pharmacotherapy

1. Nurses **should** act as strong advocates for pain management plans that incorporate opioid dose-sparing strategies initiated early in the course of treatment, e.g., on admission, before surgery, during surgery, and early after surgery. Class I
 - A. Multimodal analgesic therapy that combines opioids with nonopioids, e.g., acetaminophen, NSAIDs, anticonvulsants, and antidepressants, **has proven efficacy** in the treatment of pain.

- B. Nurses **should** be informed of the evidence surrounding the potential additive or synergistic effects of combining some pharmacologic classes of analgesics, particularly those that produce sedation, e.g., anticonvulsants, antidepressants, and high-dose clonidine.
- 2. Observation and assessment of sedation and respiratory status regardless of the type of opioid administered **is recommended**. Class I
- 3. Observation and assessment of sedation and respiratory status **is still necessary** when acetaminophen and NSAIDs are administered concomitantly despite evidence that these may have opioid dose-sparing effects. Class IIa
- 4. More intensive and frequent observation of patients and assessment of sedation and respiratory status **are recommended** when sedating agents are administered concomitantly with opioids, especially during the post-operative period. Class I
 - A. Anticonvulsants such as gabapentin and pregabalin, antidepressants, such as the tricyclic antidepressants and duloxetine, and alpha₂-adrenergic agonists, such as clonidine and dexmedetomidine, may increase sedation when they are administered concomitantly with opioids.
 - B. Individualized assessment and monitoring plans of care are always required when ketamine and dexmedetomidine are administered for analgesia, and careful consideration should be given to the dose, duration of therapy, and clinical status of the patient.

Recommendations for Education

1. All nurses caring for patients receiving opioid therapy **should** be educated about patient and pharmacologic factors contributing to increased risk for unintended advancing sedation and respiratory depression and parameters and criteria for identifying sedation and respiratory concerns. Class I
2. The development and implementation of educational programs that focus on analgesics in addition to the pharmacology and medication administration content presented in orientation **are reasonable**. Class IIa
3. Educational programs **should** include content on the mechanisms of action, pharmacodynamics/pharmacokinetics, and adverse effects of the various doses and routes of administration for analgesics, including patient factors and practices that place patients at risk for excessive sedation and respiratory depression. Content **should** be updated regularly to include new pharmacologic agents and practices. Class IIa
4. Assessment and safe medication administration with monitoring practices **must** be addressed. Skill and knowledge with proficiencies should include: the proper use of assessment scales/tools;

programming/operating, maintaining, and troubleshooting medication delivery devices and monitoring technology; interpretation of trends in sedation and respiratory status; and understanding how to move patients from one opioid or route of administration to another. Class IIa

5. Relevant policies and procedures and requirements for documentation practices **should** be specified in educational programs. Class IIa

Implementation Strategies

1. Establish policies and procedures that direct nurses to assess, communicate, and document sedation and respiratory status and trends in patients receiving opioids.
2. Outline specific parameters for assessing and monitoring sedation and respiratory status during opioid treatment in the plan of care and nursing or prescriber orders, and specify the frequency, intensity, duration, and method of monitoring.
3. Teach prescribers and clinical nurses about the pharmacology of analgesics and the synergistic effects of concomitant administration of opioids with other sedating medications and the potential for increased sedation that may require more intensive and frequent monitoring of sedation levels and respiratory status.
4. Develop policies and procedures for the administration of adjuvant agents, especially for ketamine, clonidine, and dexmedetomidine, to help ensure their safe administration. Policies and procedures should include guidelines for monitoring sedation and respiratory status during the administration of these agents.

PATIENT MONITORING PRACTICES

Definition

The ASPMN's definition of "monitoring" is the practice of using nurse observations including, but not limited to, the use of sedation assessment scales and technologies to collect serial measurements to anticipate and recognize advancing sedation or respiratory depression.

Search Strategies

A substantial review of the literature was conducted in PubMed and CINAHL to identify relevant research and clinical articles defining the practice of monitoring for patients receiving opioid analgesics for pain management. MeSH terms used included: pulse oximetry combined with sedation, opioid, or respiratory depression and capnography combined with sedation, opioid, or respiratory depression. Literature related to nursing practice with opioid therapy was also examined. No research articles or clinical practice guidelines were identified from an extensive

search of articles in CINAHL using the terms respiratory rate and opioid, nurse and consciousness and opioid, nurse and assessment, nurse and sedation, and plethysmography and level of consciousness. The following MeSH terms yielded limited results: nurse and monitor, nurse and opioid and assess, nurse and respiratory depression and assess, and nurse and respiratory rate. Several articles were retrieved that form the basis of the present scientific review; however, it was not possible to assign an ASA evidence category to research conducted on sedation and respiratory depression monitoring practices.

Monitoring Practices

Opioid-Induced Sedation. Few publications define the role of nurses and best practices in the routine monitoring of patients receiving opioid analgesics for pain control. An early clinical guideline proposed recommendations for monitoring during IV PCA and purported that nurses are the “mainstay” for monitoring opioid-induced sedation and respiratory depression during that therapy (Campbell & Plummer, 1998). In more recent publications, authors have provided recommendations for assessment and monitoring practices for sedation and respiratory depression during a variety of opioid-based therapies (Dunwoody, Krenzischek, Pasero, Rathmell, & Polomano, 2008; Nisbet & Mooney-Cotter, 2009; Pasero, 2009; Pasero & McCaffery, 2002; Pasero, Quinn, Portenoy, McCaffery, & Rizos, 2011; Young-McCaughan & Miaskowski, 2001a, 2001b).

There is agreement that the frequency, intensity, and duration of sedation monitoring should be based on the type of opioid therapy, patient and iatrogenic risk factors, and response to treatment. Equally important is the ongoing need for research on opioid-induced sedation to estimate its prevalence in hospitalized patients receiving opioids and to establish accepted criteria for defining sedation and validate its measurement through various means, such as sedation scales (Young-McCaughan & Miaskowski, 2001b).

A study conducted to determine the level of importance nurses assign to sedation assessments in providing guidance as to whether or not to administer an opioid found that only 66% of the 602 nurses surveyed responded that sedation assessments were one of the most important considerations before administering an opioid (Gordon, Pellino, Higgins, Pasero, & Murphy-Ende, 2008). A chart audit conducted at six community hospitals after an educational intervention to increase documentation of pain and related data, including sedation levels, revealed that although the intervention group showed some improvement, documentation of assessment, treatment, and treatment outcomes was infrequent

and inconsistent at all study sites (Dalton, Carlson, Blau, Lindley, Greer, & Youngblood, 2001).

Case-study approaches can be useful to illustrate the importance of nurses performing serial sedation assessments during opioid therapy. Two examples of case-based reports in the literature demonstrate how the nurse’s recognition of advancing sedation as a sensitive indicator of impending respiratory depression can facilitate decision making (Pasero, Manworren, & McCaffery, 2007; Smith, 2007).

Despite the critical importance of serial sedation assessments to identify unintended advancing opioid-induced sedation with pain therapy, only a few studies have described the effectiveness of nurses’ systematic sedation assessments on improving patient outcomes (Young & Miaskowski, 2001). Moreover, there are limited data from validation studies outside of purposeful sedation to demonstrate the psychometric properties of sedation scales. Nisbet and Mooney-Cotter (2009) conducted a descriptive study to test the validity and reliability and performance of three sedation scales commonly used for sedation assessments with opioid therapy for pain management: the Inova Health System Sedation Scale (ISS), the Richmond Agitation and Sedation Scale (RASS), and the Pasero Opioid-Induced Sedation Scale (POSS). A sample of 96 nurses was exposed to several scenarios online, and after reading the scenarios they completed an online survey with sedation ratings and appropriate nursing actions. Percentage agreement was highest for the POSS for both the selection of the sedation score and appropriate nursing action, such as decreasing the opioid dose when excessive sedation is detected. These findings support what has been previously cited anecdotally: that the use of sedation scales tested in purposeful sedation settings may not be appropriate for the measurement of sedation during opioid administration for pain management outside of these settings (Pasero & McCaffery, 2002; Smith, 2007). It is acknowledged that use of the RASS, which measures both sedation and agitation and was originally tested in critically ill populations, has expanded to medical-surgical general care settings. More research is needed, however, to validate this measure in specifically detecting levels of opioid-induced sedation.

Sedation Scales. Various reliable and valid instruments are used to characterize levels of sedation both in clinical practice and research. Most have been tested in patients who are critically ill and require purposeful sedation or in those requiring procedural sedation and analgesia. As such, considerable variations exist in measurement domains that are apparent by differences in levels of consciousness and presence of descriptors for agitation, pain, hemodynamic status,

TABLE 5.
Summary of Common Sedation Scales with measures of validity and reliability

Name	Original Report	Validation study	Population	Evaluation			
				Assessment	Internal Consistency	Reliability	Validity
Aldrete Scoring System	Aldrete & Kroulik, 1970; Aldrete, 1995	—	Adult PACU	—	—	—	—
Ramsay/Modified Ramsay Scale	Ramsay et al., 1974	Carrasco, 1993	102 adult patients	1,040 measurements (? no. of raters)	—	—	Validity vs. modified GCS; correlation coefficient $r = 0.89-0.92$
Sedation Agitation Scale (SAS)	Riker, 1994	—	Adult ICU	—	—	—	—
Richmond Agitation and Sedation Scale (RASS)	Sessler, 2002	Ely, 2003	Adult ICU	290 paired observations by nurses	—	IRR = weighted κ 0.91; superior to GCS (weighted κ 0.64)	Face validity 92% of critical care nurses agreed or strongly agreed with the scoring system (n = 26)
Pasero Opioid-Induced Sedation Scale (POSS)	Pasero, 1994	Nisbet & Mooney-Cotter, 2009	96 Adult Med/Surg Nurses 15 Content experts (written scenario)	96 scores from staff nurses on the same written clinical scenario illustrating advancing sedation	—	Cronbach α 0.903; $p \leq .05$; compares with RASS at α 0.770; $p \leq .05$	Percent agreement with clinical experts (n = 15) and staff nurses (n = 96) Correct score: 78.9%; Correct actions: 80% (both highest among 3 scales tested)

GCS = Glasgow Coma Scale; IRR = interrater reliability.

and/or ventilator compliance or tolerance (de Jonge, Cook, Appere-de-Vecchi, Guyatt, Meade, & Outin, 2000). Scales that are commonly used for assessment during purposeful sedation include the Ramsay Scale (Ramsay, Savage, Simpson, & Goodwin, 1974); the RASS (Sessler, Gosnell, Grap, Brophy, O'Neal, Keane, Tesro, & Elswick, 2002), and the Riker Sedation Assessment Scale (Simmons, Riker, Prato, & Fraser, 1999; Fraser & Riker, 2001). The Aldrete Scoring System evaluates multiple indicators including level of consciousness to determine readiness for discharge from the PACU (Aldrete & Kroulik, 1970; Aldrete, 1995).

The POSS differs from these scales in that it is intended only for use following opioid administration for pain management and captures a single domain of sedation level with suggested clinical actions coinciding with a score (Pasero, 2009; Pasero et al., 2011). Responsiveness of a sedation scale to detect changes over time during opioid administration is an important feature for its utility in clinical practice as well. Table 5 provides information, including measures of reliability and validity, about the commonly used sedation scales.

Opioid-Induced Respiratory Depression. In the clinical setting, opioid-induced respiratory depression is usually described in terms of decreased respiratory rates (<8 or <10 breaths/min), decreased SpO₂ levels, or elevated ET/CO₂ levels. Nurses can prevent adverse events related to respiratory dysfunction and reduce morbidity and mortality with proper respiratory assessment and early recognition and intervention when patients demonstrate signs of deterioration (Considine, 2005b). A clinical review by Duff, Gardiner, and Barnes (2007) discussed the positive impact on patient outcomes when surgical nurses performed focused assessments of respiratory status including depth and rhythm, work of breathing, use of accessory muscles, symmetric chest movement, and auscultation of lung fields using a stethoscope. Additionally, those authors reported that the literature has not adequately addressed the educational needs of nurses to develop competencies in respiratory assessments. Although nursing assessment, documentation, and communication of respiratory indicators and trends are paramount to early identification of patients at risk for complications, research shows that nurses do not perform adequate respiratory assessment (Pasero et al., 2011). For example, a review of documentation practices noted that nurses recorded respiratory rates $<50\%$ of the time prescribed (Hogan, 2006).

Given the paucity of research to demonstrate the effect of nursing education and support for specific guidelines for respiratory monitoring, the ASPMN Expert Consensus Panel members advocate for ongoing

research that uses universally accepted criteria for opioid-induced respiratory depression and that measures the effects of vigilant monitoring on reducing episodes of respiratory depression, improving the quality of recovery from hospitalizations, and eliminating the need for reversal agents such as naloxone.

Technology-Supported Monitoring. The value of technology-supported monitoring to prevent adverse events secondary to opioid-induced respiratory depression has not been established. Studies that used technology monitoring (e.g., pulse oximetry and capnography) in patients receiving opioid analgesia do not provide sufficient evidence to support their use as standard of care in all patients receiving opioid analgesics (Burton, Harrah, Germann, Dillong, 2006; Kopka, Wallace, Reilly, & Binning, 2007; Overdyke, Carter, Maddox, 2007); however, there may be an important role for technology-supported monitoring during opioid therapy in patients who are at high risk for respiratory depression.

Use of Pulse Oximetry Monitoring. Pulse oximetry is commonly used to detect decreases in oxygen saturation. The strongest level of evidence for the use of SpO₂ monitoring comes from systematic reviews. A recent Cochrane Database systematic review of five studies evaluating the role of pulse oximetry in the perioperative setting (OR and PACU) confirmed that the technology is capable of detecting hypoxemia and undesirable events that require intervention to avoid complications or death in this setting; however, the review questioned whether this type of monitoring improved patient outcomes and the effectiveness and efficiency of care (Pedersen, Møller, & Hovhannisyian, 2009). An earlier systematic review of four RCTs (21,773 patients) was conducted to clarify the effect of perioperative monitoring with pulse oximetry and to identify adverse events that might be prevented or improved by its use (Pederson, Moller, & Pederson, 2003). Compared with the control group, those who were monitored with pulse oximetry had 1.5-3 times fewer hypoxemia episodes but similar complication rates, length of stay, and deaths. The authors concluded that it was difficult to determine the benefits of pulse oximetry monitoring because the numbers of patients studied were small and episodes of hypoxemia were rare.

A randomized nonblinded study of 1,219 cardiothoracic surgical patients on a general care unit found that the routine use of continuous pulse oximetry in non-ICU care was not associated with an overall reduction in the need for patient transfer back to the ICU, mortality, or estimated total costs of hospitalization (Ochroch, Russell, Hanson, Devine, Cucchiara, Weiner, et al., 2006). However, a later study reported that ICU transfers declined from 5.6 to 2.9 per 1,000 patient-days with the

implementation of a patient surveillance program that included continuous pulse oximetry monitoring with radiotransmitted nurse notification when an 80% oxygen saturation threshold was triggered (Taenzer, Pyke, McGrath, & Blike, 2010). Extensive rapid response call criteria were also used in that program, which makes it difficult to evaluate the sole effect of continuous pulse oximetry on the findings in that study.

Oxygen saturation monitoring provides a surrogate measure of oxygenation but does not measure ventilation, and therefore it has limited ability to recognize respiratory depression before it becomes clinically significant. A recognized disadvantage of pulse oximetry is that it will yield high oxygen saturation readings despite the presence of respiratory depression in patients receiving supplemental oxygen (Fu, Downs, Schweiger, Miguel, & Smith 2004; Overdyk, Carter, & Maddox, 2006).

The timing and duration of the use of pulse oximetry are important considerations. For example, some institutions implement periodic pulse oximetry readings (spot checks); however that practice may lead to inaccurate assumptions about the patient's respiratory status. Respirations are often adequate during wakefulness but become rapidly insufficient at the onset of sleep. The process of applying the pulse oximeter sensor is likely to stimulate the patient to take a deep breath, which can yield a higher SpO₂ reading than the patient has when not stimulated (Pasero, 2009; Pasero et al., 2011).

Another drawback is the lack of accuracy of pulse oximetry readings in patients with dark pigmented skin; darker skin may exhibit false high SpO₂ readings (Bickler, Feiner, & Severinghaus, 2005). This effect is thought to be from the calibration of the technology using lighter-skinned individuals.

Use of Capnography Monitoring. End-tidal CO₂ values obtained via capnography are a surrogate measure of perfusion and ventilation. Capnography is considered to be a more sensitive measure and early indicator of respiratory compromise, including respiratory depression from decreased central respiratory drive and diminished chemoreceptor responsiveness as well as decreased airway tone resulting in obstruction (Kopka et al., 2007). Research shows that capnography can detect compromised respiratory status before oxygen desaturation or diminished chest excursion is observed (Burton, Harrah, Germann, & Dillion, 2006).

Most studies evaluating the effect of capnography on patient outcome have been conducted with patients undergoing procedural sedation (Burton et al., 2006) or in the intraoperative setting (Soto, Fu, Vila, & Miguel, 2004). Few studies have examined its use during opioid

therapy in patients receiving routine postoperative care. One observational cohort study used continuous transcutaneous capnography (PtcCO₂) in 28 patients before and after elective major laparotomy; patients were maintained on supplemental oxygen (4 L) and received either epidural fentanyl plus bupivacaine or IV PCA morphine (Kopka, Wallace, Reilly, & Binning, 2007). Preoperative PtcCO₂ readings were similar between the two analgesic groups in that study; however, after surgery, those who were receiving IV PCA experienced considerable and prolonged hypercapnia despite normal respiratory rates and SpO₂ readings. Another observational study that used both continuous capnography and pulse oximetry to monitor 178 postoperative patients detected episodes of oxygen desaturation (SpO₂ <90%) and bradypnea (respiratory rate <10 breaths/min) lasting ≥3 minutes in 12% and 41% of the patients, respectively (Overdyk et al., 2007). False alarms were common in that study, and the nurse response rate to alarms was low, which the authors attributed to short-duration bradypnea and desaturation events which generated a brief alarm. This underscores concerns related to alarm fatigue and desensitization of nursing staff that care for multiple patients who are mechanically monitored simultaneously. The authors of that study noted that ETCO₂ accuracy has been shown to correlate with alveolar ETCO₂ only on a full vital-capacity breath, which rarely occurs in the postoperative setting. Furthermore, they acknowledged that the thresholds they established for bradypnea and desaturation influenced the results obtained in their study and stated that the value of monitoring ETCO₂ may lie in trend analysis. Lynn and Curry (2011) echo concerns about threshold monitoring and the need for improved technology that will allow trend analysis of more than one physiologic measure and earlier detection of respiratory insufficiency.

Although no specific guidelines exist for the use of capnography in routine clinical care, the Emergency Nurses Association (ENA) recently published recommendations for the use of capnography during procedural sedation and analgesia (PSA) in the emergency department (Proehl, Arruda, Crowley, Egging, Walker-Cillo, Papa, et al., 2011). The ENA concluded that capnography is a useful adjunct technique for detecting respiratory depression and a more sensitive indicator of respiratory depression than SpO₂ or clinician assessment during PSA, but there is a lack of evidence to support the assertion that the use of capnography during PSA directly improves patient outcomes. It remains logical that the use of capnography is not necessary in situations where the patient is directly observed by nursing staff.

Summary of Evidence

Clearly, more evidence is needed to support the development of specific guidelines and formulation of recommendations for technology-supported monitoring of patients receiving opioids for pain management. At this time, the ASPMN Expert Consensus Panel recommends that the use of pulse oximetry and capnography to detect respiratory compromise in the ongoing care of patients who are receiving continuous opioid therapy be determined by patient risk factors, iatrogenic risk, and institutional policies. (See Table 2 for risk factors.)

Recommendation Statements

Recommendations for Monitoring

1. The frequency, intensity, duration, and nature of monitoring (assessments of sedation levels and respiratory status and technology-supported monitoring) **should be individualized** based on a patient's individual risk factors, iatrogenic risks, and pharmacologic regimen administered to treat pain. Class I
2. It **is generally recommended** that monitoring practices for patients receiving opioid therapy be defined by institutional policies and procedures that are aligned with published evidence-based guidelines and expert opinion. Class IIa
3. Serial sedation and respiratory assessments **are recommended** to evaluate patient response during opioid therapy by any route of administration. Class I
 - A. Include regular sedation and respiratory assessments during wakefulness and sleep as part of the plan of care to evaluate patient outcomes with requirements for documentation.
 - B. Sedation scales with acceptable measures of reliability and validity for pain management outside of purposeful sedation and anesthesia and critical care should be selected.
 - C. Be aware that unintended advancing sedation from opioids is often a sign that the patient may be at higher risk for respiratory depression, suggesting the need for increased frequency of assessment of sedation levels and respiratory status.
 - D. Respirations should be counted for a full minute and qualified according to rhythm and depth of chest excursion while the patient is in a restful/sleep state in a quiet unstimulated environment.
 - E. Patients should not be transferred between levels of care near peak effect of medication.
4. Patients found to have signs of respiratory depression (e.g., rate defined as <8 or <10 breaths per minute and/or paradoxical rhythm with little chest excursion), evidence of advancing sedation, poor respiratory effort or quality, snoring or other noisy respiration, or desaturation **should be aroused immediately** and instructed to take deep breaths. Intervene and communicate with other team members per practice policy and continue patient monitoring until patient recovers.
5. Technology-supported monitoring (e.g., continuous pulse oximetry and capnography) **can be effective** for the patient at high risk for unintended advancing sedation and respiratory depression. Class IIa
 - A. Technology-supported monitoring should be directed by patient risk including preexisting conditions, response to therapy, overall clinical status, practice environment, and concurrent medication administration.
 - B. The use of capnography in the postoperative period can be a useful indicator for respiratory depression in high-risk patients.
 - C. Technology monitoring systems that integrate with medication delivery features, such as modular ETCO₂ devices, may interfere with individualizing analgesic therapy or effective analgesia.
6. More vigilant monitoring of sedation and respiratory status **should be performed** when patients may be at greater risk for adverse events, such as at peak medication effect, during the first 24 hours after surgery, after an increase in the dose of an opioid, coinciding with aggressive titration of opioids, recent or rapid change in end-organ function (specifically hepatic, renal, and/or pulmonary) or when moving from one opioid to another or one route of administration to another. Class I

SUMMARY

To coincide with the mission of the ASPMN “to advance and promote optimal nursing care for people affected by pain by promoting best nursing practice,” clinical practice guidelines have been developed for monitoring patients at risk of advancing sedation and respiratory depression with opioid analgesia. This report has been executed with methodologies that include scientific rigor in the appraisal and summary of evidence and consensus building in the formulation of recommendations that focus on quality and safe patient care. Results from the extensive review of literature in combination with expert opinion and findings from a survey of ASPMN members served as the basis for promulgating recommendations for nursing practice, education, and leadership in the prevention and early detection of opioid-related adverse events. To this end, these clinical practice guidelines focus on aspects of accountable care to promote and maintain the health of hospitalized patients experiencing pain and the quality of their recovery.

Recommendations in this report are written in a manner that reflects the uniqueness of patients, autonomy in nurses' judgments and decision making, and foundations of professional nursing practice. These

guidelines are intended to guide nursing care and are therefore not prescriptive or restrictive in specifying timeframes and intervals for patient assessments and monitoring practices. ASPMN acknowledges the diversity of patient populations and uniqueness of their needs and health states, and recognizes that accountability for quality and safe patient care lies with professional nurses who care for patients, nurse leaders, and health care organizations. It is envisioned that these guidelines will be interpreted and applied as appropriate to patient care and the clinical setting. Responsible opioid prescribing and administration along with appropriate monitoring practices tailored to the individual needs of patients promotes safer and improved pain control with a greater likelihood of decreasing episodes of serious opioid-induced adverse events.

The development of research- and expert-based guidelines is associated with limitations. The most significant limitations in the formulation of these guidelines are the lack of RCTs examining outcomes associated with monitoring techniques and the lack

of standardized well defined outcomes across studies. As new technologies, medications, and changes in health care delivery emerge, it will be important for nurse researchers to incorporate recommendations from these guidelines into future studies that test monitoring practices and measure outcomes associated with these practices. In the near future, it is anticipated that current SPO₂ and ETCO₂ monitoring devices will be replaced by integrated technology systems that will capture more than one physiologic measure, enabling greater capacity for detecting opioid-induced advancing sedation and respiratory depression. Improvements in monitoring technology are also likely to allow trend analysis of clinical information and to address the problem of alarm fatigue and desensitization. Despite these advances, nurses should remain patient focused with the continued goal of providing optimal and safe pain management.

The complete list of references is available online at www.painmanagementnursing.org.

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GLOSSARY: DEFINITIONS OF TERMS

Adjuvant analgesic: A drug that has a primary indication other than pain but is analgesic for some painful conditions. Examples of classes of adjuvant analgesics include anticonvulsants, antidepressants with NE reuptake inhibiting properties, sodium channel blockers, and selective muscle relaxants.

Alpha₂-adrenergic agonist: A class of drugs that bind to alpha₂ receptors located in pre-synaptic sympathetic nerve endings and noradrenergic nerve endings in the dorsal horn of the spinal cord receptor sites and

activate endogenous inhibitory pathways thereby diminishing pain. Examples of alpha₂-adrenergic agonists are clonidine, dexmedetomidine, and tizanidine.

Anatomical anomalies: Physical characteristics that deviate from the usual anatomical structure of the airway including pharyngeal and craniofacial abnormalities, (i.e. Retrognathia - a type of malocclusion referring to an abnormal posterior positioning of the maxilla or mandible).

Apnea: A cessation or significant reduction in inspiratory airflow for at least 10 seconds.

Apnea Hypopnea Index (AHI): The AHI is a measure of the number of apneic/hypopneic events (central and/or obstructive type) per hour on average over the period of sleep, and is used as an indicator for the severity of sleep disordered breathing measured during polysomnography or sleep studies.

ASA Classification System: The American Society of Anesthesiologists (ASA) Physical Status Classification System assesses the fitness of patients before surgery. The classification system is used to predict risk of harm from undergoing surgery and includes 6 classes from P1 (ASA status 1) a normal healthy patient to P6 (ASA status 6) a declared brain-dead patient whose organs are being removed for donor purposes within the system. An "E" is added after the class number if the surgical procedure is emergent. This classification, while the standard of practice for all patients undergoing surgery, is limited by the application of broadly defined criteria open to subjective interpretations.

Assessment: Processes by which nurses gather and evaluate clinical data by physical examination, interviews, and/or observations to recognize or detect changes in a patient's status. Assessments for opioid-induced sedation can be accomplished with the use of criteria- or category-based valid and reliable level of sedation scales or measures or descriptions of a patient's level of consciousness. Observations of opioid-induced respiratory depression can be described in terms of criteria for respiratory rates (< 8 or 10 per minute), depth of respirations, breathing patterns and airway status. Problems with oxygenation associated with opioid-induced respiratory depression can be detected by technologies such as pulse-oximetry or capnography. Nurses may employ various methods and procedures for assessment, and the ability for nurses to recognize and accurately interpret clinical findings indicative of opioid-induced sedation and respiratory depression are often dependent on nurses' level of experience and education with pain management.

Authorized agent controlled analgesia (AACA): An analgesic therapy whereby one person is designated to be a patient's primary pain manager with responsibility for pressing the PCA button to administer an analgesic dose to a patient who is a candidate for PCA but is unwilling or unable to manage his or her own pain. Examples of authorized agent controlled analgesia include parent-controlled analgesia (administered to children too young to use PCA); caregiver-controlled analgesia (administered by a significant other, often at end of life); and nurse-activated dosing (administered by the patient's primary nurse).

Bariatrics: The specialty area of health care that deals with the causes, prevention, and treatment of obesity.

Basal rate infusion: Continuous (or background) infusion with patient-controlled analgesia (PCA) demand dosing.

Body Mass Index (BMI): A statistical term used to denote body size; calculated by mass (kg)/ [height (m)]². Normal BMI is defined between 18.5 - 25.

Capnography/capnometry: A noninvasive method of estimating the patient's arterial carbon dioxide (pCO₂) by measuring end tidal CO₂ (ETCO₂), the partial pressure or maximal concentration of CO₂ at the end of an exhaled breath expressed as a percentage of CO₂ or mmHg, through a nasal cannula or sensor. Capnography provides a surrogate measure of perfusion and ventilation.

Central sleep apnea (CSA): The repeated absence of breath during sleep for periods of > 10 seconds due to the temporary loss of ventilatory effort.

Co-morbidity: The presence and effects of two or more health conditions or disorders, which may contribute to or pose risks for complications, unanticipated events, or adverse events from analgesic therapies.

Concurrent medications with additive effects: Drugs administered concurrently with opioids that have potential to increase sedation and risk for diminished respiratory drive (i.e. barbiturates act synergistically with opioids to cause respiratory depression where as antihistamines and benzodiazepines act synergistically to produce excessive sedation).

Continuous peripheral nerve block: An anesthetic/analgesic technique whereby an initial nerve block is established followed by placement of a catheter for infusion of local anesthetic via an infusion device, with or without PCA capability.

Continuous wound infusion: An analgesic technique whereby a catheter is placed inside the surgical wound and local anesthetic is continuously infused via an infusion device.

Desaturation: A trend for developing hypoxia (O₂ saturation < 90%) that can be caused by the respiratory depressing effects of opioids, pre-existing respiratory conditions, factors contributing to impaired ventilation such as type surgery, age, sedation, and obstructive sleep apnea.

Environment of care: Refers to the practice environment including the adequacy of resources, skill mix, interdisciplinary collaboration, education and leadership.

Extended-release epidural morphine (EREM): An extended-release liposome morphine sulfate formulation for epidural administered through a single perioperative injection, which provides extended analgesia up to 48 hours.

“Failure to rescue”: Death among patients with treatable serious complications: available at www.qualityforum.org?Topics/Safety_Definitions.aspx.

Hand-off communication: Exchange of patient information that occurs from one health care professional to another, for example, nursing shift changes, physicians transferring responsibility for a patient, staff temporarily leaving a unit, patients moving from the ER to a patient care area, and preoperative area, to surgery, then the post anesthesia care unit and transfer to the inpatient care unit.

Iatrogenic risk: Conditions, circumstances and interventions that predispose a patient to increased risk for unintended advancing sedation or respiratory issues.

Local infiltration analgesia: An analgesic technique whereby a catheter is placed inside the surgical wound and local anesthetic is injected in a systematic fashion (e.g., scheduled intermittent bolus doses).

Monitoring devices: Technologies such as pulse-oximeters that provide SpO₂ measurements and capnography for end tidal CO₂, which are used at the bedside.

Multimodal analgesia: A method of pain control that combines medications from two or more pharmacological analgesic classes.[e.g., mu-receptor agonists (opioids), norepinephrine reuptake inhibitors (antidepressants), sodium channel stabilizers (anesthetics/anticonvulsants), voltage-gated calcium channel blockers (alpha-2-D subunit receptor agonists such as gabapentin/pregabalin), prostaglandin inhibitors (NSAIDs)] that target different pain mechanisms and pathways. Multimodal approaches often allow the administration of lower doses of analgesics thereby decreasing the potential for adverse events. Multimodal analgesia can result in comparable or greater pain relief than can be achieved with any single analgesic agent.

Neuraxial: Delivery of either an opioid or a local anesthetic or both, into the epidural, subarachnoid (intrathecal), or intracerebroventricular space.

Nonsteroidal anti-inflammatory drug (NSAID): A drug that produces analgesia primarily by inhibiting the enzyme cyclooxygenase (COX)-2, thus blocking the production of prostaglandins, which ultimately reduces the transmission of pain from the periphery to the central nervous system. Examples of NSAIDs are naproxen, ibuprofen, ketorolac, and celecoxib.

Obstructive sleep apnea (OSA): The recurrent absence of breath during sleep for periods of > 10 seconds due to collapse of the lower posterior pharynx.

Opioid analgesia: Pain relief produced by opioid agonists or opioid agonist-antagonists binding to the mu, delta, and/or kappa opioid receptor sites in the central and/or peripheral nervous systems. Examples of opioid agonists are morphine, hydromorphone, fentanyl,

oxycodone, and methadone. Examples of opioid agonist-antagonists are nalbuphine, butorphanol, and buprenorphine.

Opioid dose-sparing strategies: Pain management approaches and techniques that facilitate the administration of the lowest effective opioid dose with the goal of minimizing opioid-induced adverse effects. Examples include the addition of nonopioid analgesics, such as acetaminophen and an NSAID, to an opioid regimen; continuous peripheral nerve block; and continuous wound infusion,

Opioid-induced respiratory depression: A concerning decrease in the effectiveness of an individual’s ventilatory function after opioid administration.

Opioid-induced sedation: Refers to a disordered level of consciousness in which both arousal mechanisms and content processing are functional but attenuated as a result of mechanisms of action of opioids at receptor sites within the central nervous system.

Opioid-naïve: A term used to describe an individual without recent and/or has had minimal exposure to an opioid medication. The opposite is opioid tolerant.

Patient-controlled analgesia (PCA): An interactive method of pain management that allows a patient to self-administer doses of pain medication on demand as needed. This technique for medication delivery requires that a patient understand the concept of PCA and is capable of delivering self-administered doses of medication via the most common routes of intravenous and epidural, or less commonly oral and subcutaneous.

PCA by proxy: Unauthorized administration of a PCA dose by another person.

Purposeful, goal-directed sedation: Sedation that is intended to calm the agitated patient, usually to improve tolerance of mechanical ventilation in the critically ill.

Perineural nerve block or peripheral nerve block: A regional anesthesia/analgesia technique accomplished by the injection of a local anesthetic agent into or near a major nerve through the use of a single one-time injection or bolus or continuous infusion.

Pulse oximetry monitoring: A noninvasive method of estimating peripheral arterial hemoglobin oxygen saturation (SaO₂) through the use of infrared light technology from a probe attached to the patient’s finger or ear lobe which is linked to a computerized unit yielding a percent SpO₂ reading.

Rapid response team: A multidisciplinary team prepared to respond to patient care emergencies (typically outside of critical care areas) with the goal of providing emergent care and reducing patient morbidity and mortality.

Respiratory depression: Although there is no one definition, consensus generally includes parameters such as respiratory rate < 8 to 10 breaths/minute, oxygen

saturation (SpO₂) < 90% end tidal carbon dioxide < 30 mmHg or > 50mmHg to represent inadequate ventilatory function to sustain homeostasis.

SBAR: A communication technique/method that stands for situation, background, assessment, and recommendations often used as a method for ensuring quality improvement and patient safety with nurse-to-nurse communication.

Sedation continuum: The range of possible levels of diminished consciousness (e.g. fully alert (no sedation) to comatose (just preceding death).

Sedation scales: Measurement indicators possessing reliable and valid criteria that are applied in clinical practice by nurses during the assessment of sedation continuum level.

Sleep disordered breathing: A term that encompasses obstructive sleep apnea, central sleep apnea, and upper airway resistance syndrome.

Staffing ratios: The number of nurses per patient.

Technology-supported care: The use of pulse oximetry, apnea monitors and capnography to detect respiratory and ventilation issues such as desaturation and respiratory depression.

Unintended advancing opioid-induced sedation: Sedation that occurs at increasingly higher levels along the continuum of sedation as a result of opioid administration for pain management, impairing both arousal mechanisms and content processing.

EXTERNAL REVIEW

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