# REDUCING ADVERSE DRUG EVENTS RELATED TO OPIOIDS IMPLEMENTATION GUIDE


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# Section I: Introduction
# Reducing Adverse Drug Events Related to Opioids (RADEO) *Implementation Guide*

If you are reading this *Implementation Guide* it may be because a patient, maybe even your patient, was harmed, or possibly died from opioid-related respiratory depression, at your workplace. Perhaps your facility has not had a serious safety event related to opioid administration, but you are a chief medical officer (CMO), chief quality officer (CQO), chief of staff (CoS) or a member of your hospital's safety committee and have noticed there are frequent activations of your hospital's rapid response team due to opioid-related sedation or respiratory depression. Many of these events may have resulted in respiratory failure and unplanned transfers to your intensive care unit (ICU). Alternatively, you may be a member of your hospital's pharmacy and therapeutics committee and you have noted that there continues to be a persistent, and what seems to you to be too frequent, use of unplanned opioid reversal agents in your facility. Perhaps you are part of the frontline staff, a nurse or hospitalist who has noticed many "near misses" due to prescribing too high a dose of hydromorphone, or an incorrect patient-controlled analgesia (PCA) setting. These errors were caught, but if perhaps the nurse or pharmacist had been less experienced, there would have been patient harm.

If any of these situations describes why you are referencing this *Implementation Guide*, then you are in good company. The patient safety movement is well into its second decade.[1] Decreasing opioid-related adverse events in all settings is an important and growing body of work that will result in fewer patients harmed.[2] Specifically in the hospital setting, opioids are the most commonly prescribed class of medications, and the second most common class of medications to cause adverse patient events.[3] Described by some as the "dead in bed" syndrome, respiratory arrest and death related to opioids has an incidence that is hard to measure but is real as evidenced by frequent case reports.[4] One review identified 700 patient deaths directly attributed to PCA between 2005 and 2009.[5] Lesser events, such as respiratory failure, unplanned mechanical ventilation, reversal agent administration and unplanned transfers to the ICU, should all be considered near misses and are common. Approximately one in 200 hospitalized post-operative surgical patients experiences post-operative respiratory depression.[6] Other adverse reactions related to opioids, such as constipation or nausea, are even more common. In spite of all these facts, most hospitals have either incomplete or outdated policies or procedures when it comes to safe opioid prescribing and administration. In addition to being common, and at times devastating to patients and caregivers alike, adverse events related to opioids are costly. In a 2011 study, yearly costs in the United States associated with opioid-related post-operative respiratory failure were estimated at $2 billion.[7]

Though the evidence is incomplete, many systems have shown a decrease in patient-related harm with the implementation of rigorous quality improvement (QI) programs to improve opioid prescribing and administration. The Joint Commission recommends specific steps every hospital should take to reduce opioid-related respiratory depression. They include implementing effective processes, safe technology, education and training, and effective tools.[2] This *Implementation Guide* will review how your hospital can meet The Joint Commission recommendations and move toward reducing adverse events related to opioid prescribing and administration.

This work is challenging. Complicating factors include patient expectations. In part, patient expectations are driven by government-mandated surveys. The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) is a government-mandated survey of the patient's experience in the hospital. The results are publicly reported and are tied to hospital reimbursement. Eight dimensions are reported, all of which must meet a threshold level for hospitals to be eligible to recuperate a Medicare reimbursement withhold. One of the dimensions is Pain Management. The HCAHPS survey question reads: "During your hospital stay, how often was your pain well-controlled?" The outcome reported is "always," 4 on a 4-point Likert Scale. It is unknown if hospitals that score well on this answer have more opioid-related respiratory depression. Additionally, in 2001 The Joint Commission brought to light evidence that pain was undertreated in the hospital setting, and recommended measurement and more aggressive treatment of pain for inpatients.[8],[9] Since that alert, use of opioids as well as related adverse events has increased.[10]

The purpose of this *Implementation Guide*, **R**educing **A**dverse **D**rug **E**vents related to **O**pioids, or **RADEO**, is to provide step-by-step instructions for your hospital to implement a successful QI program to make opioid prescribing safer, with fewer adverse events, and much less likely to result in dangerous sedation, respiratory depression and death. Its scope is for hospitalized patients. The *Guide* provides the essential building blocks for developing a QI initiative to improve inpatient safe opioid prescribing and administration including forming a quality improvement project team in your hospital, gaining institutional support and securing buy-in of frontline staff to ensure successful implementation. The *Guide* will also provide strategies for facilitating policy formation, evaluating current processes, tracking progress against implementation goals and identifying best practices. Although the scope of this *Guide* is inpatient patient safety as it relates to opioid prescribing and administration, the *Guide* also discusses transitions of care for patients in the outpatient setting on opioid therapy.

Like many patient safety issues, there is not always clear evidence. The *Implementation Guide* will present evidence and best practice where it exists. Each hospital's QI team will be required to learn from best practices around the country and the medical literature as presented in this *Guide*. Also important will be the experience, culture and environment in your own institution. Implementation will look different site to site, especially where the evidence is not clear-cut. Your QI team will provide the structure and support to combine evidence, best practices and local experimentation to learn what works, or does not, in your hospital to achieve the goal of less patient harm related to opioid administration.

This is exciting work. Dig in, have fun and work together to make a real positive difference in the safety environment in your hospital and the well-being of each individual patient!

**Summary**

- Opioids are one of the most common medications associated with serious patient harm in hospitalized patients.
- Rigorous quality improvement will decrease patient harm associated with inpatient pain management.
- This is a step-by-step *Guide* to improve safety and reduce adverse events for inpatients receiving opioids.

# Section II: How to Implement and Sustain an Improvement Project at Your Hospital to Reduce Adverse Events Related to Opioid Prescribing and Administration

# Step 1: Form an Interdisciplinary Team with a Common Goal

Quality improvement in healthcare requires engaging stakeholders in process analysis and redesigns that result in improved health outcomes for individuals and populations. By definition, this is a team-based activity. Quality improvement design and implementation are much more likely to be successful if frontline staff, those who live with care processes every day, are involved upfront. Step 1 will outline how to form your QI team.

## 1.1 Assembling the Team and Team Rules

When instituting a program to reduce adverse events from opioid prescribing and administration at your institution, the initial step should be the formation of an interdisciplinary team to assess current processes, analyze baseline data and design and implement improvement interventions. Prior to creating a team, your institution will need:

### A Champion

The champion should be a well-respected individual, typically a clinician, who is passionate about quality improvement and able to articulate why it is important to reduce potential opioid-related harm in your institution. The main role of the champion will be to help everyone understand why this is an important project at your facility. The champion will be the salesperson for the project!

### Executive Sponsors

Your institution's team will need sponsorship – an individual or individuals at the C-Suite level who will be able to secure your team financial and personnel resources, keep the work high profile and remove barriers. Typically the executive sponsor(s) are the chief medical officer (CMO) and/or the chief nursing officer (CNO). The sponsors are active in creating the team charter, and work with the champion to gain approval for the project and the team charter from the medical staff and administrative leadership. They work with the team leader to ensure the team meets targets and deliverables.

### Team Leader

This person may or may not be the champion. This person needs administrative, leadership and political skills. The team leader needs dedicated time to ensure project success. The team leader is responsible for providing overall guidance to the project – especially ensuring that frontline staff members are influential in the project team decisions. The team leader should have an understanding of QI and the clinical processes around safe opioid prescribing and administration, but need not be a subject matter expert in either area. The team leader is the interface between the QI team and the sponsors to gain support and resources, and to have barriers to success removed. The team leader keeps medical staff and sponsors updated and dedicated to the success of the project.

### Project Manager

The project manager is the day-to-day coordinator of the initiative. This person schedules meetings, leads meetings, creates minutes, creates agendas, keeps the project budget if needed, creates capital requests, keeps dashboards, provides data analysis, provides between-meeting communication and ideally provides expertise in quality improvement techniques such as lean processes and Six Sigma. Like the team leader, this person needs to have dedicated time for the project. Typically the project manager will be from the quality department, but can be anyone, including a clinician who has sufficient project management skills.

### Team Members

It is critical to have representation from a diverse group of hospital constituents. Most team members should be frontline staff. Including the perspectives of different stakeholders, subject matter experts and frontline staff will lead the team to better solutions.

Essential frontline clinician team members include:

- Nursing
- Pharmacy
- Hospitalists
- Surgery
- Anesthesia
- Emergency Department
- Respiratory therapy

Other team members will probably include:

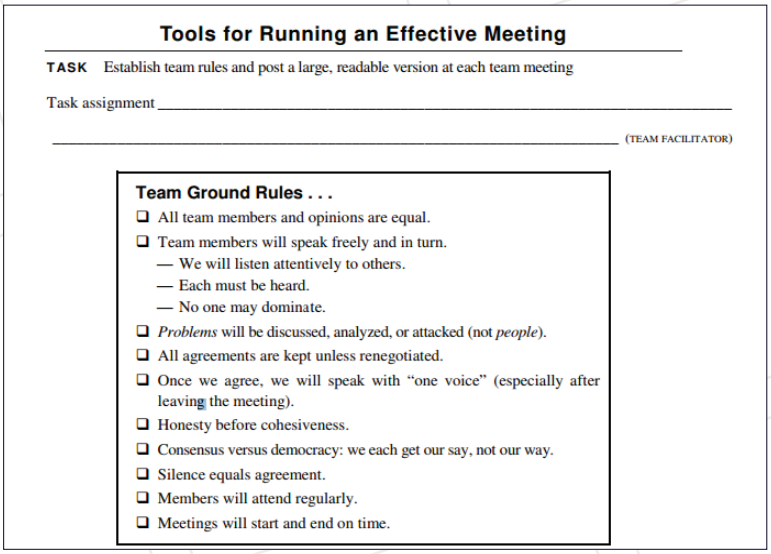
- Hospital leadership
- Primary care physician
- Pain management specialist
- Physician assistants (PAs) and advanced practice nurses (APNs)
- EHR analyst

An analysis of team members should ensure that multiple layers in the organization are represented and that there is a mix of frontline clinical expertise, leadership and subject matter expertise. Team rules are designed to ensure participation among team members without regard to level in the organization. Unless the frontline staff are encouraged and invited to freely share observations and ideas, and unless these ideas are taken seriously, you will lose their essential insights that your team needs.

**Team Rules**

It is also critical when assembling your team to establish team rules. This can be conducted at your first meeting, and it is typically useful to have all team members formally sign a document agreeing to mutually agreed-upon rules. The facilitator is usually tasked with gaining the consensus and enforcing the rules. The Society of Hospital Medicine's (SHM's) Team Rules Task Sheet, which can be utilized as a tool for running an effective meeting when establishing team rules, is shown in Figure 1.

*Figure 1: Team Rules Task Sheet*



**Tools for Running an Effective Meeting**

**TASK** Establish team rules and post a large, readable version at each team meeting

Task assignment _____

_____ (TEAM FACILITATOR)

**Team Ground Rules . . .**

- ❑ All team members and opinions are equal.
- ❑ Team members will speak freely and in turn.
  - — We will listen attentively to others.
  - — Each must be heard.
  - — No one may dominate.
- ❑ *Problems* will be discussed, analyzed, or attacked (not *people*).
- ❑ All agreements are kept unless renegotiated.
- ❑ Once we agree, we will speak with "one voice" (especially after leaving the meeting).
- ❑ Honesty before cohesiveness.
- ❑ Consensus versus democracy: we each get our say, not our way.
- ❑ Silence equals agreement.
- ❑ Members will attend regularly.
- ❑ Meetings will start and end on time.

## 1.2 Developing a Charter

Your sponsors, together with the team members, should create a QI project charter (see Figure 2). The purpose of the charter will be to keep your project focused and on track. Your project charter should have these components:

- Project Name
- Statement of Purpose
- Goals/Aims of QI Project
- Scope/Out of Scope
- Impacted Services/Departments
- Executive Sponsors
- Team Leader
- Project Manager
- Team Members
- Medical Staff, Committee and Administration Reporting Structure and Approvals
- Deliverables and Time Line

*Figure 2: Sample Project Charter*

| **Your Health System Sample Project Charter** | | | | | |
|---|---|---|---|---|---|
| **Project Name:** *Reducing Adverse Events from Inpatient Opioid Prescribing and Administration* | | | | | |
| **Purpose:** | | | | | |
| **Opportunity:** | | | **Scope:** | | |
| | | | **Out of Scope:** | | |
| | | | **Impacted Departments:** | | |
| **Objectives:** | | | | | |
| **Executive Sponsors:** | | | **Team Members, contact information and roles:** | | |
| **Project Lead:** | | | | | |
| **Project Manager:** | | | | | |
| **Preliminary Project Plan*** | | **Target Date** | | **Actual Date** | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| *** Attach detailed plan** | | | | | |
| **Prepared by:** | | | **Approved by:** | | |
| **Date:** | | | **Date:** | | |
| | | | | | |

**Project Goals and Aims**

Some of your team's first work will be to set aims and objectives. Initially, objectives will be broad. Your project charter will lay out the scope of your work based on direction from the project sponsors. Initial objectives will deal with both outcomes and process, and should be based on initial data review. Initial objectives will also be broad in scope. For example, an initial outcome-related objective could be to decrease the incidence of opioid-related complications in high-risk patients. The process objectives should directly relate to expected project outcomes. Associated process objectives could be to map specific processes related to monitoring high-risk patients who are prescribed opioids and to review specific policies related to opioid monitoring of high-risk patients. Initial data review along with the initial broad statement objectives should allow for a list of more specific project aims in the areas of data collection, process and outcomes. Continuing with the example of decreasing opioid-related complications in high-risk patients:

Process objectives:

- Pre-operative screening for obstructive sleep apnea
- Risk assessments for patient receiving high-dose opioids or a patient-controlled analgesia (PCA)
- Sedation assessments for patient receiving high-dose opioids or a PCA

Data measurement objectives:

- Track pre-operative STOP-Bang assessment and increase percentage from X percent to Y percent
- Track risk assessment frequency for high-risk patients and increase assessment percentage from X percent to Y percent
- Track sedation assessment compliance for high-risk patients and increase compliance percentage from X percent to Y percent

Outcome objectives:

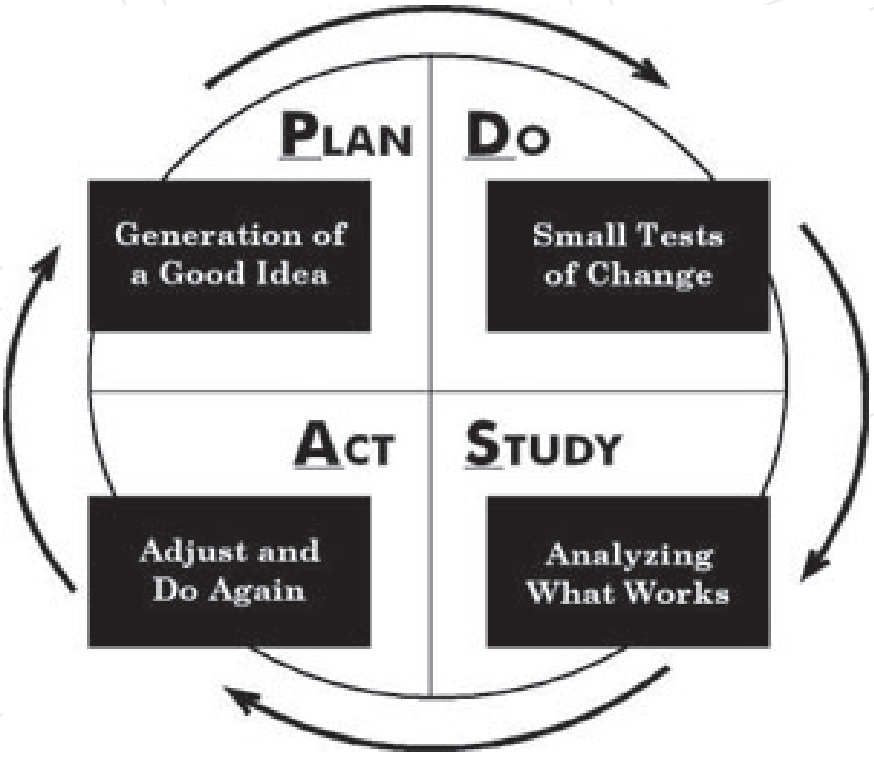
- Decrease naloxone use in high-risk patients from X usages to Y usages per month
- Decrease opioid complications resulting in transfer to a higher level of care from X percent to Y percent
- Decrease post-operative respiratory failure related to opioids from X percent to Y percent

**QI Tools**

A complete review of quality improvement tools is beyond the scope of this *Implementation Guide*. QI tools mostly fall into the categories of evaluating and improving processes, and data tracking and presentation related to process improvement. At least one member of your team should have a level of expertise in QI methods. The hospital quality department should be able to provide the team with expertise in these areas. There are many sources of excellent information on quality improvement. The *Institute for Healthcare Improvement* (IHI) website is an excellent resource. The *American Society for Quality* has a section of its website related to healthcare quality tools.

**P**lan, **D**o, **S**tudy, **A**ct, or **PDSA**, is a basic tool for evaluating all tests of change. See Figure 3 for the PDSA cycle.

*Figure 3: Plan, Do, Study, Act*




Your RADEO team will have many excellent ideas for process changes based on their experience. PDSA brings a structured and tested approach to process improvement. The IHI website has detailed information on how to apply PDSA.

**Summary**

- RADEO in your facility starts with forming an interdisciplinary team dedicated to quality improvement in safe opioid prescribing, administration and monitoring.
- Buy-in depends upon gaining support from frontline staff, and they need to be members of your QI team.
- Your team will need to be appropriately resourced with time and talent.
- To ensure success, administrative and medical staff leadership must support the project and your team.
- A project charter that outlines membership, reporting relationships, goals and objectives, and decision rights will help your team stay on track.
- Your RADEO team should follow a structured approach using the tools of quality improvement.

# Step 2: Obtaining Institutional Support and Moving Forward with the Project

Institutional support is critical to any QI project's success. Support needs to come from all levels of the organization. Support from leadership is needed to gain access to the resources required to change current hospital practices, policies and processes. QI efforts should align with the hospital's mission and vision, and address issues identified as care delivery and operational priorities. Support from the frontline is critical both for process design and implementation. The middle levels of management will be the project workhorses, supporting the QI team, preparing presentations, collecting and analyzing data, and providing subject matter expertise.

The success of any quality improvement project, including reducing adverse drug events (ADEs) from opioid prescribing and administration, will depend upon 1) creating a shared vision in your institution around the value of RADEO, and 2) gaining support from key stakeholders.

## 2.1 Shared Vision

Your RADEO QI project charter should clearly articulate the shared vision. The shared vision should include elements such as:

- The current state in your institution of adverse events related to opioids. This might include financial and/or reputational threat to your organization if there is a failure to improve.
- A statement of the desired future state of adverse events related to opioids.
- A clear articulation of the need for improvement based on the key business and clinical drivers, which include:
  - Patient safety
  - Financial – the cost of adverse events, especially in light of value-based reimbursement
  - Regulatory and compliance
  - Legal protection
  - Institutional reputation
- A statement that ties the RADEO work to the mission and values of the organization.

## 2.2 Gaining the Support of Key Stakeholders

Stakeholders are people or groups whose support will be needed to improve current processes, and who can influence the project's success. Analysis of stakeholder positions will allow formulation of strategies on how to best initiate change.

Gaining the support of key stakeholders is a shared responsibility of the project champion and the project sponsors. First, key stakeholders need to be identified – in some cases by function and role and in other cases by title and name. For example, key stakeholders at your institution will probably include:

- Patients
- Nursing, including nursing leadership
- Hospitalists
- Surgeons
- Anesthesiologists and certified registered nurse anesthetists
- Respiratory therapists
- Pharmacists

- Chief financial officer (CFO)
- Chief executive officer (CEO)
- Chief medical officer (CMO)
- Chief nursing officer (CNO)
- Medical staff leadership including the Medical Executive Committee

It is imperative to evaluate the current beliefs at your institution with respect to safe opioid prescribing and administration and the potential for improvement. The assessment should reveal the answers to these questions about each stakeholder or stakeholder group:

What is the level or type of support needed from each stakeholder? For example, from nursing it is essential that they support the project and that they are very involved in any design work. On the other hand, the CFO will be more concerned with how the capital or full-time employee (FTE) requests affect budget and cash flow, and how these requests support the vision and overall financial performance of the organization.

What risks might this project pose for each stakeholder? For example, for a surgeon this project may represent a perceived loss of clinical autonomy. For a pharmacist or a nurse, this project might represent an increased workload or significant changes in processes.

What benefits will this project have for each stakeholder? Benefits should be identified for each key stakeholder. For example, in the case of nursing, respiratory therapy and hospitalists, a benefit will be fewer unplanned transfers to the ICU.

It might be worthwhile to categorize each stakeholder's level of support, such as shown in the hypothetical example in Table 1:

*Table 1: Level of Support*

| | Strongly Against Change | Moderately Against Change | Neutral | Moderately in Favor of Change | Strongly in Favor of Change |
|---|---|---|---|---|---|
| Nursing | | X | | | |
| Hospitalist | | | | X | |
| Anesthesia | | | | X | |
| Surgery | X | | | | |
| CMO | | | | | X |

Based on this analysis, the sponsors and project champion will devise strategies to engage each of the stakeholders in this work. This type of grid can inform the champion and sponsors where they can count on support and who they can leverage to help gain the support of others who are initially less supportive. Strategies can then be developed to move key stakeholders into the "Strongly in Favor of Change" category. The strategies could include everything from appeals to logic and data to compromises based upon your institution's politics and anything in between.

In addition to individual benefits for each stakeholder, part of creating a shared vision is creating a shared understanding of mutual benefit to all stakeholders. This involves creating a shared understanding that the project will result in higher-

quality care. The self-selected individuals who work in healthcare, especially those who work on quality improvement and in direct patient care, in most instances will engage in a project that has a significant potential to reduce patient harm.

The key to engagement is to involve all stakeholders in the design work, especially frontline staff. The frontline staff will ultimately make or break the project based upon their buy-in to the new policies and procedures that will be implemented with the QI project.

## 2.3 Navigating the Bureaucracy

Buy-in from leadership is important for the success of any initiative, and this must be gained early in the process. Successful implementation of a quality initiative addressing Opioid-Related Adverse Events (ORAEs) will require multidisciplinary coordination.

It is likely the initiative will have to be approved by one or more committees. Gaining buy-in from these stakeholders will facilitate moving forward with the initiative. Knowing how to shepherd an initiative through the necessary committees is important to ensure success.

First, assess the committee structure in your facility. Points to be considered include:

- What are the bylaws addressing committees?
- How are issues brought to committee?
- What is the committee structure? (A large teaching hospital will likely have a different committee structure compared with a community, or a rural critical access, hospital. Integrated health systems have different structures than individual hospitals.)

Second, identify the committees likely to be involved, which may include:

- Facility Executive Committee or equivalent (Hospital CEO, CoS, CNO, etc.)
- Medical Executive Committee
- Quality Improvement Committee or equivalent
- Pharmacy and Therapeutics Committee
- Records Committee
- Education Committee
- Information Technology Committee

Third, identify the following for each committee potentially impacting the policy:

- Committee membership
- Meeting frequency, including when material has to be submitted for consideration at a committee meeting
- Procedure to present an item to the committee
- How resources are allocated to staff the committee
- Where the work of the committee goes for approval

Fourth, ascertain which committee will ultimately oversee your RADEO project. Find out how often they will expect reports, how they expect reports to be delivered or formatted, and the specific data and metrics they would like to see tracked over time.

## 2.4 Personnel and Fiscal Resources

Personnel and fiscal resources are essential to successful implementation of a quality improvement initiative. The following issues must be addressed:

- What is the budgeting and capital allocation process in your facility?
- What is the procedure to request project management resources (fiscal and personnel)?
- How is frontline clinician time set aside to work on the initiative?

## 2.5 Other Factors to Consider When Moving Forward with the Project

As you create a model for establishing policies within your facility, here are important additional considerations that will help ensure success:

### a. Setting goals, achievable versus motivational

Over an extended time horizon, the only appropriate goal for serious harm, such as in-hospital death related to opioid respiratory depression, is zero. But the goals for your team must be consistent with your institution's performance culture. For some institutions any goal other than zero serious harm will not be properly motivational. However, at others a more modest approach may be called for. Based on this and on examination of the current state, the project team and leaders must then determine desired outcomes and program goals. Incremental improvement and meaningful trends in positive directions are more attainable and motivational in one setting, more aggressive goals more effective in others.

### b. Transparency

Depending on your institution's culture, transparency of results to the general medical and hospital staff and even to the public can be a strong motivator and help your team gain institution-wide visibility and support for continuous improvement.

### c. Perform environmental scan

An environmental scan is an assessment of an organization's internal and external environments to detect opportunities and threats that may influence its current and future plans. Step 3 addresses the internal environment. Elements of the internal environmental scan should include an analysis of your organization's readiness for change, your data collection processes and methods, your access to QI resources and tools, and your hospital's current support for quality improvement, including personnel bandwidth to add an additional QI project. Specifically related to opioid prescribing and administration, an assessment needs to be made of the following: 1) your current clinical tools, such as order sets; 2) policies related to opioid prescribing, administration and monitoring; 3) clinical support, whether it be technologic such as clinical decision support or availability of specialized personnel such as pharmacy or pain management specialist consultation; 4) the level of education and sophistication with reference to opioid medications among the medical and hospital staff; 5) the availability of technology such as capnography. The environmental scan will also need to include baseline historical data related to your project's aims – for example, the baseline level of naloxone use outside of emergency department and post-anesthesia units. Your hospital's quality department should be able to aid your QI team in performing your environmental scan.

**d. Charter and formal proposal**

Critical feedback should be invited from all stakeholders on the project charter, and your team's formal proposal should be revised based on this input **(see Step 1)**.

**e. Understand current behavior**

Current behavior of providers and nurses should be examined. For example:

- Who are current leading prescribers of opioids?
- What opioids, and in what doses, are usually prescribed?
- Is there a high concentration of patients receiving opioids on any particular nursing unit?
- What do providers and nursing staff see as problems with opioid prescribing, or in the care and monitoring of patients receiving opioids?

This information can be gathered through informal interviews, group discussions and stakeholder analysis.

**f. Create a data collection system**

Next, the team should obtain baseline metrics. These metrics may include:

- Medical Emergency Team (MET) calls related to opioid administration
- Naloxone usage, excluding post-anesthesia units and the Emergency Department (ED)
- Unplanned transfers to the ICU based on adverse opioid-related patient events
- Any root-cause analysis data available for the hospital quality department for any opioid-related adverse patient events

The Quality Improvement Department may be able to provide these metrics. The Information Technology (IT) Department should be involved early in the process.

**g. Decide how to report baseline results to your target audience**

Reporting these baseline metrics not only will help document performance but also will inform the stakeholders and motivate them to support the project. The results must be interpretable and actionable.

When reporting these baseline results consider the audience, as well as your institution's culture regarding transparency (see consideration b above):

- Background
- Familiarity with project goals
- Familiarity with data reports

**h. Select and introduce behavior change strategies**

After this preparation, behavior change strategies can be selected and introduced. Behavior change must be supported by leadership. Keep in mind that passive strategies, such as educational programs or simply telling providers to assess patients receiving opioids for their risk of obstructive sleep apnea (OSA), are less effective than active strategies such as EMR-embedded tools and reminders for assessing these patients when an opioid is ordered.

**i. Re-evaluate performance and modify behavior as necessary**

ORAEs are high-impact but low-incidence events. This low incidence affects when the follow-up should be done after implementation of behavioral strategies. For example, weekly reporting will not likely reveal any results for a number

of weeks. Monthly or quarterly reporting may be more desirable. The low incidence of adverse events also necessitates measurement of adherence to new processes such as how often staff is correctly using revised order sets or pathways.

Based on follow-up, the behavior change strategies should be examined and modified as necessary. For example, if strategies have included solely educational interventions then consideration of active interventions such as EMR-based reminders may be indicated.

**Additional resources include:**

Policy evaluation and implementation:

- Gilbert T, Taylor JS. *Fam Pract Manag.* 1999 Mar-6(3):28-33

Quality improvement strategies:

- Sharon Silow-Carroll, Tanya Alteras and Jack A. Meyer, Health Management Associates
- Cook DJ et al. Changing behavior to apply best evidence in practice. In Guyatt G, Rennie D, Meade M, Cook DJ, eds. *Users' Guide to the Medical Literature.* 2nd ed. New York:McGraw-Hill; 2008:721-742.

Visit the Quality 101 section of SHM's website for additional information and resources on Steps 1 and 2 of initiating a QI program at www.hospitalmedicine.org/quality101.

**Summary**

- Your RADEO QI team will need the support of key stakeholders who will view the project from different points of view and with varying levels of support and enthusiasm.
- Stakeholder analysis and creating individual approaches to gain support will eventually help create the shared vision needed for success.
- It is important to understand the clinical and political environment of your institution to achieve a shared vision.

## Step 3: Assess the Current State of Safe Opioid Use

This section will guide your RADEO team through the expectations that outside organizations have with reference to RADEO.

### Environmental Scanning

Environmental scanning can be defined as the study and interpretation of the internal and external political, economic, social and technological events and trends that will impact your RADEO QI project. For safe opioid use an environmental scan may include taking an inventory of current structures, processes and outcomes of opioid use. Are there appropriate computerized physician orders for opioids, and do they include safety alerts? What are the hospital drug administration formulary restrictions, policies and guidelines, trends in patient-safety net event reports and local cultural opioid use practices? Scan for policies and practices through all phases of opioid use including risk screening, ordering, opioid administration (initial dosing, titration and tapering) and ongoing clinical monitoring of patients receiving opioid therapy. **See Section 2.5** for more information about the internal environmental scan.

There are external organizations that have policies related to safe opioid administration and prescribing. The Joint Commission suggests following evidence-based actions in four areas to help avoid adverse events associated with opioids: 1) effective processes, 2) safe technology, 3) appropriate education and training and 4) effective tools.

- Effective processes include:
  - Medication reconciliation processes including routine checks of state Prescription Monitoring Program (PMP) on admission
  - Policies and procedures that allow for a second-level review by a pain management specialist or pharmacist for high-risk opioids (e.g., methadone, fentanyl, meperidine and IV hydromorphone)
  - Policies and procedures for tracking and analyzing opioid-related incidents for quality improvement purposes
- Safe technology includes:
  - Use of information technology to monitor prescribing of opioids
  - Red flags/alerts in e-prescribing systems for all opioids. The red flags can be either for dosing limits or alerts, or for verifications.
  - Separation of look-alike sound-alike (LASA) opioids, and use of tall man lettering
  - Conversion support systems to calculate correct doses of opioids to help prevent problems with conversions from oral, IV and transdermal routes
  - Use of smart infusion pumps with dosage error reduction software
- Appropriate education and training includes:
  - Use of both pharmacologic and non-pharmacologic alternatives to opioids
  - Potential effect of opioid therapy on sedation and respiratory depression
  - Difference between ventilation and oxygenation
  - Emphasis on how to assess patients and recognize advancing sedation
  - Patient and caregiver education (verbal and written)
- Effective tools include:
  - Patient Safety Net (PSN) reporting system
  - Risk-screening tools including
    - **STOP-Bang** Questionnaire
    - Opioid Risk Tool (ORT)
      Example: **https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf**

**Monitoring tools**

**Prescription monitoring programs (PMPs)** are now operating in 49 states, and have demonstrated their value on many levels. These databases contain the history of all controlled substances dispensed by state-licensed facilities and providers. The PMP offers key clinical benefits such as identifying duplicative drug therapy, dangerous drug combinations, other providers involved in the patient's care, signs of aberrant behaviors and possible misuse and patient's medication compliance. Providers or their qualified delegated staff should access the PMP before prescribing and as part of ongoing monitoring of treatment with controlled substances. The PMP is an important tool for providers to improve patient care and prevent opioid misuse when prescribing controlled substances.

### When to check the PMP

- Prior to prescribing opioids for a new episode of pain or for transferred patients who are already using opioids
- During the transition from intermittent to chronic opioid treatment
- Routinely for patients for whom you are prescribing chronic opioids and/or other controlled substances
- Regularly for patients who are being treated for a substance abuse disorder
- When conducting an admission or preoperative history and medical exam
- When there is evidence of aberrant behaviors

Other resources include:

- Pasero Opioid Induced Sedation Scale
  Example: IHI: https://www.ihatoday.org/uploadDocs/1/paseroopioidscale.pdf
- Ramsey Sedation Scale – Test of Reusability
- Comfort Scale – Valuable Pain Assessment Tools
- Urine Drug Testing (UDT) Guidelines and Interpretation Resources — An algorithm example from University of Washington: http:enalyepts.washington.edu/anesth/education/forms/pain/UW-UDTinterpretationAlgorithm.pdf
- Patient Safety Net (PSN) reporting system

### Opioid Rules and Guidelines

Also check for state opioid guidelines/rules. Most regulations address use of opioids for chronic pain. Examples include:

- Centers for Disease Control and Prevention (CDC): Common Elements in Guidelines for Prescribing Opioids for Chronic Pain
  - http://www.cdc.gov/drugoverdose/pdf/common_elements_in_guidelines_for_prescribing_opioids-a.pdf
- Federation of State Medical Boards: Model Policy on the Use of Opioids in the Treatment of Chronic Pain
  - http://www.fsmb.org/Media/Default/PDF/FSMB/Advocacy/pain_policy_july2013.pdf
- Federal Guidelines for Opioid Treatment
  - http://www.dpt.samhsa.gov/pdf/FederalGuidelinesforOpioidTreatment5-6-2013revisiondraft_508.pdf
- Group Health Cooperative Chronic Opioid Therapy (COT) Safety Guideline for Patients with Chronic Non-Cancer Pain
  - https://www.ghc.org/all-sites/guidelines/chronicOpioid.pdf
- State:
  - California Medical Board Guidelines for prescribing controlled substances for pain
    - http://www.mbc.ca.gov/licensees/prescribing/pain_guidelines.pdf
  - Florida State Opioid Prescribing Guideline
    - http://fapmmed.net/State_Opioid_Prescribing_Policy.pdf
  - Utah Department of Health Guidelines on Prescribing Opioids for Pain
    - http://health.utah.gov/prescription/pdf/guidelines/final.04.09opioidGuidlines.pdf
  - Washington State Agency Medical Directors Group (AMDG) Opioid Guideline
    - http://www.agencymeddirectors.wa.gov/opioiddosing.asp
  - Washington State Emergency Department Opioid Guideline
    - http://washingtonacep.org/Postings/edopioidabuseguidelinesfinal.pdf

# Step 4: Review of Best Practices in Safe Opioid Use for Hospitalized Patients

Your RADEO team will need tools and an approach to improving patient safety. This section contains an overview of the current state of the art when it comes to safe opioid prescribing and administration, including screening, risk stratification, monitoring, and safe prescribing and administration. Its focus is on presenting the basic information your team will need to reduce and even eliminate serious adverse events related to opioids, particularly reducing sedation and related respiratory compromise. Other adverse reactions to opioids, such as delirium, are also briefly covered. This is not an exhaustive review, and the evidence in many areas is not complete. But this section will provide a guide to the current best practices that your RADEO team will need as a starting point.

## 4.1 Patient Risk Stratification

Before starting opioid therapy, either in surgical or non-surgical settings, it is important to identify any real or potential risks of respiratory depression or other opioid-related adverse effects. Patient comorbidities such as OSA, neurologic disorders, organ impairment, substance abuse history and other medication use are important aspects to consider. See Table 2 highlighting risk factors for opioid-induced respiratory depression.

*Table 2: Risk Factors for Opioid-Induced Respiratory Depression*

**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/m$^2$) |
| 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-naive 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-naive 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 |

Modified and used with permission from Pasero, C., Quinn, Portenoy, R., McCaffery, M., & Rizos (2011). Opioid analgesics. In C. Pasero & M. McCaffery, *Pain assessment and pharmacologic management* (p. 516). St. Louis: Mosby/Elsevier. Copyright © C. Pasero, 2011.

### 4.1.1 Obstructive Sleep Apnea (OSA) Screening

OSA is a common condition that is characterized by periodic obstruction of the upper airways during sleep or excessive sedation. This obstruction can be partial or complete interspersed with episodes of arousal and return of airway to patency. During obstruction episodes, patients can develop hypercarbia and hypoxia. Over the long term, this can lead to pulmonary and cardiovascular disease (Pickwickian syndrome). Additional problems include daytime somnolence due to frequent sleep disturbance and changes in behavior.[11], [12]

The prevalence of OSA in the United States population is estimated around 7 to 22 percent, with more than three-quarters of patients undiagnosed. Obese patients (body mass index [BMI] >30 kg/m$^2$) have a higher risk of OSA compared to the general population (70 to 95 percent) and are four times more likely to have a postoperative respiratory complication. Morbidly obese (BMI >35 kg/m$^2$) patients have even greater complication rates with increased length of stay, venous thromboembolic disease and death.[11],[13]

In the perioperative period, patients with OSA have a higher incidence of respiratory depression and episodes of hypercarbia/hypoxia due to the influence of sedating medications including general anesthetic agents and opioids.[14] Medical patients with OSA receiving opioid medication also demonstrate higher rates of respiratory depression. Frequently, the respiratory depression and respiratory arrest that occurs when OSA patients are under the influence of opioids follows a similar pattern. They start off alert, fall asleep when not observed, become apneic and die within a very brief timeline.[15],[16] Unfortunately, evaluation of sedation scores alone is not helpful since patients are often awake during nurse assessment and fall asleep very quickly when they are no longer stimulated. Identifying these high-risk patients so they can be monitored more frequently and electronically may reduce their risk of opioid-related respiratory depression and death.[15],[17],[18]

#### Sleep Studies

The gold standard for evaluating OSA is a sleep study (polysomnography), which derives an apnea-hypopnea index (AHI).[13], [15],[19] The AHI is the standard that other OSA screening tests are measured against. However, performing a sleep study is not a cost-effective or time-efficient screening tool for all hospital patients. Patients with a high degree of suspicion of OSA, based on history and physical exam, may benefit from a referral for a sleep study prior to a planned surgery or hospital admission when possible. This may be valuable before a large operation, for example, so that plans can be made for postoperative continuous positive airway pressure (CPAP)/Bilevel Positive Airway Pressure (BiPAP) needs.[13],[15] In a minority of cases, more aggressive treatment of OSA may be recommended (e.g., surgery). Patients with known OSA may be asked to bring CPAP machines/masks with them to use during their hospital stay.

#### Screening Tests

Since there is a large portion of patients with undiagnosed OSA, screening pre-operative patients for possible OSA is an important triage method for guiding in-hospital pain management and monitoring needs. A variety of screening tools have been published in the literature with varying degrees of acceptance. Three of the most common are the STOP-Bang, Berlin Questionnaire and the Epworth Sleepiness Scale (ESS).[13],[14]

#### STOP and STOP-Bang

The STOP-Bang criteria has the highest sensitivity (96 percent) for detecting patients at risk for OSA, however, it has a low specificity (16 percent) so it tends to overestimate the likelihood of OSA in patients.[19] The addition of the Bang criteria to the STOP tool greatly increases the sensitivity of the tool in detecting OSA. The tool is simple to use since it is based on a few questions and only one anatomical element. It was designed to be self-administered by the patient. The STOP-Bang tool is the most widely used screening mechanism for OSA in the pre-operative arena.[13]

1. **S**noring – do you snore loudly?
2. **T**ired – do you often have daytime tiredness, fatigue or sleepiness?
3. **O**bserved – has anyone seen you stop breathing while you sleep?
4. Blood **P**ressure – do you have or are being treated for high blood pressure?
5. **B**MI >35 kg/m$^2$?
6. **A**ge >50 years?
7. **N**eck Circumference >17 in or 40 cm?
8. **G**ender – Male?

A total of yes to three or more of these eight questions puts the patient at high risk of undiagnosed OSA. If yes to less than three items, the patient is at low risk.

### Berlin Questionnaire

The Berlin Questionnaire (BQ) is also a widely used OSA screening tool with good validation. This tool (shown in Table 3 below) provides very good sensitivity (84 percent) (although less than the STOP-Bang), but somewhat better specificity (35 percent).[19] The BQ was designed for the primary care environment and includes three categories of questions for a total of 10 questions. Snoring severity, excessive daytime sleepiness and a history of hypertension or obesity are the three categories. Categories 1 and 2 are positive for high-risk OSA when the sum of all the items within the category is ≥2. High risk of OSA is defined as persistent symptoms in Categories 1 and 2 plus presence of hypertension (>140/90) or obesity (BMI >30 kg/m$^2$).[13]

*Table 3: Berlin Questionnaire*

| Questions | Answers | Scoring |
|---|---|---|
| Category 1:<br>1. Do you snore?<br>2. If yes, how loud is it?<br>3. How often do you snore?<br>4. Has snoring bothered others?<br>5. Has anyone noticed that you quit breathing during sleep? | Items 1,4,8,10:<br>Yes (1)<br>No (0)<br>Don't know (0)<br>Item 2:<br>Slightly louder than breathing (0)<br>As loud as talking (0)<br>Louder than talking (1)<br>Very loud – heard in adjacent room (1) | Category 1: Positive = Sum ″ 2 |
| Category 2:<br>6. How often do you feel tired or fatigued after sleep?<br>7. During your waking time, do you feel tired, fatigued, or not up to par?<br>8. Have you ever nodded off or fallen asleep while driving?<br>9. If yes, how often does this occur? | Item 5, 6, 7, 9:<br>Nearly every day (1)<br>3-4 times a week (1)<br>1-2 times a week (0)<br>1-2 times a month (0)<br>Never or nearly never (0) | Category 2: Positive = Sum ″ 2 |
| Category 3:<br>10. Do you have high blood pressure? | | Category 3: Positive = Item 10 is yes or BMI >30 kg/m2 |
| High risk of OSA: 2 or more categories scored as positive | | |

*Berlin Questionnaire. OSA = Obstructive sleep apnea. BMI = Body mass index. (Adapted from Table 2: Lakdawala L. Creating a safer perioperative environment with an obstructive sleep apnea screening tool. J Nursing. 2011)*

### Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) (shown in Table 4 below) is geared to evaluating excessive daytime sleepiness. It is also a simple self-administered questionnaire, which makes it an efficient screening tool for pre-operative evaluation.[13] It has a significantly lower sensitivity (50 percent) but higher specificity (67 percent) as compared to the other two tools.[19] The presence of excessive daytime sleepiness is a very important aspect of OSA when considering opioid-related respiratory depression. However, because there can be a great degree of subjectivity in the answering of the questions, the sensitivity is compromised and the utility of this tool is reduced. The ESS may have a more useful role as a secondary confirmation-screening tool after an initial higher-sensitivity screening tool is used.

The eight questions in the tool represent real-life situations where the patient is asked to rate the likeliness of his or her dozing from 0-3 for each question. A sum is taken of all the scores and a score of ≥10 is considered high risk for OSA.

*Table 4: The Epworth Sleepiness Scale*

| |
|---|
| Use the below scale to choose the most appropriate number for each scenario:<br>0 = would never doze or sleep<br>1 = slight chance of dozing or sleeping<br>2 = moderate chance of dozing or sleeping<br>3 = high chance of dozing or sleeping |
| **Scenario:**<br>Score:_____<br>Sitting and reading _____<br>Watching TV _____<br>Sitting inactive in a public place _____<br>Being a passenger in a motor vehicle for an hour or more _____<br>Lying down in the afternoon _____<br>Sitting and talking to someone _____<br>Sitting quietly after lunch (no alcohol) _____<br>Stopped for a few minutes in traffic while driving _____ |
| Total Sum of Scores: _____<br>Scoring of Daytime sleepiness:<br>≥10 = Sleepy ≥18 = Very Sleepy |

*The Epworth Sleepiness Scale.*
*(Adapted from Table 4: Lakdawala L. Creating a safer perioperative environment with an obstructive sleep apnea screening tool. J Nursing. 2011)*

### OSA Perioperative Screening Recommendations and Summary

For the purposes of a perioperative screening assessment a simple, quick and cost-efficient tool is important for routine use. It is recommended that a screening tool be used as part of a comprehensive perioperative assessment program and may be implemented through an anesthesia pre-operative clinic visit, surgical co-management visit or even a primary care visit. Tools with high sensitivity take precedence over those with better specificity, to identify those patients at high risk of OSA-related perioperative respiratory depression.

### 4.1.2 Assessing Medical and Postoperative Risks

Obstructive sleep apnea is the number one risk factor for opioid-induced respiratory depression.[17] There are multiple medical conditions and diseases that may increase the risk of postoperative drug-induced respiratory depression as well as other opioid-related adverse events. Risk stratification using comorbid disease is one method to reduce opioid-related adverse events. The two main categories of risk are 1) patients with sleep-disordered breathing, which is most commonly due to obstructive sleep apnea and 2) patients with risk factors for postoperative pulmonary complications. Additionally there are some conditions that may increase the risk for non-respiratory opioid-related adverse events such as postoperative delirium, disruptive drug-seeking behaviors and poorly controlled pain.

### American Society of Anesthesiologists (ASA) Classification

The ASA classification system was devised to stratify a patient's medical risk for surgery and anesthesia. The system sorts patients into five categories based on comorbid medical conditions and their effect on the patient's health. This classification system has been shown to effectively predict perioperative risk of morbidity and mortality. Patients with an ASA classification of 3, 4 or 5 pose an increased risk of perioperative morbidity and mortality including opioid-related sedation and respiratory depression.[17],[18]

- ASA 3: A patient with severe systemic disease
- ASA 4: A patient with severe systemic disease that is a constant threat to life
- ASA 5: A moribund patient who is not expected to survive without the operation

### Implications of Comorbid Medical Conditions and Opioid Administration

There are a number of medical comorbidities that, in combination with opioids, may increase the risk of opioid-induced respiratory depression or other opioid-related adverse events. These include obesity, pulmonary disease, cardiac disease, renal disease, chronic pain, hepatic disease, substance abuse and major mental illness.

### Obesity

Morbid obesity (BMI >35 kg/m$^2$) is a significant factor in the development of OSA. Opioids have a clear effect on increasing apneic episodes in patients with OSA. (**See Section 4.1.1** for a detailed description of OSA screening and recommendations.)

Additionally, the obese patient may have obesity hypoventilation syndrome (OHS). The defining characteristic of OHS is daytime hypoventilation with hypercapnia ($PaCO_2$ ≥45 mm Hg) and hypoxemia ($PaO_2$ ≤70 mm Hg). Additionally, OHS patients experience sleep-disordered breathing. The identification and further evaluation of patients with obesity may improve the detection of OSA and OHS. These patients should be considered for non-opioid therapy or closer monitoring when the use of opioids is required, especially when IV opioids or combinations of opioids and other sedating agents are being administered.

### Pulmonary Disease

In addition to OSA or OHS, patients with other pulmonary comorbidities are at increased risk of opioid-induced respiratory depression. Patients with chronic obstructive pulmonary disease (COPD), restrictive lung disease and smokers have increased risk due to reduced oxygen reserves and increased $CO_2$ retention should respiratory depression occur.[18]

### Age/Gender

Older adults (>65 years old), especially those with poor health status, are more sensitive to the sedating effects of multiple drugs including opioids. Older men in particular have a higher risk of developing respiratory failure during a hospital stay.[18] Older patients are at higher risk for renal and hepatic compromise as well as cognitive effects.

### Cardiac Disease

Comorbid cardiac disease, especially poorly controlled congestive heart failure with pulmonary edema, may increase the risk of opioid-induced respiratory depression.[18] It may also compromise hepatic metabolism and renal clearance, e.g., with congestive heart failure.

### Renal Disease

Several opioids have active metabolites that are eliminated by the kidneys. The presence of renal failure increases the risk of respiratory depression, sedation and other adverse events related to opioid administration.[18] Morphine and meperidine are the most problematic opioids for patients with renal insufficiency or renal failure. Morphine is metabolized in the liver to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). The M6G metabolite is a more potent respiratory depressant than the parent drug and in renal insufficiency can result in excessive sedation and respiratory depression. The M3G metabolite is not analgesic but does cause central nervous system (CNS) excitation. Doses of morphine should be reduced with renal impairment, or morphine should be avoided altogether.

Hydromorphone also has active metabolites that could be problematic in renal failure. The primary metabolite is hydromorphone-3-glucuronide (H3G), which has CNS excitation properties but no analgesic effects. There is also a minor amount of 6-hydroxyl reduction metabolites. Due to the predominance of H3G there is likely a lower risk of respiratory depression with hydromorphone in the setting of renal failure compared to morphine.

Fentanyl is metabolized in the liver to norfentanyl, which is non-toxic and inactive. The kidneys eliminate norfentanyl but due to the inactivity of this metabolite, there is no toxic effect in renal failure. Thus, fentanyl is the safest opioid to use in advanced renal failure for acute pain management. However, due to its rapid onset and short duration of action, fentanyl can often be difficult to dose in some situations.

### Hepatic Disease

Like renal impairment, hepatic dysfunction may result in increased sedation and respiratory depression from opioid administration. All of the opioids are metabolized via the liver. Mild hepatic dysfunction is generally not sufficient to cause a clinically significant decrease in metabolism. However, in severe hepatic failure the active parent drug may not be metabolized and each dose may have a longer duration of action and more potent activity as a result of impaired metabolism. A reduction in opioid dose and increase in interval between doses may be necessary. Patients requiring high doses of opioids will need additional monitoring for safety. Patients with a history of alcoholism, ascites and other evidence of hepatic failure have been shown to have a higher risk of developing respiratory failure in general in the hospital,[18] which is then compounded with the addition of opioids.

### Neurologic Disorders

Patients with altered mental status due to neurologic disorders or CNS injury may be more sensitive to the sedating effects of multiple drugs including opioids. Pre-existing cognitive impairment or confusion increases the risk of postoperative delirium from opioids and other causes.[19] Reduction of dose or a change to non-sedating medications may be necessary, along with close monitoring for sedation or delirium. Additionally, the method of administration may need to be considered when prescribing opioids. Neurologic conditions that affect cognitive function may make the use of PCA inappropriate due to the difficulty in patient comprehension. **(See Section 4.2.4 regarding PCA prescribing.)**

### Chronic Pain

Patients with a history of chronic pain pose a special problem for management of acute postoperative pain. Chronic pain is a risk factor for difficult-to-control acute pain, and these patients usually require higher opioid doses regardless of their pre-hospital opioid use.[20] Additionally, patients with pre-hospital opioid use may be at further risk of poorly controlled pain due to opioid tolerance. Frequently chronic pain patients experience continued pain symptoms despite developing respiratory depression since the analgesic tolerance developed from long-term opioid consumption does not make them immune to opioid-induced respiratory depression. In addition to multimodal, non-opioid analgesia, higher doses of opioids will likely be required **(see Section 4.3).** Due to the high opioid dose requirements, these patients often require increased monitoring as well. Early identification of patients with comorbid pain conditions and pre-hospital maintenance opioid therapy may allow for the careful design of an individualized analgesic regimen during their hospital admission that can prevent delays in pain management and extended hospital stays. Assistance from a pain specialist may be necessary.

### Substance Abuse

Patients with either a current or remote history of substance abuse pose a special challenge with regard to pain management during hospitalization. Issues of opioid tolerance, withdrawal and addiction behavior complicate acute pain management. However, patients with current or historic substance abuse disorders still have a right to pain management when admitted to the hospital for an acute illness, surgery or trauma. Immediately following a serious illness or major surgery is not the appropriate time to initiate drug detoxification therapy. However, this right to pain management does not require the use of any particular analgesic agent or route of administration. A careful assessment of the patient's history of substance use and abuse along with recent legitimate and illicit substance use is an essential starting point. Use of an opioid abuse risk stratification tool such as the Opioid Risk Tool (ORT) may also be of use in assessing the likelihood of opioid abuse in a particular patient.[21]

For patients admitted with a known or suspected history of substance abuse it may be useful to order a urine drug screen at admission to evaluate for recent substance use. A query of the state prescription drug monitoring program database can provide another important piece of information regarding valid prescribing and any evidence of "doctor shopping." Patients who are exhibiting aberrant drug-seeking behaviors are potentially disruptive to their own care or the care of others and may place their health in jeopardy. Some examples of aberrant drug-seeking/use behaviors in the inpatient setting include:

- Use of opioids from outside of the hospital without consent or permission
- Resisting changes to medication dose, route or drug despite adverse effects
- Hoarding opioid medications
- Injection of an oral opioid formulation
- Seeking over-sedation as a consequence of pain treatment
- Use of opioids for sleep or anxiety management

- Lack of correlation between patient's report of pre-hospital opioid use and the prescription drug monitoring program database
- Requesting rapid intravenous (IV) push administration of opioids and/or rapid flush after IV administration
- Requesting IV antihistamine administration with or immediately after IV opioid administration
- Altering or tampering with PCA pumps

In patients with aberrant drug-seeking/use behaviors it is important to acknowledge the desire to manage their pain but place clear limits on the aberrant behaviors. This may include the use of a behavioral contract. Hospital policies that address the appropriate use of IV opioids for pain management may be one means of providing guidance for prescribing these agents and limiting their use for non-analgesic purposes. The use of an analgesic plan for patients who are frequently admitted with pain crises and may have a history of aberrant behaviors may also allow for consistency of the analgesic plan for each admission and reduce the possibility of manipulation among various providers and nurses.

**Major Mental Illness**

As with patients who have substance abuse histories, patients with mental illness have a right to appropriate pain management when admitted to a hospital with an acute painful condition. Withholding opioids for severe acute pain is likely to exacerbate anxiety, depression and other symptoms of mental illness. Pre-admission anxiety is a risk factor for increased consumption of opioid analgesics.[20] Patients with major mental illness are potentially at increased risk of a comorbid substance disorder and may experience other adverse psychological effects from opioid administration. Opioid use may mask or mimic mental illness. A psychiatric consultation may help to differentiate opioid intoxication, abuse or dependence from mental illness to aid in developing an appropriate treatment plan.

### 4.1.3 Assessing the Additive Sedation Risk from Non-Opioid Medications

The primary focus of this text has been to discuss the sedating and respiratory depressant risks of opioid medications in hospitalized patients. However, the combination of opioids with other sedating non-opioid medications should also be considered. Often, patients in the hospital are on several sedating medications. Some of this stems from baseline home medications, while other patients are on complex multimodal analgesic regimens to help avoid opioid escalation. Awareness of the sedating potential of different medication classes and more aggressive monitoring for these patients may help reduce respiratory events in patients also receiving opioids. Frequent monitoring of sedation level is necessary for these patients.

**Benzodiazepines**

Benzodiazepines are inhibitors of GABA-A receptors, which have a heavy concentration as inhibitors in brainstem respiratory centers. When used alone they are mild respiratory inhibitors but when combined with opioids there is a synergistic respiratory inhibition. The combination of opioids and benzodiazepines has been implicated in numerous pre- and in-hospital cases of fatal respiratory depression. Patients are often on chronic benzodiazepines prior to arriving in the hospital for a variety of reasons including anxiety/depression, muscle spasms and sleep disorders. In addition, hospitalized patients receive benzodiazepines as premedication for procedures and to assist with in-hospital anxiety, sleep disturbance and occasionally as a muscle relaxant. Depending on the patient's prior tolerance to these medications, benzodiazepines can be very sedating, particularly when combined with opioid therapy. Care must be taken when patients are prescribed both medications. Common benzodiazepines include alprazolam, lorazepam, clonazepam, diazepam, temazepam and midazolam.

### Anticonvulsants/Gabapentinoids

Several meta-analyses have demonstrated that perioperative administration of gabapentinoids such as gabapentin or pregabalin can lead to significant postoperative sedation. There is limited evidence regarding the risk of respiratory depression in patients receiving opioids and gabapentinoids, however, there is some evidence showing a trend in that direction. However, since there is evidence for the opioid-sparing analgesic effect of perioperative gabapentinoids, they will continue to be used for many patients as part of a multimodal pain regimen. Care must be taken during initiation and titration of gabapentinoid therapy. Situations that need more aggressive monitoring include immediately after surgery when other sedating medications are used and effects of anesthesia are lingering, when using higher-than-normal starting doses of a drug, in elderly patients and in patients with comorbidities, especially renal failure.

### Muscle Relaxants

Muscle relaxants are frequently used as adjunctive analgesia in multimodal protocols, particularly for abdominal and spine surgery. All muscle relaxants have sedative effects that may be additive when combined with other centrally acting drugs, including opioids. Combining muscle relaxants with opioids can lead to greater sedation, especially in patients who are elderly or naïve to these medications. Patients frequently complain of dizziness and lightheadedness as early signs. Common muscle relaxants of concern are cyclobenzaprine, baclofen, methocarbamol and tizanidine. Carisoprodol is a precursor to a barbiturate and should be avoided.

### Antidepressants

Antidepressant medications come in a variety of classes, all of which carry some sedating potential, particularly with initiation of therapy. Patients taking antidepressants prior to admission may be tolerant to the sedating potential of these medications, and suddenly stopping chronic antidepressant therapy can be harmful for the patient. However, occasionally some situations may arise where patients are started on an antidepressant in the hospital due to mood disorders, sleep disorders or as an adjunct for pain management.

Tricyclic antidepressants, such as nortriptyline or amitriptyline, can be used as mood stabilizers and as pain adjuncts but have significant sedative properties. Mirtazepine is a tetracyclic antidepressant that patients are sometimes prescribed for nighttime sleep disturbance. Trazadone is an atypical antidepressant that is commonly used for the treatment of insomnia. When the dose of these medications is increased, or the drug is administered with opioid medications, excessive sedation can occur. Serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine can also be used as pain adjuncts and are less sedating than older antidepressants. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline are typically much less sedating but lack analgesic efficacy.

### Antipsychotics

Antipsychotic medications can be given to patients for a variety of reasons in the hospital including agitation, mood disturbance, sleep disturbance, delirium and nausea. These medications can be very sedating and should be used carefully in conjunction with opioids. Common antipsychotic medications used in the hospital include haloperidol and risperidone.

### Pain Adjuvants

Multimodal analgesia utilizes multiple non-opioid pain adjuvants to help reduce opioid consumption. However, some of these medications carry their own sedation risks.

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist anesthetic, which is often used for perioperative pain management. The opioid-sparing analgesic effects could have a beneficial effect on opioid-related respiratory depression

since ketamine alone has no respiratory depressant effects. Ketamine does produce dose-dependent sedation and dissociative anesthesia. There is limited data regarding the co-administration of ketamine and opioids and whether there is a positive or negative effect on net respiratory depression.

Clonidine is an alpha-2 agonist, which is sometimes added to pain treatment regimens. It can be given with intrathecal injections, in epidural solutions, with peripheral nerve blocks, intravenously or orally in order to enhance analgesia. There is evidence that clonidine produces dose-dependent sedation and that doses in excess of 150 mcg are associated with excess sedation and adverse events. Doses <150 mcg have not been consistently associated with excess sedation. Caution must be used in elderly patients or patients with existing delirium.

Dexmedetomidine is a more selective alpha-2 agonist used for ICU sedation and has been shown to have analgesic effects as well. It produces sedation without any respiratory depression and has been shown to have opioid-sparing analgesic effects on postoperative pain. However, it may certainly cause additive sedation.

### Antihistamines

Antihistamine medications such as diphenhydramine and hydroxyzine are often used for itching, sleep, nausea and medication reactions. However, antihistamines can be very sedating and have been shown to have a combined respiratory depressant effect with opioids. Antihistamines are commonly prescribed for opioid-induced pruritus despite the fact that most opioid-induced pruritus is not histamine mediated and there is little clinical evidence of antihistimines' efficacy for opioid-induced pruritus.[22]

### Antiemetic Medications

Patients frequently become nauseated with opioid medications, and antiemetics may be used to prevent or treat this side effect. Promethazine and prochlorperazine are common antiemetics that can have profound sedating effects with a potentially additive respiratory depressant effect with opioids. Ondansetron causes less sedation in most patients and can function as an alternative antiemetic when needed. Droperidol, which is related to haloperidol, has a significant dose-dependent sedating effect that, when combined with opioids, may potentiate respiratory depression.

*Table 5: Drug Class and Percentage of Patients Experiencing Somnolence or Sedation*

| Drug Class | Medication | Percentage of patients experiencing somnolence or sedation |
|---|---|---|
| Hypnotic Agents | Zolpidem (*Ambien®*) | 2-15 |
| | Trazodone (*Desyrel®*) | 24-46 |
| Antihistamines | Diphenhydramine (*Benadryl®*) | 10-25 |
| Antiemetics | Prochlorperazine (*Compazine®*) | Specific percentage not reported; drowsiness reported as a common side effect |
| | Promethazine (*Phenergan®*) | Specific percentage not reported; respiratory depression reported in the pediatric population |
| | Metoclopramide (*Reglan®*) | 2-10 |
| Benzodiazepines | Alprazolam (*Xanax®*) | 23-76.8 |
| | Clonazepam (*Klonopin®*) | 25-50 |
| | Diazepam (*Valium®*) | 9 |
| | Lorazepam (*Ativan®*) | Specific percentage not reported; sedation and respiratory depression at high doses |
| | Temazepam (*Restoril®*) | 9 |
| Muscle Relaxants | Baclofen (Lioresal®) | 10-63 |
| | Cyclobenzaprine (Flexeril®) | 39 |
| | Methocarbamol (Robaxin®) | Specific percentages not reported; drowsiness, dizziness, lightheadedness reported as common |
| Other | Hydroxyzine (Vistaril®) | Specific percentage not reported; drowsiness, sleepiness, and respiratory depression has been reported |
| | Gabapentin (Neurontin®) | 4.5-21.4 |

*(Adapted from: Jarzyna D, Jungquist C, Pasero C, Willens J, Nisbet A, Oakes L, Dempsey S, Santangelo D, Polomano R. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. Pain Manag Nurs. 2011;12:118-145)*

*Table 6: Pharmacologic Agents: Summary of Evidence*

**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. |

*(Adapted from Table 4: Jarzyna D, Jungquist C, Pasero C, Willens J, Nisbet A, Oakes L, Dempsey S, Santangelo D, Polomano R. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. Pain Manag Nurs. 2011;12:118-145)*

### 4.1.4. Overall Risk Assessment – Building a Tool That Will Work in Your Hospital

An overall risk assessment for opioid-related respiratory depression in a hospitalized patient can be challenging to implement. Most guidelines and tools that have been published for standardizing risk assessment are related to surgical patients. However, medical patients often have the same risk factors as surgical patients, and the following recommendations can be adapted for local development of a tool for use throughout the hospital just as effectively. Identification of high-risk patients before admission by their primary care physician or surgeon, or early after admission by the primary team or pharmacists, can help steer the care pathway toward a safer approach. Preoperative screening, by the surgeon, anesthesiologist, nurse anesthetist, primary care physician or in a multidisciplinary preoperative screening clinic, can further elucidate high-risk patients for high-risk operations. Communication between the relevant parties, standardized processes for decision making and coordination with inpatient services is essential to the safe care of these complex patients.

Although no perfect risk assessment tool has been built that addresses all concerns, all evaluations should start with a thorough history and physical exam. Clarification regarding a patient's medication history and comorbidities, as well as any planned surgeries or procedures, can be pivotal to determining the appropriate next steps.

Identifying OSA is an important part of the preoperative assessment. OSA is a major risk factor for opioid-induced respiratory depression in the hospital and for patients who are discharged home on continued opioid therapy. Triaging which patients require extra monitoring, which require changes in pain management plans and which may have the need for CPAP or BiPAP is necessary for cost-effective care that also avoids major respiratory events. **(See Section 4.1.1 for OSA screening tools.)** Choosing an OSA screening tool is the first step in identifying high-risk patients. The STOP-Bang tool is a commonly used self-administered questionnaire that has a high sensitivity for undiagnosed OSA. Patients can complete this survey during their intake paperwork completion.

Taking a thorough history of comorbidities that might affect the metabolism of opioid medications or increase a patient's sensitivity to opioids is an important next step to creating a tool. This, too, can be initiated on a patient's intake form and then can be followed up on while taking a complete history. Conditions such as renal disease, pulmonary disease, cardiovascular disease, as well as allergies and chronic opioid dependence **(see Section 4.1.2)** need to be considered before establishing a pain management plan.

The invasiveness of any operations, procedures and anesthesia need to be accounted for in the assessment as well. Superficial surgery under sedation or minimal anesthesia poses minimal risk to a patient since it often doesn't create significant pain requiring high doses of opioids. In contrast, general anesthesia combined with major invasive surgery (e.g., spine surgery) can create the situation for residual anesthesia-related respiratory depression in addition to high opioid doses for pain control in the postoperative period. These patients would require closer monitoring and careful opioid dosing.

Lastly, many patients are on a variety of non-opioid medications that can potentiate the sedation and respiratory depression of opioids taken in the hospital. Medications such as benzodiazepines, antihistamines and antidepressants can interact with higher doses of opioids while the patient is in the hospital. Pre-admission evaluation of any home opioid use along with the opioid dosing regimen, duration of use and a review of other past pain medication use can help guide inpatient management strategies and expected side effect issues. Ongoing monitoring and clinical decision support tools for newly prescribed medications can be useful to practitioners to avoid creating an unexpected polypharmacy situation.

The American Society of Anesthesiologists (ASA) has created a scoring system (shown in Table 7) to estimate perioperative risk for patients with OSA. This system does not take into account comorbid medical conditions or the presence of polypharmacy, but it can be useful as part of a larger screening profile before patients go to the hospital.

*Table 7: ASA Scoring System for Perioperative Risk from OSA: Example**

**Table 2.** Scoring System for Perioperative Risk from OSA: Example*

| | |
|---|---|
| A. Severity of sleep apnea based on sleep study (or clinical indicators if sleep study is not available) | |
| Point score: (0–3)†‡ | |
| Severity of OSA (table 1) | Points |
| None | 0 |
| Mild | 1 |
| Moderate | 2 |
| Severe | 3 |
| B. Invasiveness of surgery and anesthesia | |
| Point score: (0–3) | |
| Type of surgery and anesthesia | Points |
| Superficial surgery under local or peripheral nerve block anesthesia without sedation | 0 |
| Superficial surgery with moderate sedation or general anesthesia | 1 |
| Peripheral surgery with spinal or epidural anesthesia (with no more than moderate sedation) | 1 |
| Peripheral surgery with general anesthesia | 2 |
| Airway surgery with moderate sedation | 2 |
| Major surgery, general anesthesia | 3 |
| Airway surgery, general anesthesia | 3 |
| C. Requirement for postoperative opioids | |
| Point score: (0–3) | |
| Opioid requirement | Points |
| None | 0 |
| Low-dose oral opioids | 1 |
| High-dose oral opioids, parenteral or neuraxial opioids | 3 |
| D. Estimation of perioperative risk: | |
| Overall point score: the score for A plus the greater of the score for either B or C: (0–6)§ | |

* A scoring system similar to the above may be used to estimate whether a patient is at increased perioperative risk of complications from OSA. This example, which has not been clinically validated, is meant only as a guide, and clinical judgment should be used to assess the risk of an individual patient. † One point may be subtracted if a patient has been on CPAP or NIPPV before surgery and will be using his or her appliance consistently during the postoperative period. ‡ One point should be added if a patient with mild or moderate OSA also has a resting $PaCO_2$ >50 mmHg. § Patients with score of 4 may be at increased perioperative risk from OSA; patients with a score of 5 or 6 may be at significantly increased perioperative risk from OSA.

CPAP = continuous positive airway pressure; NIPPV = noninvasive positive pressure ventilation; OSA = obstructive sleep apnea.

*Adapted from Table 2: American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology. 2014;120(2):268-286.*

Pre-admission identification of a high-risk patient should be communicated with the inpatient teams to allow for appropriate preparation. For surgery, avoidance of general anesthesia when possible, increased monitoring during postoperative care (particularly in the first 24 to 48 hours), inpatient use of CPAP/BiPAP, avoidance or cautious dosing of continuous and scheduled opioid medications (including neuraxial or continuous IV PCA) and clear discharge instructions regarding the risk of respiratory depression at home can all be addressed once a high-risk patient has been identified. Similar precautions can be taken for medical patients admitted for acute pain events.

Patients with a high risk of respiratory depression in the hospital, particularly patients with OSA, multiple comorbidities, having large operations or on multiple medications, can develop sudden respiratory compromise when given opioids for pain control. Aggressive management, close monitoring and coordination can facilitate safer care in these patients. However, identifying high-risk patients before an event occurs is essential to delivering the necessary care in an efficient manner.[22]

## 4.2 Safe and Evidence-Based Prescribing and Dispensing

Clinical evidence, pharmacological principles, safety principles and the regulatory environment will all play a role as your RADEO team improves the opioid prescribing and administration processes in your hospital to make them safer. Hospital medical staffs vary in their levels of sophistication and experience with opioid safety. The following section will review for your RADEO team the principles of clinical opioid pharmacology in a practical way that focuses on patient safety for both opioid-naïve and -tolerant patients. Also presented are tools to compensate for the knowledge deficits and potential prescribing errors of providers.

### 4.2.1. Dose, Route, Frequency and Range Order Consideration

#### PRN Range Analgesic Orders

Use of pro re nata (PRN) opioid orders (e.g., 'morphine 2-8 mg IV q2h PRN') is a practice designed to provide flexibility in dosing to meet an individual's unique and changing needs. However, orders with a wide dose range or vague wording have been shown to be a source of medication errors due to unsafe interpretation. A dose range should be at least two times, but generally no larger than four times, the smallest dose.

Following the release of the pain management standards and development of national patient safety goals, The Joint Commission (JC) surveyors began inquiring into institutional policy and procedures surrounding the use of PRN range opioid orders. During accreditation reviews, surveyors encouraged detailing in range orders, such as the designation of specific dose or route of analgesia based on pain intensity ratings. Pain as the "fifth vital sign" was originally developed to increase visibility of pain assessment in the clinical arena but became misconstrued by some as an edict to treat to a target pain rating. With the encouragement of JC surveyors, many institutions created policies that led to the development of PRN orders based solely on patient report of pain intensity indexed with a numeric scale. In response to questions and concerns by clinicians about the course of range order policies, the American Society for Pain Management Nursing, in collaboration with the American Pain Society (APS), developed a national consensus statement to support and clarify the use of PRN opioid analgesic range orders.[23],[24] Even though many practice guidelines recommend that the choice of analgesic be based on the severity of pain, orders linking opioid doses to pain intensity ratings have been associated with increased rates of significant adverse events.[25],[26]

***Considerations for writing and interpreting PRN range opioid orders:***

- **Avoid therapeutic duplication consisting of more than one type of PRN opioid by the same route.** If PRN opioids from different routes are ordered, give clear indication for use (i.e., use oral route unless patient is nil per os (NPO) or vomiting, use IV route prior to dressing change).
- **Avoid prescribing a dose based on pain ratings.** While severe pain may require more aggressive analgesic treatment, a nonlinear relationship has been demonstrated between opioid dose and the visual analog scale.[27] There is high variability in individual responses to opioid doses.
- **Reasonable range.** A range order should be large enough to provide options for dose titration, but small enough to ensure safety. The maximum allowable difference between the high and low dose for analgesic dose range orders should be no more than four times the lowest dose (e.g., four times 2 mg is 8 mg).
- **Patient's prior drug exposure.** If the patient is opioid naïve, the first dose administered should be the lowest dose in the range. If the patient is opioid tolerant, or has received a recent dose with inadequate pain relief and tolerable side effects, a dose on the higher end of the range is acceptable.
- **Prior response.** Inquire about the patient's response to previous doses. How much relief did prior doses provide, and how long did it last? Did the patient experience side effects?
- **Age.** For very young or elderly patients, start low and go slow – begin with a low dose and titrate up slowly and carefully.
- **Liver and renal function.** If your patient has hepatic or renal insufficiency, anticipate a more pronounced peak effect and a longer duration of action.
- **Pain severity.** As a general rule, for moderate to severe pain increase the dose by 50 to 100 percent; do not increase by >100 percent at any time. To "fine-tune" the dose once pain is at a mild level, increase or decrease by 25 percent.
- **Anticipated pain duration.** Is the pain acute, chronic or progressive (likely to worsen)? In other words, is the patient likely to require more or less analgesic over time?
- **Pharmacokinetics.** Know the onset, peak and duration of action for the specific drug ordered. Unlike scheduled long-acting opioid formulations, doses of short-acting opioids can be increased at each specified dosing interval.
- **Comorbidities**. Debilitated patients, or those with respiratory insufficiency, may be at more risk for hypoxia if over-sedated. Patients with cognitive impairment are more likely to become confused.
- **Use of other sedating drugs.** When other CNS depressants are administered in combination with opioids, the dose of each medication required to achieve the desired effect may be 30 to 50 percent less than if either drug was administered alone.
- **Combination drugs.** Limit doses of combination drugs: opioids with acetaminophen or a nonsteriodal anti-inflammatory drug (NSAID). Average adults should not receive more than 4,000 mg of acetaminophen in 24 hours. If substantial upward dose titration is required or anticipated, use opioid-only preparations.
- **Avoid administration of a partial dose.** Partial doses at more frequent intervals may result in ineffective pain relief and create time delays in the ability to administer a full dose within the allowed range (i.e., giving oxycodone 5 mg every hour when the order reads 5 to 15 mg every three hours).

***Examples include:***

- Opioid-Naïve
  - Oxycodone 5-15 mg PO every 3h PRN pain
  - morphine sulfate 1-3 mg IV every 2h PRN pain if unable to tolerate oral analgesia
- Opioid-Tolerant
  - Oxycodone 10-40 mg PO every 3h PRN pain
  - morphine 1-4 mg IV every 15 minutes, max 3 doses for dressing changes, boluses to be completed in 1 hour, may repeat every 4 hours PRN

*Example: Administrative Policies and Procedures*

**RANGE ORDERS**

**POLICY:**

The purpose of this policy is to define the guidelines for interpretation of range orders.

**PROCEDURE:**

Medication orders that express the dose with a lower and upper limit are considered "range orders." Range orders shall be interpreted as follows:

1. The initial dose of a new range order will be interpreted as the lowest dose. The nurse may initiate therapy with doses higher than the minimum on the original order if there is information (such as patient history) that would indicate that smaller doses would be ineffective for that patient.
2. The patient's response to the initial dose should be assessed earlier than the prescribed interval.
3. Within the parameters of the order, the nurse may adjust subsequent doses higher, incrementally, if he/she has assessed the response to the initial dose to be suboptimal.
4. If the initial dose is suboptimal, the nurse may give supplemental doses earlier than the prescribed frequency. In such cases the cumulative dose should not exceed the maximum dose in the specified time interval.

If a frequency range is written, it will be entered into the pharmacy system using the shortest interval. E.g., every 2-4 hours PRN will be entered as every 2 hours PRN.

**4.2.2 Initiating Opioids: Opioid-Naïve Patients**

**Choosing an appropriate route of delivery**

The preferred route for administering opioid analgesics should be orally whenever feasible. The slower rate of onset provides a safer method of delivering opioid analgesics for patients who are able to tolerate oral intake. In the immediate postoperative period or when pain onset is rapid and unpredictable, it will be necessary to use the intravenous route. Intravenous medication should be offered for acute pain if faster onset is needed or if the patient is unable to take medications by mouth. Some combination of oral and intravenous may be necessary for some patients with acute

pain, especially post-surgical pain. In order to give clear prescribing instructions to nurses it is important to have clear orders for when they should use each drug and route. The use of the term "breakthrough pain" has been employed for such circumstances when oral administration is the preferred route but an intravenous agent is administered for pain exacerbations. The concept of breakthrough pain is usually associated with cancer-related pain when the patient has spikes of pain that "break through" their usual baseline analgesic regimen. In the patient who is only on PRN opioids after surgery this definition becomes less clear. An alternative is the creation of specific orders that allow for a "rescue dose" of either an oral or an intravenous opioid when the standard PRN opioid is either not available (between the dosing interval) or has been given but did not work to control the pain.

Patients who are not able to take oral agents can be placed on PRN intravenous opioids for moderate amounts of pain. However, for a patient requiring around-the-clock IV bolus opioid more frequently than every three to four hours it is preferable to utilize a PCA. The use of continuous intravenous infusions of opioids, with or without a PCA option, should be avoided in the opioid-naïve patient outside of the ICU. Continuous administration of opioids in the naïve patient places him or her at elevated risk of respiratory depression.

The transdermal route of delivery is an inappropriate route for opioid-naïve patients or for the treatment of acute pain. The onset is too slow to adequately treat acute pain and titration is very difficult. In the opioid-tolerant patient who is already on transdermal opioids, continuation of the transdermal agent is appropriate. **See Section 4.2.3** for continuation of opioids in the opioid-tolerant patient.

**Choosing an appropriate drug**

There are essentially three intravenous opioids available for the treatment of acute pain in hospitalized patients: morphine, hydromorphone and fentanyl. There are potentially a wider selection of choices for oral immediate-release opioids but for economic and practical reasons the main choices will be morphine, hydromorphone, oxycodone and hydrocodone/acetaminophen.

Many hospitals have a preferred drug for use as the first-line intravenous or oral opioid. Obviously there will be patient-related reasons to choose a different agent including true allergy and, much more commonly, intolerances to one opioid or another. For the intravenous route, most hospitals will choose to use morphine or hydromorphone. Neither drug has clear advantages over the other. Some providers may feel that hydromorphone produces less pruritus or nausea than morphine but there is no clear data to prove this. There may be a slight safety advantage to using morphine over hydromorphone, especially with patient-controlled analgesia because hydromorphone is often dosed in fractions of a milligram (i.e., 0.5 mg IV PRN, or 0.2 mg q10 min in a PCA). This presents the opportunity for misreading the decimal or incorrectly programming the PCA pump with a whole number instead of a fraction. Fentanyl has one clear disadvantage over the other two agents as a first-line analgesic outside of the perioperative and intensive care settings. While its onset is more rapid than morphine or hydromorphone, its duration of action is much shorter. Thus, for PRN dosing it would require more frequent administration.

The selection of a preferred opioid for oral administration is somewhat less clear. There are some who would advocate using the same drug for intravenous and oral administration. This has the advantage of reducing confusion for patients and providers. Also, if there are side effects, it would be clear which drug is causing the side effect. However, the two primary intravenous opioids, morphine and hydromorphone, have some distinct disadvantages as first-line oral opioids. Morphine immediate-release tablets come only in 15mg increments. One 15mg tablet is often too large a dose for moderate pain, certainly in the frail or elderly patient. Additionally, a 30mg tablet is likely too large an increase from 15mg in the opioid-

naïve patient. Morphine is available in an oral liquid formulation and some providers will utilize this for patients who are frail or sensitive (e.g., palliative population).

Hydromorphone comes in somewhat smaller increments but the lowest dose tablet (2mg) is still the equivalent of 10mg of morphine, which may be larger than necessary for moderate pain. Also, the next dose increase would be 4mg of hydromorphone or 20mg of morphine. Again this is a significant change from 10mg for the opioid-naïve patient.

The hydrocodone/acetaminophen products provide a smaller dose increment since they come in 5mg tablets equivalent to 5mg of morphine. This dosing increment allows for more flexibility for smaller doses in the elderly or frail and stepwise increases in those whose pain is not adequately being controlled. Unfortunately immediate-release hydrocodone is only available in combination tablets with acetaminophen. This increases the risk of accidental acetaminophen overdoses if a PRN dose of acetaminophen is given or if the patient requires more opioid for pain than the maximum number of hydrocodone/acetaminophen tablets would allow. Additionally, the small amount of acetaminophen in each individual tablet (325mg) likely provides very little analgesic advantage compared with much larger doses. Research on acetaminophen for acute dental pain has shown that a larger individual dose, up to 1000mg, is more effective.[28] There is also data in the orthopedic literature that the use of scheduled doses of acetaminophen as part of a multimodal analgesic regimen can have an opioid sparing effect.[29] The use of hydrocodone-acetaminophen combination products makes this difficult.

The final oral option is a short-acting oxycodone. This agent provides smaller dosing increments like the hydrocodone products but is available with or without the admixed acetaminophen. For this reason, it may be the most advantageous agent to use as a first-line immediate-release opioid in hospitalized patients.

### Age-based dosing of opioids

Clearance of opioids decreases with age and thus dosing intervals may need to be longer and/or doses lowered to avoid accumulation. Additionally, drugs with active metabolites may pose a more significant issue in the older adult.[25] The use of short-acting agents with short half-lives will help to reduce accumulation-related opioid adverse effects. Older patients are also more sensitive to the sedating effects of opioids and, in conjunction with comorbid respiratory or cardiac diseases, are at higher risk of opioid-related respiratory depression.

### Appropriate intervals for PRN opioids

As needed or PRN administration of opioids for moderate and short-lived pain is common in hospital settings. It is important to provide education to patients who are prescribed PRN analgesics that they must ask for the pain medication and that it is important that they ask in order to "stay on top of the pain." The duration of action of oxycodone, morphine and hydromorphone is similar, in the range of three to four hours. The oral administration of immediate-release opioids results in an analgesic onset at around 30 to 45 minutes while the intravenous administration of most opioids will have an analgesic onset in approximately 10 to 20 minutes. The standard starting dose interval is three to four hours.[30] Some patients requiring intravenous opioids will achieve better coverage with an interval of two hours. However, patients requiring intravenous administration every two hours are generally better managed with a PCA. For patients with continuous pain, the use of some scheduled opioid analgesic instead of only PRN opioids is likely to provide better pain control.[30]

### Multimodal Analgesia

A number of groups have published guidelines regarding hospital and perioperative pain management with recommendations for the use of multimodal analgesia.[30],[31] One of the principles of safe opioid prescribing is to use the lowest acceptable dose to limit the risk of adverse events. The purpose of multimodal analgesic therapy is to improve analgesia and reduce opioid requirements and the resulting opioid-related adverse effects. Opioid-naïve patients may be

at higher risk of opioid-related sedation and respiratory depression, so the use of multimodal analgesia may provide better pain relief than opioids alone while reducing opioid-related adverse effects.

There are a number of drugs and techniques that are employed in a multimodal, opioid-sparing, analgesic regimen. Adding multiple agents and techniques allows the use of lower doses of each analgesic with lower risk of adverse effects. A complete description of the use of these agents and techniques is beyond the scope of this *Guide.* The following drugs and techniques have been employed with some evidence for opioid sparing effects:[30],[31]

- Acetaminophen – prescribed in around-the-clock scheduled, moderate to larger doses
- Non-steroidal anti-inflammatory drugs – prescribed as needed or scheduled
- Gabapentin/Pregabalin – given in larger doses pre-operatively and continued at lower doses post-operatively
- Ketamine – low-dose infusions in the range of 0.3-0.5 mg/kg/hr
- Lidocaine – low-dose infusions in the range of 1-2 mg/kg/hr
- Peripheral Nerve Blocks – perineural injection or infusion of local anesthetics
- Neuraxial Analgesia – single injection or continuous infusions either intrathecally or epidurally of local anesthetics with or without opioids or other adjuvants

**Assessment and reassessment**

When administering PRN opioids through intravenous or oral routes, it is important to have a clear policy with regard to the assessment and reassessment of pain. Nurses must have an indication when administering any drug PRN. Pain is an inherently subjective experience. The most widely established means of assessing pain is the patient self-report. In most clinical settings with adults this takes the form of the Numeric Rating Scale (NRS) for pain, which asks the patient to rate his or her pain on a scale of 0-10 with 0 meaning no pain and 10 meaning the worst pain he or she can imagine. Nursing reassessment should also include impact of pain on function, side effects of treatment and risk factors for adverse events. Treatment based solely on patients' reported pain intensity rating is inappropriate. In those patients who cannot give a self-report due to age, dementia or other cognitive dysfunction, there are a number of behavioral pain scales that allow nurses to determine whether or not the patient has pain. However, most of these behavioral scales have been validated to determine whether pain is present or absent; they have not been validated to determine pain intensity. Only a self-report can determine intensity.

When PRN opioid analgesics are administered for pain it is important to reassess the patient afterwards. This allows the nurse to ensure the pain treatment was effective at relieving pain and that there have not been undesirable side effects such as nausea, excessive sedation or respiratory depression. The hospital should have an established policy of when to reassess after the administration of an opioid analgesic. The reassessment time should coincide with the peak effect of the analgesic administered. For simplicity it may make sense to assume a peak effect of 30 minutes for all intravenous opioids and one hour for all oral immediate-release opioids. Reassessing too early will risk re-dosing and dose stacking if the pain is not yet controlled. Reassessing too late may miss significant respiratory depression or sedation.

**Treating Anticipated Pain**

Patients who are undergoing procedures that are known to aggravate or cause pain and who will be participating in painful activities should have this pain treated in advance. Such procedures may include dressing changes, wound packing, line placements, chest tube removal or suture removal. Painful activities may include physical therapy, ambulation or turning. Treating this anticipated pain prior to these activities or procedures will improve patient compliance and progress with therapy. Standard orders for PRN opioids may not adequately allow for nurses to pre-treat expected anticipated pain. For instance, if the patient has orders for an opioid for moderate and severe pain but his or her pain prior to physical therapy

is in the mild range, the nurse may not be able to pre-treat without calling the provider for a one-time order. Building the option for an anticipated pain dose and drug into pain orders may improve the flexibility required to address anticipated pain. Documentation must include the correlating painful condition or activity.

**Use of Sustained-Release Opioids**

The use of sustained-release opioids in the opioid-naïve patient may be appropriate in some circumstances for postoperative pain. However, use of short-acting "as needed" (PRN) opioids should be the foundation for acute severe pain in the opioid-naïve patient. For the opioid-tolerant patient, do not add or increase extended-release or long-acting opioids for the immediate postoperative period. At time of hospital discharge avoid continuing or adding new prescriptions of benzodiazepines, sedative-hypnotics, anxiolytics or CNS depressants. Counsel patients and families about risks of using alcohol and other CNS depressants with opioids. The advantage of such a regimen is to lower the pill burden of PRN opioids and improve analgesia and recovery. Discharge with such regimens requires clear instructions to patients on when to take which drug and which drug to stop using first as the pain improves. It is not recommended to have the entire analgesic requirement for an opioid-naïve patient consist of sustained-release opioid. Patients on sustained-release opioids for acute pain who require no PRN opioids are at risk of overdose as their acute pain continues to improve. No more than 50 percent of a patient's acute pain opioid requirement should be in sustained-release formulation in order to assure that patients are not receiving more opioid than necessary.

**A stepwise safety-oriented approach to uncontrolled pain**

A stepwise approach your institution may take to patients with increasing or uncontrolled pain in the opioid-naïve patient follows (see Table 8 and Table 9). Reassessment of risk, sedation and the intensity of monitoring for respiratory depression become increasingly more important as patients require higher equianalgesic dosages of opioids.

*Table 8: Stepwise Approach to Uncontrolled Acute Pain: PO*

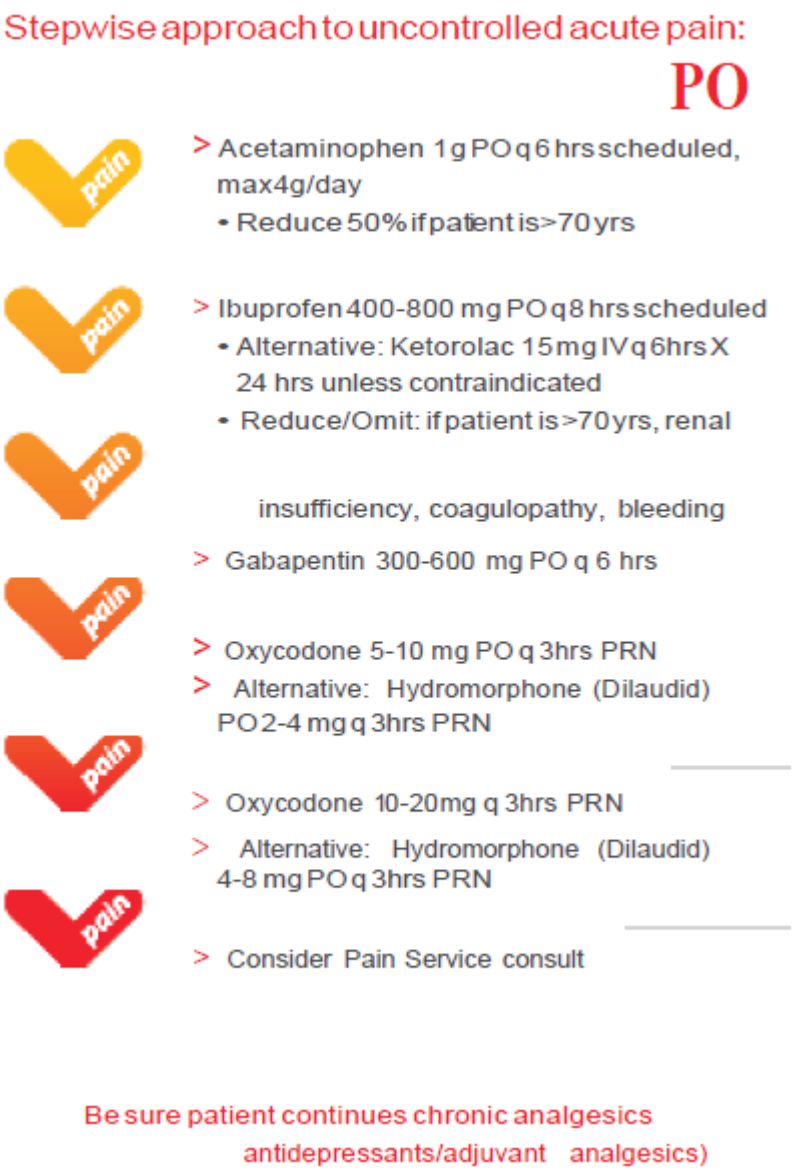
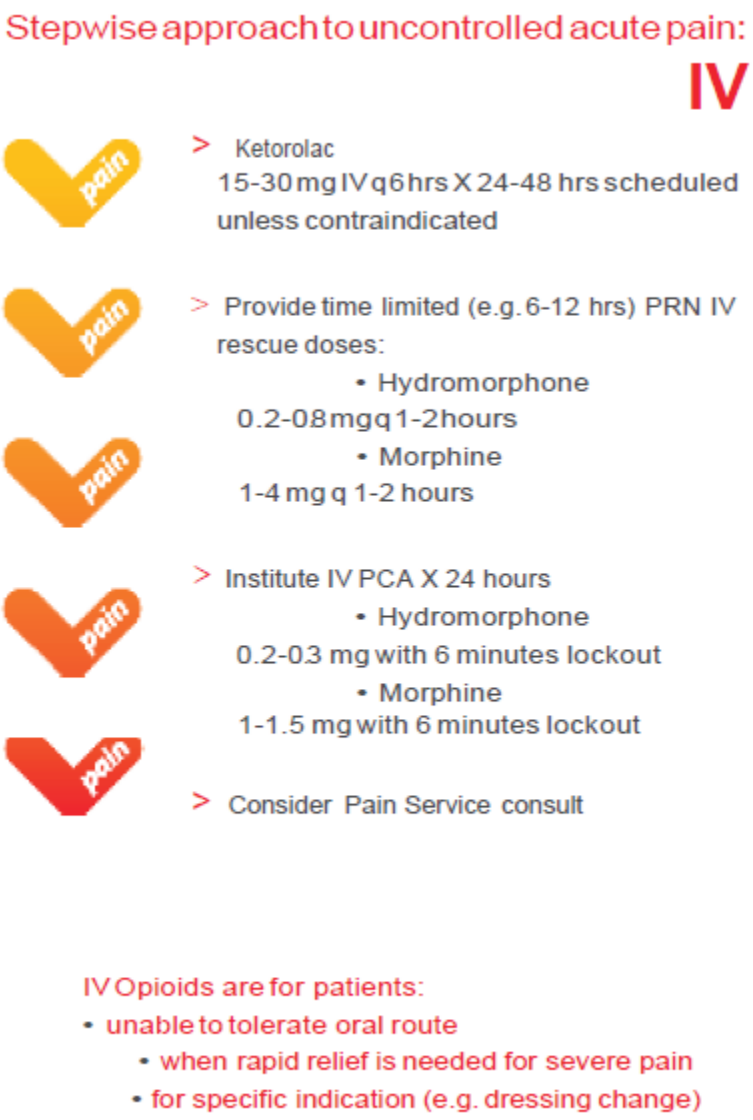


*Table 9: Stepwise Approach to Uncontrolled Acute Pain: IV*

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### 4.2.3 Continuing Opioids: Opioid-Tolerant Patients

#### Determining Baseline Opioid Requirements

The most important factor in determining what drugs and doses to give opioid-tolerant patients for acute pain is to determine their home dose and most recent usage pattern. This may not always be apparent from their outpatient prescriptions or medication reconciliation. Chronic pain patients may have been given a prescription for an immediate-release opioid such as morphine 15mg with prescribing instructions to take one tablet every four hours as needed. However, they may be prescribed only 60 tablets for a one-month supply, nowhere near six tablets per day that the instructions imply. Conversely, some patients may take many more tablets than they are prescribed and obtain additional tablets from other providers or non-legitimate sources. A clear discussion with the patient regarding not only what he or she is prescribed but exactly how the tablets are being taken and how much is being used per day on average is key to determining the patient's baseline opioid requirements. For patients who cannot give a clear story due to cognitive deficits or altered mental status it is important to seek verified information from alternative sources:

- Outpatient pharmacy records
- Opioid prescriber(s)
- Family members
- State prescription drug monitoring program database

The larger the apparent prescribed dose and the sicker the patient, the more important this reconciliation becomes.

#### Continuing Sustained-Release Opioids

Patients on a verified, regular dose of a sustained-release opioid should have it continued if the clinical condition of the patient allows. For patients on an oral sustained-release opioid who cannot swallow and absorb sustained-release tablets or capsules, an alternate route and/or drug should be administered in doses to avoid withdrawal. If a different opioid is used, 30 to 50 percent of the equianalgesic dose should be ordered to account for different levels of tolerance to different medications. This is one of the better reasons for use of a basal rate on a PCA. For those patients on fentanyl transdermal patches as outpatients, the regular recent use of these patches should be verified. The patches in place at admission should be removed and new patches then placed and dated to ensure the dosing interval is maintained while hospitalized. For those patients with significantly increased pain due to surgery or other causes, an increase in their sustained-release opioid may be reasonable, especially as part of a transition off of a PCA nearer the time of discharge.

#### Fentanyl patches

Fentanyl patches pose a particular risk to patients who have acute pain, due to the slow onset of analgesia. Patients chronically using the patches prior to admission are at risk for opioid misadventures. The fact that patches can be overlooked at admission poses an added risk when additional opioids are being administered without the nurse or prescribers being aware that fentanyl patches are present. In addition to medication reconciliation, a skin check for the presence of any patches, including fentanyl patches, should be a part of all patient admission processes.

#### Buprenorphine

Buprenorphine is an agonist-antagonist opioid, manufactured as sublingual films or tablets (Suboxone, Subutex) with or without admixed naloxone, and has been approved by the Food and Drug Administration (FDA) for the treatment of opioid addiction.[32],[33] Outpatient use of these drugs for addiction therapy requires a special Drug Enforcement Administration (DEA) certification, but the patches may be used for chronic pain management without a special certification. During an acute hospital admission these drugs, as well as methadone, can be continued for the treatment of addiction and prevention of withdrawal without any special licensing or certification. The continuation of these agents for substance

abuse maintenance therapy during an acute hospital stay for the treatment of pain is also allowable. Buprenorphine is also available as an injection and as a transdermal patch for acute and chronic pain, respectively.

One of the unique properties of buprenorphine is the high binding affinity the drug has for the Mu opioid receptor and slow dissociation. Because of this high binding affinity, buprenorphine may prevent other opioids from binding to the receptor, preventing analgesia. There are a variety of recommendations regarding what to do with buprenorphine during an acute hospital admission with acute pain, but no clear consensus.[32],[33] These recommendations fall into two main types:

1. Stop buprenorphine before admission and use conventional, full-agonist opioids for the treatment of acute pain.
2. Continue buprenorphine and be prepared to use much larger-than-expected full agonist opioids in addition to the buprenorphine.

If the patient admission is elective and expected to result in significant acute pain, the first strategy is likely preferable. Coordinate with the buprenorphine prescriber to stop the drug for at least two to three days prior to surgery. If the admission is unplanned or if buprenorphine use is not made known until after admission, then the second strategy is likely preferable. Caution should be used in stopping buprenorphine while also using large doses of full-agonist opioids, as the respiratory depressant effect of the agonists may be pronounced as buprenorphine dissociates from the receptors and is metabolized.

For more information, view the below presentation:

Bummett, Chad. "Management of Sublingual Buprenorphine (Suboxone and Subutex) in the Acute Perioperative Setting. University of Michigan Health System

### Methadone

If methadone is part of a chronic pain management regimen or addiction maintenance program, every effort should be made to continue this therapy. If a patient is not able to take methadone orally, it may be converted to an IV formulation, with a conversion of 1:2 (IV:PO), but caution is always warranted. Transitioning to another opioid is very challenging due to methadone's long half-life and should be avoided if possible. For acute pain situations, short-acting opioids may be added to methadone and then tapered off down to maintenance or to off after discharge by the patient's outside prescriber.

### Intrathecal Pumps

The implantation of intrathecal drug delivery systems for the treatment of cancer-related chronic pain, or refractory spasticity with intrathecal baclofen, has helped some patients to better manage their pain or spasticity with lower doses and fewer side effects. However, these implanted devices can complicate an inpatient admission. It is important to have a system in place to ensure that providers or nurses routinely ask or check for implanted drug delivery devices on admission to the hospital. Patients with such devices may be able to provide detailed information regarding the drug(s) doses and refill dates. However, many may not be able to do so either due to cognitive deficits or altered mental status. If the patient is unable to give a clear history and provide a recent printed refill report that lists drugs, doses, delivery rates and refill interval, the pump should be interrogated by either a qualified pain specialist or the pump manufacturer's device representative. The doses delivered in these pumps can range from very modest to very high doses of opioids, baclofen and possibly various analgesic adjuvants. There is a risk of serious withdrawal should a patient miss a required refill. Additionally, it should be noted somewhere on the patient's chart, preferably on the Medication Administration Record

(MAR), that the patient has an intrathecal drug delivery device and the drugs and doses being administered. In the event of a code blue situation or other adverse event, the responding providers need to know about these agents.

For the purposes of acute pain management, the inpatient providers should assume that the intrathecal pump is providing no more than the baseline opioid or analgesic requirements for their patient. Additional intravenous and/or oral opioids can and should be provided on top of the intrathecal drugs to treat acute pain. In most situations, it is best not to increase the intrathecal pump to treat acute pain while in the hospital.

**Intrathecal Pump Drugs:** Multiple agents have been used in intrathecal pumps either alone or in combinations.[35] The recommended daily starting doses are quite low compared to intravenous or oral routes of delivery. However, there is wide variation among those who implant and manage patients with regard to dose escalation, and some implanted pumps may have extremely high doses of opioids. There are only three drugs that are FDA approved for intrathecal use:

- Morphine
- Baclofen
- Ziconotide

Baclofen intrathecal is approved for the treatment of severe refractory spasticity. The abrupt discontinuation of intrathecal baclofen can cause severe, life-threatening withdrawal symptoms.

Ziconotide is an N-type calcium channel blocker with a narrow therapeutic window. It is only available as an intrathecally administered agent. It is approved for the treatment of severe refractory pain and can be used alone or in conjunction with opioids or other analgesics. It does not result in respiratory depression, but in overdose can cause altered mental status and other neurologic changes including dizziness, ataxia, nystagmus, psychiatric effects or cataplexy.[34]

Several other drugs are commonly used off-label in intrathecal pumps:

- Hydromorphone
- Bupivacaine
- Fentanyl
- Sufentanil
- Clonidine

### Increased Opioid Requirements

There are no simple calculations for determining a postoperative or acute pain dose of opioid for those with pre-existing opioid tolerance. The postoperative opioid requirements may be more than double the pre-operative daily opioid use.[35],[36] For those on moderate to larger doses of opioids (75-200mg of oral morphine equivalent) prior to admission, the providers should consider doubling their opioid-naïve PCA starting dose. Subsequent increases in dose may need to occur with frequent reassessments until adequate analgesia is obtained. For severe acute pain and significant opioid tolerance, the achievement of adequate analgesia with as-needed intravenous or oral opioids is much more difficult, and a low threshold for starting a PCA should be maintained.

### Multimodal Analgesia

A number of groups have published guidelines regarding hospital and perioperative pain management with recommendations for the use of multimodal analgesia.[37],[38] One of the principles of safe opioid prescribing is to use the lowest acceptable dose to limit the risk of adverse events. The purpose of multimodal analgesic therapy is to improve analgesia and reduce opioid requirements and the resulting opioid-related adverse effects. In patients with significant

pre-hospital opioid tolerance, the use of multimodal analgesics may provide better pain relief than the use of opioids alone given the significant tolerance and relative lost efficacy of the opioids.[5]

There are a number of drugs and techniques that are employed in a multimodal, opioid-sparing, analgesic regimen. Adding multiple agents and techniques may allow for lower doses of each analgesic with lower risk of adverse effects. A complete description of the use of these agents and techniques is beyond the scope of this *Guide.* The following drugs and techniques have been employed with some evidence for opioid-sparing effects:[37],[38]

- Acetaminophen – prescribed in around-the-clock scheduled, moderate to larger doses
- Non-steroidal anti-inflammatory drugs – prescribed as needed or scheduled
- Gabapentin/Pregabalin – given in larger doses pre-operatively and continued at lower doses postoperatively
- Ketamine – low-dose infusions in the range of 0.3-0.5 mg/kg/hr
- Lidocaine – low-dose infusions in the range of 1-2 mg/kg/hr
- Peripheral Nerve Blocks – perineural injection or infusion of local anesthetics
- Neuraxial Analgesia – single injection or continuous infusions either intrathecally or epidurally of local anesthetics with or without opioids or other adjuvants

### Coordination with Regular Opioid Prescriber

For patients on high-dose chronic opioid therapy or those on especially complicated regimens, it is wise for the primary service provider to coordinate with the patient's outpatient opioid prescriber. This allows the inpatient providers to check on the prescribed home regimen and doses. Additionally, it allows for coordination of discharge appointments to ensure that the larger dose of opioid the patient is likely to require at discharge is prescribed in large enough amounts to last until a follow-up appointment. It also prevents the patient from having a large surplus of medications in his or her possession.

### Transitioning Opioid-Tolerant Patients Off PCA

The opioid-tolerant patient may be more difficult to transition off of a PCA than the opioid-naïve patient. This is especially the case when there is some psychological dependence on opioids or aberrant drug-seeking behaviors. The typical opioid-naïve patient may benefit from a slow transition from IV PCA to oral PRN medication. The opioid-habituated patient, especially when a component of psychological dependence and/or addiction is present, may be less likely to reduce use of the PCA with the addition of an oral PRN medication as part of a transition strategy. In such patients a better strategy may be to taper the PCA dose or increase the lockout interval over a few days. When the usage has moderated somewhat and the patient and providers are ready, then convert the patient's 24-hour PCA usage to a reasonable oral dose and stop the PCA. The use of a moderate amount of IV PRN opioid as a "rescue" or backup can then ease the transition period.

## 4.2.4 Safe PCA Prescribing – Opioid-Naïve and Opioid-Tolerant Patients

PCA, which allows patients to self-administer small doses of opioids intravenously, has been available since the 1960s. A pump is programmed to allow the patient to administer a set dose of drug at timed intervals, referred to as the Patient Initiated Dose (PID). This allows patients to have control over their analgesia delivery without waiting for the nurse or other healthcare professional to retrieve the requested medication and administer it. PCA is designed to maintain a desired level of analgesia with minimal side effects. PCA use has been shown to improve satisfaction in both adults and children (over the age of five). Whether it is associated with improvements in pain control and safety remains controversial.

Indications for use of PCA include management of moderate to severe pain in patients who require parenteral analgesia for more than a few hours. This may include patients who are postoperative, NPO, in sickle cell crisis or in some persons with cancer pain. PCA can also be the preferred way to deliver parenteral opioids to persons with a history of substance abuse disorder. Appropriate patient selection is imperative for successful therapy. PCA is not appropriate for patients who are too young (age-wise or developmentally) or have cognitive or physical impairments that prevent them from using the button to deliver the medication.

**Initiating Therapy**

There is no specific advantage of one opioid over another, however there can be inter-patient variability. Morphine has a long-acting active metabolite that can accumulate, resulting in side effects in patients with renal insufficiency, and is often avoided in such patients. The opioid choice should be based on previous patient experience and/or known intolerances.

*Table 10: PCA Opioid Dosing for Opioid-Naïve Adults and Children with Acute Pain*

Doses, lockouts and limits must be adjusted based on the required loading dose, age, state of health and presence of opioid tolerance

| Patient Population | Drug | Usual Starting Dose after Load | Usual Dose Range | Usual Lockout (Minutes) |
|---|---|---|---|---|
| Pediatric (less than 50kg) | Morphine | 0.02mg/kg/dose | 0.01-0.03 mg/kg/dose | 10 |
| | Hydromorphone | 0.003-0.004 mg/kg/dose | 0.003-0.005 mg/kg/dose | 10 |
| | Fentanyl | 0.5-1 mcg/kg/dose | 0.5-1 mcg/kg/dose | 10 |
| Adult – opioid naïve | Morphine | 1mg | 0.5-2.5mg | 10 |
| | Hydromorphone | 0.2mg | 0.1-0.3mg | 10 |
| | Fentanyl | 25mcg | 10-25mcg | 10 |
| Adult – opioid tolerant* | Morphine | 2mg | 0.5-5mg | 10 |
| | Hydromorphone | 0.4-0.5mg | 0.2-0.5mg | 10 |
| | Fentanyl | 25mcg | 10-50mcg | 6 |

**This dose may vary based on a person's chronic opioid regimen. Consider restarting a person's long-acting opioid regimen ASAP or replace it with the use of a basal rate (continuous infusion).*

### Loading Dose

It is important to note that IV PCA is designed to maintain a level of analgesia; therefore, prior to initiating PCA therapy patients should be medicated to a level of pain relief that can be maintained through the use of PCA therapy. This is generally accomplished through the use of a loading dose. A loading dose should be considered at the start of therapy and with each increase in PCA regimen. The loading dose is generally determined as either:

- 100-150 percent of established starting hourly dose, or
- 0.03mg/kg of morphine or the equivalent dose of another opioid agonist every 10 minutes until the patient reports satisfactory relief.

### Consideration of a Basal Rate

A continuous infusion (basal rate) is NOT recommended for opioid-naïve patients with acute pain. A number of prospective randomized controlled trials have failed to demonstrate an analgesic benefit from addition of a basal rate for postoperative pain. Use of a continuous infusion can increase the risk of sedation and respiratory depression. However, basal rates are often appropriate when managing pain in persons who are on chronic opioid therapy. For example, when managing chronic cancer pain, a basal rate can be used to provide the necessary around-the-clock dose of opioid and the PCA dose can be set to deliver the patient's "breakthrough" dose at intervals of 15 to 60 minutes depending on patient needs.

If used, the continuous basal rate may be calculated as one-sixth of the total loading dose given. For example: A patient weighs 80kg. A loading dose of 2.4mg of morphine (80 x 0.03mg) is administered 4 times over ~40 minutes to achieve 30 to 50 percent reduction in the pain. The total loading dose of 9.6mg is divided by 6 to give the starting basal rate of 1.6mg/hr.

### Lockout Intervals

This allows a demand dose of medication to be given at a specified interval. These usually reflect the onset of a dose of IV opioid. Lockout intervals shorter than 10 minutes have been associated with more naloxone use due to respiratory depression. For example, if a patient administers 1mg of morphine every five minutes over a period of several hours, the morphine metabolite will accumulate and cause respiratory depression. The PCA lockout is a safety feature, and its use needs to reflect the pharmacokinetic profile of the drug. In the ICU, they may utilize a shorter interval to allow the patient to "catch up" after surgery, but these patients may be ventilated and have continuous monitoring. Some providers prefer a larger demand dose with a longer lockout interval to determine if the demand dose is effective. The lockout interval should certainly be utilized if there is known or potential for renal insufficiency (particularly if using morphine).

### PCA Titration

PCA titration must be handled carefully. Decimal point errors in programming and individuals other than the patient activating the PCA demand button put patients at risk for opioid-related adverse effects. Some clinical pearls on PCA titration are as follows:

- For pain that is uncontrolled, provide an order that allows frequent nurse-administered bolus doses. The PRN nurse-initiated IV bolus dose is usually two times the PCA dose or equal to the hourly basal rate.
- Do not increase the PCA dose more frequently than every eight hours. Do not increase the dose by more than 100 percent at any one time, no matter how many bolus/breakthrough doses have been used.
- Always consider the use of a loading dose at the time of a dose increase.
- Keep in mind the hourly limit should be set to approximately three to five times the projected hourly requirement.

- The ratio of PCA dose to the hourly basal rate should generally remain approximately 1:2. For example, if the basal rate is 0.6mg/hour, the patient initiated doses (PIDs) would be 0.3mg.
- Full effects of initiating or increasing a continuous basal dose (without first administering a loading dose) will not be seen until steady state is reached, approximately five half-lives (10 to 12 hours for morphine or hydromorphone).

**Special Considerations in Children**

With appropriate training, most patients over the age of seven can use PCA, as can some as young as five years of age. As with adults, continuous basal rate is not recommended for opioid-naïve patients. PCA-by-Proxy (administered by someone other than the patient or nurse) is discouraged, but if it is determined to be appropriate for an individual patient, specific instruction must be documented including how and when to assist the patient to deliver a PCA dose.

**Transitioning Off PCA**

Transitioning patients to oral opioid analgesics as soon as they are tolerating fluids and advancing diet can provide better pain control with fewer side effects. A balanced, multimodal approach combining analgesics with differing mechanisms of action along with non-pharmacologic interventions is generally most effective. Patients do not have to be weaned off PCA before being transitioned to oral analgesics but appropriate administration parameters must be specified to prevent duplication. PCA therapy can be discontinued at the time of the first oral dose or overlapped with oral dosing for a number of hours depending on the patient's level of pain and anxiety. Caution should be used if consulting an equianalgesic chart for this transition. When making a plan for transition, it may be safer to characterize the patient along a spectrum: from one who is opioid-naïve with acute pain that is likely to rapidly resolve to someone who is on chronic opioid therapy and has progressive pain.

### 4.2.5 Safe Opioid Conversions

Since opioids differ from one another in potency, it is important to have some point of reference in comparing these drugs. Equianalgesic tables provide listings of opioid doses that produce approximately the same amount of analgesia based on bioavailability and potency. Two doses are considered equianalgesic if they provide approximately the same amount of pain relief, and thus an equianalgesic table provides a listing of opioids at doses that produce approximately the same amount of analgesia.[43] Equianalgesic tables can be helpful when switching from one opioid to another, or when changing between the oral and parenteral route, so that the same amount of analgesia can be maintained. Equianalgesic dose calculation provides a basis for selecting the appropriate starting dose when switching opioids or changing routes. Erroneous equianalgesic calculations can lead to needless suffering for patients, either from unrelieved pain or from unnecessary toxicity.[44]

Equianalgesic tables have several weaknesses.[45],[46] Many of the relative potencies listed on equianalgesic tables are derived from single-dose or short-term studies with limited control on subject differences such as psychological characteristics, previous degree of opioid exposure, nature and severity of pain, random fluctuations in pain severity, age and sex. Equianalgesic tables compare only the agonists, and the oral and parenteral (intravenous/subcutaneous/intramuscular) routes. When opioids are administered by other routes, such as topically, epidurally or intrathecally, other factors must be considered such as opioid lipid solubility and the proximity of drug delivery to opioid receptors.

It is critical to remember that the doses are approximate and most are based on single-dose studies. The doses are to be used only as a guide for calculating an initial conversion dose. Doses listed on the table were selected for the purpose of convenience to make comparisons easy. Clinicians may erroneously assume the doses listed are recommended starting doses. This is not the case. They suggest the ratio or proportion to use when calculating a new dose.

Because of incomplete cross-tolerance, caution must be used when an equianalgesic dose of a different opioid is administered. When switching to a different opioid, it is recommended that only 30-50 percent of the calculated equianalgesic dose should be administered initially, particularly when pain is being controlled by the current drug.[47] Information other than the equianalgesic calculation should be taken into consideration in determining the new dose, including the drug's half-life, bioavailability, drug interactions, hepatic and renal clearance, the patient's type of pain and prior opioid exposure. As always, individual patient response must be observed, and doses and intervals between doses need to be titrated according to the patient's response.

A number of smartphone applications (apps) for opioid conversion are available,[48] however there is no robust regulation and peer review to ensure the accuracy and reliability. Again, conversion of opioids demands patient assessment and clinical judgment with careful consideration of a number of factors.

*Table 11: Equianalgesic Table (based on single immediate-release dosage forms)*

| Drug | Parenteral | PO | Parenteral:PO Ratio | Duration of Action (hr) |
|---|---|---|---|---|
| Morphine | 10 | 30 | 1:3 | 3-4 |
| Hydromorphone | | | | |
| | 1.5 | 7.5 | 1:5 | 3-4 |
| Oxymorphone | | | | |
| | 1 | 10 | 1:10 | 3-4 |
| Oxycodone | | | | |
| | N/A | 20-30 | — | 3-4 |
| Codeine | 130 | 200 NA | 1:1.5 | 3-4 |
| Hydrocodone | | | | |
| | — | 30 | — | 3-4 |
| Meperidine | | | | |
| | 75 | 300** | 1:4 | 2-3 |
| Fentanyl | | | | |
| | 0.1 | — | — | 1-3 |

Duration of action based on use of short-acting formulations.

NA = equianalgesic data unavailable. Codeine doses should not exceed 1.5mg/kg because of an increased incidence of side effects with higher doses.

** Avoid multiple dosing with meperidine (no more than 48 hrs or at doses greater than 600mg/24hrs). Accumulation of toxic metabolite normeperidine (half-life 12-16 hrs) can lead to CNS excitability and convulsions. Contraindicated in patients receiving MAO inhibitors. Oral meperidine is not recommended due to very poor oral bioavailability.

*Adapted from Gordon DB, Stevenson KK, Griffie J, et al. Opioid equianalgesic calculations. J Palliat Med. 1999;2(2):209-218.*

### 4.2.6 Special Safety Considerations – Methadone and Buprenorphine

Certain opioids deserve special consideration for safety including methadone and buprenorphine. Due to the complexity of these agents, transitioning patients to and from the hospital who have been taking these agents (for pain or maintenance therapy for opioid addiction) is challenging. Please see **Section 4.2.3** for additional information.

#### Methadone

Methadone is used commonly now for chronic pain management as well as opioid addiction maintenance therapy. It has a number of unique characteristics that increase the need to use greater caution. Key features include:[50],[51]

Methadone has no known active metabolites so it is a good choice for patients with chronic pain and renal insufficiency. Less than 1 percent is removed by peritoneal or hemodialysis.

It is synthetic so this may be an option for patients with a true morphine allergy, though this is very rare.

It has a long and unpredictable half-life (12 to 120 hours). The duration of action is three to six hours when methadone therapy is initiated and extends to eight to 22 hours with repeated dosing. Because of its long half-life, it may take five to seven days for plasma levels of methadone to reach steady state. Also, due to its extended time to reach steady state, it is not a good choice for acute pain. If it is given frequently for acute pain, it will accumulate and may result in a delayed respiratory depression.

Methadone's complex pharmacokinetic profile makes opioid conversions very difficult. Many equianalgesic dosing tables suggest that 20mg of oral methadone is equianalgesic to 30mg of oral morphine, however the equianalgesic dose ratio between methadone and other opioids is much more variable than that. Validated methadone conversion charts should be utilized.

Risk of QTc interval prolongation and torsades de pointes,[51] particularly with high doses (>200mg oral methadone/day) and IV administration (in the latter case, the preservative chlorobutanol may be responsible). This can also occur with other agents that prolong the QTc interval (e.g., citalopram, ondansetron, droperidol, several anti-infectives).

*Table 12: Interactions of Methadone with Other Medications or Medical Conditions*

| Mechanism | Drugs or Condition | Consequence |
|---|---|---|
| Cytochrome enzyme induction* | Antiviral agents: nevirapine, ritonavir, efavirenz<br>Anticonvulsants: carbamazepine, phenobarbital, phenytoin<br>Antituberculosis agents: rifampin, rifabutin<br>St. John's wort<br>Chronic alcohol ingestion and smoke | Increased clearance, resulting in poor analgesia and may precipitate withdrawal |
| Cytochrome enzyme inhibition* | Antifungal agents: fluconazole, ketoconazole, itraconazole<br>SSRI: fluvoxamine, paroxetine, fluoxetine<br>Acute alcohol ingestion<br>Antibiotics: clarithromycin, erythromycin, ciprofloxacin<br>Desipramine | Decreased clearance, resulting in increased serum levels |

| Mechanism | Drugs or Condition | Consequence |
|---|---|---|
| Competition for cytochrome enzymes | Nifedipine | Variable |
| Pharmacodynamic interaction | Benzodiazepines, barbiturates, other opioids and other CNS depressants | Increased respiratory depression and sedation |
| Increase plasma level of AAG $a_1$ acid glycoprotein (acute reactant protein) | Stress reactions, cancer, opioid addiction and concurrent administration of amitriptyline | Inadequate analgesia or withdrawal |
| Changes in gastric pH or activity of P-glycoprotein | Verapamil, quinidine | May increase methadone absorption |
| Potentiation of QT prolongation | Fluoroquinolones, macrolides, tricyclic antidepressants, citalopram, ondansetron | May precipitate torsades de point |

**This is not an exhaustive table. Different medications induce or inhibit specific cytochrome enzyme subtypes. There is tremendous inter-individual variability in the cytochrome P450 activity. For simplicity, the drugs are grouped according to the overall effects on the whole cytochrome enzyme system rather than a specific enzyme subtype.*[52], [53]

### Buprenorphine

Buprenorphine is a semi-synthetic, lipophilic, partial Mu-opioid receptor agonist and a kappa receptor antagonist developed more than 20 years ago. In the United States, the drug is available in a parenteral form, sublingual tablets with and without naloxone, and a transdermal patch. The drug can be used for pain management or in the treatment of addiction.[54-56]

As a partial agonist, buprenorphine binds to the Mu receptor but does not fully activate the receptor and therefore produces limited agonist effects. It reportedly binds 25 to 100 times as strongly as morphine and because of its high affinity for the Mu receptor, adding additional opioids (for surgery, acute injury, procedure, etc.) is ineffective.[57] Buprenorphine should be tapered or switched to a full agonist prior to any elective procedure **(see Section 4.3.3)**.[58]

### Clinical Points Related to Pharmacokinetics, Metabolism and Excretion[57]

- It is metabolized by the cytochrome P450 in the liver (CYP3A4 and CYP2D6). There are no clinically relevant pharmacokinetic interactions reported with other drugs metabolized by the P450 system.
- Excretion of buprenorphine and metabolites is 70 percent by feces, therefore the drug can be administered in normal doses to the elderly and patients with renal insufficiency (unlike most opioids that are cleared by the kidney).
- It cannot be dialyzed and very high doses or continuous infusions of naloxone may be needed to reverse respiratory depression because of the slow dissociation from the receptor.
- Although withdrawal symptoms are less severe than with full opioid agonists, gradual reduction is recommended (i.e., reducing the daily dose by 2mg or by 50 percent every week).

**Differences between buprenorphine and methadone use in addiction maintenance programs:**

- Maintenance (substitution) therapy involves replacing abused opioids with medically prescribed opioids that are slow in onset, long-acting, prevent craving and less likely to be abused. Maintenance medications prevent withdrawal and compete for opioid receptor binding sites, blocking the effects of any self-administered illicit opioids such as heroin.
- A special DEA license is required to prescribe methadone or buprenorphine for addiction maintenance; no such license is needed when it is prescribed for pain control (in some jurisdictions "for pain" required on Rx).
- Methadone maintenance is a schedule II opioid that is more restricted to licensed addiction treatment centers, whereas buprenorphine is a schedule III opioid and it is approved by the FDA for the office-based treatment of opioid addiction by certified physicians.
- For detoxification (withdrawal) or maintenance, the initial dose is typically 4mg sublingually.[57] Additional doses of 2 to 4mg may be needed to ameliorate withdrawal symptoms. Subsequent dosing is increased over three to four days to achieve a total maintenance dosage of 8 to 32mg daily, usually in divided doses given BID to QID. 8-16 mg per day has been found to be superior to 20-40 mg of methadone per day (low dose) and equitable anywhere between 50-70 mg (moderate dose) to up to 100 mg (high dose).

*The combination tablet (buprenorphine plus naloxone–Suboxone) was developed to deter abuse. Naloxone has poor bioavailability when taken sublingually but if injected the naloxone effect predominates and will precipitate withdrawal in persons physically dependent on opioids or will produce no subjective effect (euphoria) in persons who have never taken opioids.

### 4.2.7 Special Safety Considerations – Alternative Routes of Administration

Significant caution and monitoring is required for any patient receiving oral and IV opioid medications. Much effort has been put into ensuring safety of dosing and frequency to avoid accumulation of opioids and subsequent opioid-induced side effects, particularly respiratory depression. However, many patients may be receiving opioids from multiple sources simultaneously. This poses a unique challenge since opioids administered through different routes can alter their absorption and reduce the predictability of opioid-induced effects. The most common multiple-route scenario is when oral and IV opioids are given simultaneously. Intravenous medications given either through IV boluses or IV PCA in addition to scheduled or PRN oral opioid medications can lead to unexpected peaks and metabolite accumulation with potentially fatal consequences.

#### Infiltration

Infiltration of opioids around wounds or in joints is common during surgery. Typically this is a single dose that may be absorbed into the circulation over the first 24 hours. Caution must be used when administering additional opioids in this scenario until the infiltrated opioid has been absorbed and cleared.

#### Neuraxial

Epidural and intrathecal infusions also frequently contain opioids. Hydromorphone, morphine, fentanyl and sufentanil are some of the opioids frequently used in epidurals. The intent is to increase the analgesic effect with a lower dose of overall opioid as compared to IV administration. However, absorption and clearance from the epidural space opioids can vary

significantly. The drug lipophilicity, single dose versus continuous infusion of opioid, and the overall drug dosage all affect the systemic blood concentration of these opioids and therefore their risk for respiratory depression. Intrathecal morphine in particular has a known risk for biphasic respiratory depression with an early phase due to systemic absorption and a delayed phase six to 18 hours later due to cephalad spread to the brainstem causing central respiratory depression.[59] In chronic pain patients with intrathecal pain pumps, the opioid concentrations can be significantly higher than normal in the cerebrospinal fluid (CSF) and consultation with a pain physician is recommended. Some health systems are switching to non-opioid epidurals to avoid the added opioid.

**Transdermal**

Transdermal patches also provide continuous opioid administration with a pharmacokinetic profile that may not be familiar to many. Delayed onset after the initial administration and delayed clearance after patch removal may give a false sense of security when other opioids are administered. Initiation of fentanyl and buprenorphine patches can take up to two to three days to reach steady state.[60] In the case of fentanyl, the application of heat (either intended or unintended) can increase the systemic concentration by up to threefold.[61] Care must be taken to ensure that opioid overdosing does not occur in this situation. For buprenorphine, application of the patch can lead to opioid withdrawal if the patient has been using opioids on a regular basis. Neither transdermal system is appropriate to initiate for acute pain management.

**Transmucosal**

Fentanyl transmucosal systems (intranasal, sublingual) have a very rapid onset and can have profound effects. These medications can provide rapid onset analgesia in a non-invasive form. However, the medications are very potent and must be considered carefully when establishing the overall opioid management plan. These agents should not be used in opioid-naïve patients.

Goals of care should include minimizing multiple routes of opioid administration as well as reducing variability. If more than one route of opioid administration is required, attempting to maintain a stable dose as a baseline without variability with the second opioid used as needed for breakthrough pain reduces the opportunity for confusion and enhances predictability of side effects. Increasing the number of routes, as well as varying the dosing and frequency of opioids, should warrant greater monitoring. Monitoring can include more frequent nurse evaluations and/or electronic monitoring (e.g., pulse oximetry, continuous respiratory rate or capnography) **(see Section 4.3)**. Increased awareness and vigilance for these patients is the key to safe opioid administration.

### 4.2.8 Assessing and Addressing Provider Knowledge Deficits

**Introduction**

Knowledge deficits could be a reason for the problem with ORAEs in a facility. An early step is to address these deficits. Identification of a physician champion to lead hospital-wide education efforts is critical. An individual with visibility and respect within the institution can be used to effectively communicate the quality gap and discuss tools available to assist in provider decision-making. The quality improvement team in conjunction with the education department can develop a continuing medical education (CME) program led by physician leaders or other pain management champions in the institution with expertise in ORAEs. Frontline hospitalists, pharmacists, academic leaders, anesthesiologists and nurse anesthetists can provide education in structured CME formats.

However, relying on education alone to bring about change in behavior is insufficient. Education must be supplemented with bedside alerts and other tools, facility leadership must support the change, and the effect of the interventions must be measured and reported.

### Methods to address knowledge gaps

A quality improvement team should engage providers in educational seminars and lectures to increase visibility on the need for evidence-based assessments. Some basic points to remember regarding teaching methods are:[62]

- Live media is more effective than print.
- Multimedia is more effective than single media interventions.
- Multiple exposures are more effective than a single exposure.
- Interactive techniques are more effective than didactic techniques.
- Simulation methods are effective for improving psychomotor and procedural skills.

With this in mind, some approaches to address knowledge gaps include:

- Educational programs
    1. Grand rounds, noon conferences or division meetings, one-on-one mentoring
    2. The focus of these sessions should be to review current guidelines to reduce ORAEs as well as methods to assess patients for risk of ORAEs
    3. Distribution of educational materials (e.g., pocket cards with opioid equivalency chart, OSA scoring)
- Links to educational materials within order sets in the EMR environment. At the time of completion of an admission order set, links to the literature and/or institution-specific guidelines would be an excellent opportunity to provide valuable references that would assist in education of ORAEs.
- Creation of visibility of ORAE initiative on patient floors. Posters, signs and project boards at your institution provide visible reminders of the key concepts of your QI project to all constituents in the hospital.
- Development of RN education campaign that could involve all members of the interdisciplinary team. By focusing education efforts on all members of the healthcare team, your efforts would be potentiated, as team members could work in conjunction with providers.
- Use of Web-based education tools that can be incorporated into the credentialing and re-credentialing process. Requirements to complete a Web-based program on common QI metrics could include methods to decrease ORAEs.
- Development, promotion or dissemination of mobile applications that could be used by providers. Examples include OSA screening tools and opioid equivalency charts or pocket guides.
- Identification of medical-based calculators incorporating ORAE assessments that can be used in the decision-making process.

### Other considerations

Dissemination of information about quality initiatives at medical staff meetings is important. Incorporating data on the ORAEs quality initiative at staff meetings amongst other topics most often discussed (such as value-based purchasing, patient satisfaction, readmission rates and other adverse events) will assist in the staff education process. By educating providers about the importance of assessing patients for risk of ORAEs and using guidelines to lessen their occurrence, outcomes will be positively impacted as providers become self-compliant. However, other interventions will need to be layered into your QI project to reduce ORAEs.

### 4.2.9 Utilizing Systems and Processes to Help Providers Make Safe Decisions

Medication ordering and administration in the hospital is a complex process involving multiple providers in different care environments. The use of opioids is particularly dangerous due to their risk of life-threatening side effects. Establishing standardized policies, protocols and processes can help reduce variability and improve patient safety during opioid administration.[63-64]

In order to avoid medical errors in prescribing, verifying and administering medications, all providers need to be able to collect the relevant patient information, combine it with information about the opioid medication and put those orders into the context of the patient care environment.[65]

Development of standardized hospital policies requires participation from all relevant parties.[63] By developing a multi-level committee at the outset, buy-in for a new policy is enhanced. Often the goal is to develop processes and tools, such as decision support systems and computerized order entry, which enhance workflow without impeding it. Frequently, development of hospital policies necessitates limitations of physician and nurse practice, such as the breadth of hospital formulary or availability of PRN medications. These limitations must be carefully considered and balanced with adequate flexibility of patient care. Observations of nurse behavior have shown a large variety of workflows. If a new system is perceived as overly restrictive, this only encourages workarounds that can jeopardize safety. If the system is overly burdensome or time-consuming, there is frequently resistance to implementation. However, when a new process provides meaningful information and simplifies patient care, adoption can be rapid.

An institution-specific survey of current practices can reveal normal work behavior and delineate opportunities for improvement.[63,65] Frequent issues include:

- Pharmacokinetic understanding of the medications by the ordering provider
- Availability of adequate clinical data to the provider when needed
- Medication administration schedules with overlapping medications
- Alerts regarding combinations of medications that may potentiate side effects
- Real-time access to lab data regarding renal or hepatic function that may alter drug dosing
- Electronic monitoring use and the corresponding response processes to critical events
- Medication error checking systems by pharmacy and nursing

The use of clinical decision support (CDS) systems and CPOE can be very helpful in implementing processes for safe behavior.[63-65] When developed correctly, these tools (either paper order forms or electronic based) can provide the path of least resistance for providers to order medications. This allows the institution to gather the current best data on a specific situation, e.g., IV PCA prescribing, and develop a default approach to this prescribing. This allows for dissemination of best practices as well as improving the predictability of prescribing for nurses who administer the medications. This reduction in variability also enhances awareness of situations that fall outside the hospital norm (i.e., a red flag). In addition, when new information becomes available, these tools can be modified hospital wide and ordering defaults adjusted with minimal re-education effort.

For example, if the standard IV PCA order set includes hydromorphone at 0.2 mg q15 min, then the most likely ordered IV PCA will be the default option. The nurses will come to expect that order in most situations. If an order varies from this (e.g., fentanyl instead of hydromorphone or 0.5 mg instead of 0.2 mg), there is a general greater awareness of the variance. This allows for either detection of order errors or greater awareness of high-risk situations for opioid-related side effects.

In particular, advanced CPOE "offers the potential for safer, faster patient care, as well as greater use of evidence-based therapy via built-in decision support."[64] These CPOE systems provide the added advantage of being able to collate and

present real-time integration of patient-specific variables (labs, medical conditions and prior medication administration), context-sensitive educational information and a robust tracking mechanism to monitor for changes in prescribing behavior. For example, with CPOE, a physician can see the patient's most recent creatinine and estimated creatinine clearance, can be given dose adjustment recommendations and can be tracked for potentially erroneous orders through a central computer monitoring algorithm.

Once a hospital policy has been developed and a corresponding new process has been implemented, periodic review and modification of these processes is essential to success.[63,65] Hospital clinical practice is in a state of constant evolution, and the hospital policies and processes must match this.

## 4.3 Monitoring Patients on Opioids

Safe opioid use in the hospital will depend not only on the policies, procedures and behaviors the QI team puts in place in terms of prescribing and administration but also depend upon standard monitoring practices and implementing technology that will, through early warning, reduce the likelihood of opioid-related respiratory depression and death. Patients with respiratory diseases, OSA and those receiving sedating medications are at higher risk of opioid-induced respiratory depression during their hospital stay and will need to be considered for continuous monitoring technology. Identifying a monitoring strategy to detect early respiratory depression is critical to reducing morbidity and mortality for these patients. Your RADEO team will rely on the information and evidence presented in the following section to implement or redesign safe monitoring practices in your hospital.

### 4.3.1 Bedside Nursing Assessment and Vital Signs

Effective pain care and patient safety rely heavily on vigilant 24-hour bedside nursing assessments for early detection of potential adverse effects of opioids including nausea, vomiting, constipation, hypotension, delirium, dizziness and sedation that may lead to respiratory depression if unchecked. In March 2014, the Center for Clinical Standards and Quality/Survey & Certification Group from the Centers for Medicare & Medicaid Services (CMS) updated its guidance[66] for hospital medication administration requirements to reflect the need for patient risk assessment and appropriate monitoring during and after medication administration, particularly for postoperative patients receiving IV opioid medications, in order to prevent adverse events:

> The assessment and monitoring process must be explained to the patient and/or the patient's representative, to communicate the rationale for frequent monitoring, including that it might be necessary to awaken the patient, to assess the effects of the opioid medication. Patients and their families must also be educated to alert staff to breathing problems or other reactions that may be related to medication. Finally, staffs are expected to be trained in early detection and timely intervention for IV opioid-induced over-sedation and respiratory depression.[66]

This guidance can be interpreted to mean that hospital policies should clarify expectations about the "who, "how" and "when" of important nursing serial assessments and documentation. At a minimum, nursing assessment should include:

- Vital signs (blood pressure, temperature, pulse, respiratory rate)
- Pain level
- Respiratory effort/quality
- Sedation level

Unfortunately, there is a lack of evidence[67] to inform the best practices to determine the type and frequency of nursing assessments following opioid administration. Therefore the type and timing of assessment is clinically based on the kind of opioid therapy and patient risk factors for respiratory depression **(see Section 4.1)**. With initial opioid dosing, assessments may be ordered prior to and to coincide with the time to achieve peak effects, which are typically 15 to 30

minutes after parenteral opioid or one hour after administration of an oral dose. The optimal frequency of reassessment is likely to depend on a number of factors, including the type of pain, the adequacy of initial pain relief, the presence of side effects, presence of comorbidities and changes in clinical status. Reassessments may be performed less frequently for patients with more stable pain (e.g., patients who have exhibited good pain control without side effects after 24 hours of stable therapy). Pain reassessments may be useful at the time of nursing shift changes or with new caregivers to establish a baseline and promote continuity of care, though evidence showing that routinely reassessing pain at nursing shift changes is associated with improved clinical outcomes is not available.

Monitoring should include assessments of alertness and signs or symptoms of hypoventilation or hypoxia.[67] There is insufficient evidence[68-70] to recommend the routine use of more sophisticated currently available noninvasive methods (such as capnography) for monitoring hypoventilation. When used, many organizations endorse continuous monitoring of oxygenation (pulse oximetry) rather than intermittent measurement.[67] The use of routine oxygen is discouraged as hypoxia is a late sign of respiratory compromise and this sign will be delayed still further by supplemental oxygen.[67] When supplemental oxygen is indicated, monitoring of ventilation may warrant the use of technology designed to assess breathing or estimate arterial carbon dioxide concentrations. Nursing assessment should include not only the respiratory rate but also the depth and quality of respiratory effort for a full minute before stimulating or rousing a patient. Routine serial sedation ratings along with pain intensity and other side effects should accompany respiratory monitoring.

The Institute for Safe Medication Practices (ISMP) recommends hospitals use a standard sedation scale when assessing patients.[71] A number of sedation scales are available for nursing assessment including the Pasero Opioid-induced Sedation Scale (POSS) (see below), **Richmond Agitation Sedation Scale, Ramsey Sedation Scale** and **Comfort Scale.** When compared to a number of scales, the POSS scored higher in combined measures of ease of use, nursing confidence and usefulness of information for clinical decision-making.[72]

### 4.3.2 Definition of Respiratory Depression

**Opioids depress all phases of respiratory activity including:**

- Rate
- Minute volume
- Tidal exchange
- Rhythm

Clinically, opioid-induced respiratory depression is defined as decreased respiratory rate (<8-10 breaths/min), decreased $SpO_2$ levels or elevated end-tidal carbon dioxide ($EtCO_2$) levels. Opioid analgesics depress respiration primarily by reducing responsiveness of the brain-stem respiratory centers to carbon dioxide ($CO_2$). Therapeutic opioid doses depress all phases of respiratory activity (rate, minute volume and tidal exchange) and may produce irregular breathing. The diminished respiratory volume is primarily due to a slower rate of breathing. Natural sleep produces a decrease in sensitivity to $CO_2$; the effects of opioids and sleep are additive. When $CO_2$ accumulates it stimulates central chemoreceptors resulting in a compensatory increase in respiratory rate that can mask the degree of respiratory depression. Therefore, respiratory rate alone is not a reliable indicator of the degree of respiratory depression.

**Pasero Opioid-induced Sedation Scale (POSS)[73]**

The POSS is a 5-point (S and 1 through 4) nursing assessment of opioid-related sedation with associated suggested actions:

**S** = Asleep but easy to arouse – *Acceptable; no action necessary; may increase opioid dose if needed*

1. Awake and alert –
   *Acceptable; no action necessary; may increase opioid dose if needed.*

2. Slightly drowsy, easily aroused –
   *Acceptable; no action necessary; may increase opioid dose if needed.*

3. Frequently drowsy, arousable, drifts off to sleep during conversation –
   *Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25 percent to 50 percent or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing non-opioid, such as acetaminophen or an NSAID, if not contraindicated.*

4. Somnolent, minimal or no response to verbal or physical stimulation –
   *Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.*

### 4.3.3 Oximetry

Pulse oximetry is a tool to measure $O_2$ saturation in the blood ($SpO_2$) using the different light absorption for oxygenated and deoxygenated hemoglobin (Hb). Photoplethysmography (PPG) is used to isolate the absorption difference by systolic volume increase during arterial blood flow. Transmitted light intensity decreases during systole, and the difference between systole and diastole absorption as compared with two different wavelengths of light is used to determine the difference between oxygenated and deoxygenated Hb in the arterial circulation. Errors in $SpO_2$ measurement can occur due to the presence of methemoglobin or carboxyhemoglobin (some newer oximeters use additional wavelengths of light to isolate these forms of hemoglobin) as well as problems with peripheral perfusion with inadequate arterial blood flow. Reflection pulse oximetry can be used in situations where peripheral blood flow to fingers or earlobes is restricted.[74] Continuous pulse oximetry notifies nurses regarding early desaturation and allows for interventions that may stimulate respiration or reverse opioid overdose.[75]

In one study, patients who were under continuous postoperative pulse oximetry surveillance with alarms that alerted nurses of abnormal vital signs had significantly fewer rescues and unanticipated transfers to the ICU.[76] Pulse oximetry has a high sensitivity for opioid-induced respiratory depression and allows for rapid response times (see Table 10).[77] In a recent study by Voepel-Lewis et.al., one-third of pulse oximetry alarms in patients continuously monitored on the hospital floor were for clinically relevant desaturation events and these alerts facilitated nursing response and intervention in most patients. Limitations to responding to all alarms were more related to limitations in the consistency of paging technology.[78] In another study, ICU transfers were reduced from 5.6 to 2.9 per 1,000 patient-days by implementing a comprehensive surveillance program that involved continuous pulse oximetry with nurse notification at a threshold of 80 percent oxygen saturation.[79]

#### Limitations to Oximetry Use

Although it appears that using pulse oximetry in all situations for hospital patients would improve outcomes and reduce opioid-induced respiratory complications, there are limitations to its benefit. Motion artifact and false alarms can be a constant nuisance to the patient and the nursing staff. Over time, alarm fatigue can cause complacency to warnings of low oxygen saturation or encourage patients to remove the pulse oximeter and not reapply the device in situations where it might be most useful, such as sleeping. Secondly, patients who are receiving supplemental oxygen may develop respiratory depression and hypercapnia **(see Section 4.3.4**) without having signs of hypoxemia.[80]

A large observational study from 1993 showed that although anesthesiologists felt that pulse oximetry was useful in monitoring their patients, they could not observe any significant difference in postoperative outcomes.[80] Secondly, a recent meta-analysis of studies looking at outcomes improvements between using pulse oximetry or no oximetry on general care wards has had mixed results. A recent Cochrane meta-analysis regarding pulse oximetry in the perioperative period

showed that monitored patients were less likely to have hypoxemia events and more likely to have oxygen prescribed to them; however, there was no difference in in-hospital mortality or ICU transfers from the general care floors.[75] However, caution must be used when attempting to interpret the results of these monitoring outcomes studies since study design may limit the ability to detect a difference because the knowledge of a study can affect the control group (Hawthorne effect).[81]

**Conclusion**

The use of pulse oximetry to monitor patients receiving opioids on the hospital floor may have value when used in concert with a protocol for assessing desaturation events, filtering alerts and providing algorithmic response interventions to affect patient oxygenation. Mandatory requirements for routine continuous pulse oximetry monitoring on all general care hospital patients may not be a cost-effective solution to opioid-induced respiratory depression alone. However, pre-screening for high-risk patients and selectively using continuous pulse oximetry with coordinated response protocols may improve patient outcomes and reduce morbidity.

### 4.3.4 Capnography

Opioid-induced respiratory depression is defined as a respiratory rate below 8 to 10 breaths/min, decreased $SpO_2$ or elevated $EtCO_2$.[82] Capnography is the time-based display of exhaled carbon dioxide partial pressure/concentration that allows for monitoring of both respiratory rate and a gross approximation of $EtCO_2$.[83]Traditionally this has been used in the operating room and ICU to ensure endotracheal intubation, monitor respiratory efficacy and detect changes in cardiac perfusion in sedated or anesthetized patients, but selective use for inpatients receiving opioids based on risk may prevent opioid-related respiratory failure.

**Benefits of Capnography**

On the general hospital wards, continuous electronic monitoring of ventilation may allow for more rapid diagnosis and prevention of opioid-induced respiratory depression.[84] In the presence of supplemental oxygen, pulse oximetry alone can be unreliable since patients can develop hypoventilation and hypercapnia without having a significant decline in their oxygen saturation, making changes in pulse oximetry a late detector of respiratory depression. Capnography provides a means of monitoring their respiratory rate and $EtCO_2$ in a way that monitors their ventilation directly as opposed to using oxygen saturation as a surrogate. It has been shown to be sensitive and quick, while moderately specific for respiratory depression. With continuous capnography, patients had fewer transfers to the ICU and better survival of in-hospital arrests when compared to patients who only had nurse assessment every two to four hours.[84]

Although studies of head-to-head comparisons of capnography have been limited, observational studies have shown that patients on IV PCA after surgery had frequent and prolonged episodes of hypercapnia particularly if they were on supplemental oxygen. Another study showed 41percent of patients after surgery had >3 minutes of respiratory rate less than 10 breaths/min while only 12 percent had oxygen desaturations below 90 percent.[82]

A hospital in Savannah, Georgia implemented a capnography monitoring program throughout its hospital for patients on parenteral or neuraxial opioids and has not had a significant respiratory event from opioids since the implementation of the new monitoring regimen.[84]

### Limitations of Capnography

As with all continuous monitoring technologies, false alarms are the major limitation of implementation. Alarm fatigue by nurses induces behavior changes and desensitization such that alarms are ignored or alarm sounds are deactivated with the assumption that they are false alarms.[82,84] Establishing thresholds for alarms that are not so sensitive to increase the number of false alarms but sensitive enough to capture the vast majority of hypoventilation patients is critical to avoiding alarm fatigue. The ideal settings for capnography have not been determined.

A second concern is that $EtCO_2$ only correlates with alveolar $CO_2$ concentrations during full vital capacity breathing. Routine tidal volume respiration has significant dead space ventilation that may dilute the $EtCO_2$ reading. This dilution makes quantitative evaluation of $EtCO_2$ levels very limited.[82] Potential solutions to alarm fatigue from threshold alerts and non-representative $EtCO_2$ values may lie in trend analysis in which an absolute number isn't the trigger for an event but rather a trend showing gradual hypoventilation.

In addition, large meta-analysis studies have not shown significant outcome differences with the use of capnography on a routine basis. Because of this, many people are reluctant to mandate the use of capnography for all general care patients on opioid treatment.

### Conclusions

Capnography can provide additional monitoring data, such as respiratory rate and $EtCO_2$, for patients at risk for opioid-induced respiratory depression, particularly in the setting of supplemental oxygen where pulse oximetry is less reliable. Although studies have not shown significant outcomes improvement from routine capnography use on general care wards, your RADEO team may consider implementing capnography based on risk stratification. As of yet, there are few experts who believe mandating capnography for all patients to be a cost-effective solution until further research that shows outcomes improvement is published. Future developments in trend analysis may improve the value of this technology while limiting the alarm fatigue and false alarms currently associated with the additional monitoring. Capnography is still recommended for procedural sedation and analgesia.[82,84]

**Table 1. Comparison of Available Monitoring Modalities for Detection of Opioid-Induced Respiratory Depression in the Postoperative Period**

| Monitoring Modality | Sensitivity * | Specificity | Reliability | Response Time |
|---|---|---|---|---|
| $P_{et}CO_2$ (intubated) | High | High | High | Fast |
| $S_pO_2$ (no $O_2$ supplement) | High | Moderate-High | High | Fast |
| $P_{et}CO_2$ (unintubated) | High | Moderate-High§ | Moderate | Fast |
| $P_aCO_2$ | High | High | High | Slow |
| $P_vCO_2$ | High | Moderate | High | Slow |
| $P_{tc}CO_2$ | Moderate | High | Low-Moderate‡ | Medium |
| $S_pO_2$ (with $O_2$ supplement) | Moderate | Moderate | High | Slow |
| Clinical assessment (skilled clinician) | Moderate | Moderate-High | Moderate | Slow |
| Respiratory rate (newer technology) | Moderate | Moderate† | Moderate | Medium |
| Tidal volume (unintubated) | Moderate | Moderate | Low | Medium |
| Chest wall impedance (for respir. rate) | Low-Moderate | Low† | Low | Medium |
| Clinical assessment (less skilled clinician) | Low-Moderate | Low-Moderate | Low-Moderate | Slow |

* Definitions: Sensitivity = positive in the presence of respiratory depression (low false negative rate); Specificity = negative in the absence of respiratory depression (low false positive rate); Reliability = accuracy and availability (likelihood of an available and accurate reading at the time of respiratory depression); Response time = average time from the onset of respiratory depression until the variable reads abnormally if it is going to do so.

§ If $P_{et}CO_2$ is high, this is highly specific for respiratory depression. However, if is low, because of unknown dead space, it can only be used as a measure of respiratory rate.

‡ New $P_{tc}CO_2$ technologies may be more reliable.

† In some patients, respiratory rate alone may not be a good measure of opioid-induced respiratory depression.

*(Reprinted Table 1 with permission of the Anesthesia Patient Safety Foundation from the APSF Newsletter (Spring) 2011; 26(2):21.)*

### 4.3.5 Monitoring for Transport and Procedures

Patients who are being transported off the routine hospital floor or ICU and patients undergoing a variety of non-operative sedation procedures have an inherently higher risk of respiratory depression when they are taking opioids. Special planning and consideration must be given to the management and monitoring of these patients.[85]

### Monitoring for Non-operative/ER/Bedside Procedures

According to the American Society of Anesthesiologists, sedation is rated as being minimal, moderate, deep or general anesthesia. These levels of sedation/analgesia are along a spectrum wherein the patient may develop decreasing levels of responsiveness and increasing risks of respiratory depression and airway loss. Personnel performing the sedation must be skilled in handling a level of consciousness one level deeper than their intended level and must have the appropriate resuscitative equipment to achieve that level of care.[86]

In a study by Miner et al., 44.6 percent of patients undergoing procedural sedation in the ED were noted to have respiratory depression based on $EtCO_2$ monitoring, although only a third of these patients showed a decline in oxygen saturation and received respiratory support by the supervising provider.[87] Pulse oximetry can be as effective as or even more effective than $EtCO_2$ monitoring at detecting early respiratory depression during procedural sedation when supplemental oxygen is not used.[84] $EtCO_2$ monitoring can provide detection of pre-clinical respiratory depression better than pulse oximetry alone in patients undergoing procedural sedation when supplemental oxygen is used.

Provider monitoring of level of consciousness and respiratory function by exam is recommended for deep sedation and likely beneficial for moderate sedation. Capnography is considered to be likely useful for deep sedation but of equivocal benefit for moderate sedation. Apnea monitoring by either impedance monitoring of respiratory function or end-tidal capnography is recommended for patients under moderate to deep sedation when the care provider is physically separated from the patient during the sedation. In this situation, monitoring pulse oximetry alone is not sufficient. Pulse oximetry is recommended to detect hypoxia and the risk of cardiovascular collapse and is considered better than clinical exam alone during sedation. Routine use of blood pressure and ECG monitoring is recommended for deep sedation. See the ASA "Practice guidelines for sedation and analgesia by non-anesthesiologists" for full details.[86]

For patients with significant comorbidities or other significant underlying considerations, pre-procedure consultation with an experienced provider should be considered. Immediate availability of anesthesia-trained personnel should be considered in patients receiving deep sedation.

### Monitoring for Endoscopy/TEE

Upper endoscopy and TEE (transesophageal echocardiography) procedures present a unique challenge for sedation and monitoring since the procedures occupy the airway.[89,90] Some amount of airway obstruction is prevented by the endoscope itself, but in the event of respiratory depression, maneuvers to resolve airway compromise or assist with ventilation are difficult and interfere with the procedure. Early detection of respiratory depression and careful titration of sedation are essential to safe practice. Pulse oximetry is recommended as a minimum in these patients, but capnography is also useful since supplemental oxygen is frequently utilized. Early detection, and more sensitive detection, of respiratory depression can be achieved with capnography. In one case series, 45 percent of the patients undergoing TEE had signs of respiratory depression on capnography while there was no significant change in their oxygen saturation.[91]

Personnel experienced in moderate sedation for upper endoscopy and TEE should be comfortable in interpreting capnography data when used in conjunction with pulse oximetry and be trained in basic maneuvers and treatments to resolve basic airway issues and respiratory depression.

### Office-Based Procedures

The ASA and the AAANA have developed a guideline for office-based delivery of anesthesia services. These recommendations are intended to create a safe environment that follows the standards of an ambulatory surgery center to ensure consistent care. For deep procedural sedation, the guidelines recommend maintaining a standard of safety equivalent for all anesthesia practices.[92-93]

- The anesthesia provider should adhere to appropriate clinical practice guidelines such as the "Basic Standards for Preanesthesia Care," "Standards for Basic Anesthetic Monitoring," "Standards for Postanesthesia Care," "Guidelines for Ambulatory Anesthesia and Surgery," "Standards for Nurse Anesthesia Practice" and "Postanesthesia Care Standards for the Certified Registered Nurse Anesthetist" as currently promulgated by the American Society of Anesthesiologists and the American Association of Nurse Anesthetists.
- The anesthesia provider should be physically present during the intraoperative period and immediately available until the patient has been discharged from anesthesia care.
- Discharge of the patient is a physician or licensed independent practitioner responsibility (dependent on the jurisdiction and facility accreditor). This decision should be documented in the medical record.
- Personnel with training in advanced resuscitative techniques (e.g., ACLS, PALS) should be immediately available until all patients are discharged home.
- At a minimum, all facilities should have a reliable source of oxygen, suction, resuscitation equipment and emergency drugs. Specific reference is made to the ASA "Statement on Nonoperating Room Anesthetizing Locations."
- There should be appropriate anesthesia apparatus and equipment that allow monitoring consistent with ASA "Standards for Basic Anesthetic Monitoring."

Transporting critically ill patients or patients at risk for respiratory depression due to continuous opioid or continuous epidural opioid infusions can create a setup for increased complications and morbidity. The Agency for Healthcare Research and Quality (AHRQ) states that this type of patient transport is "quite risky" and is "understudied." Events such as decreased level of consciousness, respiratory depression, deoxygenation, hypercapnia, hemodynamic instability and hypothermia are all possible and unfortunately common. Transportation of a patient within the hospital can be fraught with a variety of mishaps from systems-based issues, equipment malfunctions, human-based issues such as inadequate training or communication, inadequate monitoring and patient-based issues.[94-96]

Policies for handling transport need to be hospital specific, developed by a multidisciplinary team involving all related parties including nursing and transport services, and training regarding the policy needs to be part of the implementation strategy. Use of a standardized handoff process and tool for communication, pre- and post-transport assessment of patient status, and establishment of appropriate monitoring need to be developed within each hospital. Creating standardized documentation facilitates this communication. Periodic quality improvement and review are important aspects of keeping policies and procedures current in the environment of changing healthcare needs.[94-96]

Careful planning of transport can help reduce the chance of complications. Determining the absolute necessity of transportation versus bedside evaluation and procedures, minimizing the transportation distance and time away from routine care, and determination of appropriate staff to transport the patient are key elements for safe patient transport.[94]

Determining a monitoring strategy for transport depends on who will be with the patient during that time. For higher-risk patients **(see Section 4.3)**, and patients on continuous opioids, nurses familiar with the patient are the optimal choice for transport. Critical care patients who are on ventilators are recommended to have two escorts during transport. At minimum, the patient should receive the same level of monitoring during transport that he or she was receiving on the hospital floor. In addition, the person doing the transport should have the basic training required to respond to that monitor. Evaluation of the patient's ability to maintain his or her airway patency prior to transport can help prevent significant problems from occurring. Continuous pulse oximetry is highly recommended during transport of patients at high risk for respiratory depression. Intermittent monitoring of respiratory rate, heart rate and blood pressure is recommended. The routine use of capnography in this setting, however, has not been established as useful or cost-effective.[94-96]

### 4.3.6 Establishing Evidence-Based Alerts for Patients on Opioids

Patients receiving opioids are at risk of respiratory depression during their hospital stay. Depending on the route of opioid administration and the patient medical factors, the risk may be higher in certain populations **(see Section 4.2)**. Monitoring technology can be useful to detect patients who are developing respiratory depression: bradypnea, hypoventilation or desaturation. However, utilizing monitoring systems effectively depends on developing effective alert mechanisms and thresholds that provide adequate time for an effective response as well as minimizing erroneous values that may lead to alarm fatigue, patient and staff irritation, and complacency.[97]

Traditionally, thresholds for monitors are somewhat simplistic and arbitrary, although fairly consistent across institutions (as shown in Table 14 below).[98] These are intended to serve as the "fire alarm" for alerting personnel to respond and deal with an impending process. However, traditional alarm levels do not address the physiologic complexities involved in impending respiratory failure and arrest.

*Table 14: Alternative Choices for Numeric Thresholds*

**Table 1 Alternative Choices for Numeric Thresholds (used with permission)**

| VITAL SIGN NUMERIC THRESHOLDS | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Bradycardia** | **Tachycardia** | **Hypotension** | **Hypertension** | **Bradypnea** | **Tachypnea** | **SPO2** |
| Calzavacca (2008) | <40 | >120 | <90 | | <8 | >25 | <90 |
| Genardi (2008) | <40 | >130 | <90 | | <8 | >24 | |
| Hravnak (2008) | <40 | >140 | <80 | >200 | <8 | >36 | <85*5 min |
| Brilli (2007) | | | | | <8 | | <90 (Suppl. O2) |
| Dacey (2007) | <50*15 min. | >130*15 min | | | <8 | >30 | |
| Halvorsen (2007) | <40 | >120 | <90 | | <8 | >30 | <88 (Suppl. O2) |
| McFarlan (2007) | <51 | >120 | <91 | | <8 | >24 | <90 (RA) or <92 (Suppl. O2) |
| Offner (2007) | <40 | >120 | <90 | | <8 | >24 | |
| Sebat (2007) | | | <90 | | | >19 | |
| Garretson (2006) | <40 | >130 | <90 | | <8 | >30 | <90 (Suppl. O2) |
| Jones (2005) | <40 | >130 | <90 | | <8 | >30 | <90 (Suppl. O2) |
| Hillman (2005) | <40 | >140 | <90 | | <5 | >36 | |
| Tibballs (2005) | | | Age Index | | | | <90 (Suppl. O2) or <60 (Cyanotic HD) |
| Bellomo (2004) | <40 | >130 | <90 | | <8 | >30 | <90 (Suppl. O2) |
| DeVita (2004) | <40 | >140 | <80 | >200 | <8 | >36 | <85*5 min |
| Bellomo (2003) | <40 | >130 | <90 | | <8 | >30 | <90 (Suppl. O2) |
| Buist (2002) | | >130 | <90 | | <6 | >30 | <90 (Suppl. O2) |
| Hodgetts (2002) | | | Weighted | | | | |

*(Table 1: Lynn LA, Curry JP. Patterns of unexpected in-hospital deaths: a root cause analysis. Patient Saf Surg. 2011;5(1):3.)*

### What an alert should tell you

When a patient is developing respiratory depression, there are three different types of events that may occur separately or concurrently that can lead to unexpected hospital deaths. Type I is a Hyperventilation Compensated Respiratory Distress (e.g., from sepsis, pulmonary embolus or congestive heart failure). In Type I, patients have a stable oxygen saturation initially and an increasing $PaCO_2$. Eventually this leads to a slow then precipitous desaturation when metabolic acidosis sets in. Type II is a Progressive Unidirectional Hypoventilation or $CO_2$ narcosis event. In this case, often due to opioid or other sedative overdose, patients have a rise in $PaCO_2$ (and $EtCO_2$) first, then a subsequent fall in oxygen saturation that can be slow or rapid. Type III is a Sentinel Rapid Airflow/Oxygen Saturation Reduction with Precipitous $SpO_2$ Fall. In this Type III situation, the patient is dependent on the arousal state to maintain oxygenation. If there is arousal failure, precipitous hypoxemia develops during apnea that can lead to a sudden arrest.[97,98]

*Table 15: The 3 Clinical Pattern Types of Unexpected Hospital Death (PUHD)*

| Table 1—The 3 Clinical Pattern Types of Unexpected Hospital Death (PUHD) | |
|---|---|
| **TYPE I** | **Hyperventilation Compensated Respiratory Distress (e.g., Sepsis, PE, CHF)**<br>Stable $SPO_2$ with progressively falling $PaCO_2$ eventually yields to slow $SPO_2$ decline (mitigated by respiratory alkalosis), which is followed by precipitous $SPO_2$ decline when metabolic acidosis dominates. |
| **TYPE II** | **Progressive Unidirectional Hypoventilation ($CO_2$ Narcosis)**<br>Progressive rise in $PaCO_2$ (and $etCO_2$) and fall in $SPO_2$ over 15 minutes to many hours. (Often due to overdosing of narcotics or sedatives) |
| **TYPE III** | **Sentinel Rapid Airflow/$SPO_2$ Reductions Followed by Precipitous $SPO_2$ Fall**<br>A state of "arousal dependent survival" that occurs only during sleep. Arousal failure allows precipitous hypoxemia during apnea causing terminal arousal arrest. |

*(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)*

Due to the complex nature of these events and the potential for overlapping processes of types, no single monitor can provide adequate information in all situations to detect a respiratory event. OSA very commonly follows a Type III mechanism, which can be aggravated by the presence of opioids and other sedatives.

### Appropriate mechanism of alert

Single-value threshold alarms are likely the most common alert mechanism used in hospitals (e.g., a pulse oximetry that is set to alarm when the value decreases below 90 percent). Single-threshold alarms may be inadequate to detect an impending respiratory depression episode and can often be a late finding. Additionally, single-value threshold alarms often have a lot of difficulty distinguishing between meaningful declines in a monitor's value versus nuisance alarms. Unfortunately, these single-value alarms are the only widely available alarm systems and are the most commonly encountered. The use of multiple monitor systems in concert, even when each is set on a single threshold alert system, may help improve the reliability of the alarm system and the ability for the system to detect an early depression in the respiratory function in a patient, whether it is respiratory rate, hypercapnia or hypoxia.

One solution to this problem is the Modified Early Warning Score (MEWS).[99] The MEWS attempts to combine the threshold breaches from multiple monitors to produce a "super fusion" threshold, the idea being that this might reduce false alarms

but still maintain the sensitivity of threshold systems in multiple monitoring routes. However, simple addition may still not adequately represent the complex physiologic process that is occurring in respiratory depression.

Future development of smart technologies may include the ability to monitor for patterns of changes in vital signs over time and which could predict based on pattern and trend analysis the trajectory of a patient's respiratory status. These could theoretically provide a more sensitive means of detecting an impending event while reducing significant false alarms.

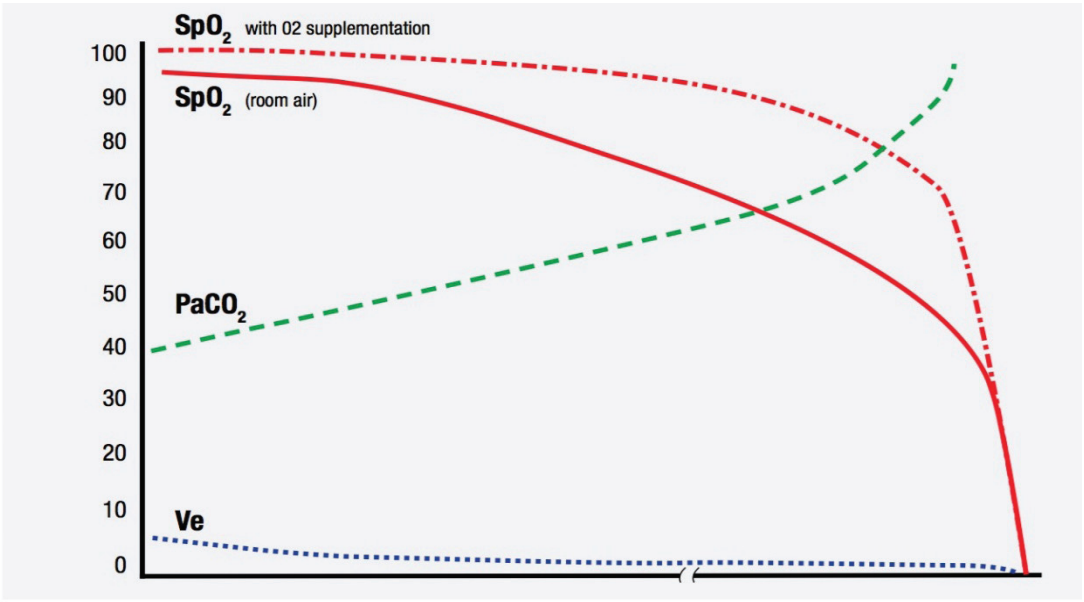
**Thresholds for Oxygen Desaturation**

Pulse oximetry is likely the most useful yet problematic monitor to establish alerts. Single-value threshold alerts for desaturation can be either too high or too low depending on the patient's situation, and the monitor is very prone to artifact and error. Patients on supplemental oxygen can have artificially elevated $SpO_2$ that does not represent an impending respiratory event until it is a very late finding. Therefore, higher alert thresholds may be useful in detecting early desaturations. However, due to brief subclinical changes in saturation or more commonly movement or detection artifacts of the monitor itself, frequent dips in oxygen saturation can occur triggering repetitive alarms. This can lead to alarm fatigue and complacency.

This is evidenced in Type II patterns of unexpected death where patients are developing hypoventilation due to opioids or other sedatives but maintaining their saturation above 90 percent even while minute ventilation is declining and $PaCO_2$ is increasing. When supplemental oxygen is used (as is common in these patients), this process can stretch out even further into the respiratory failure process before a desaturation alarm is triggered.[99]

Establishing appropriate thresholds for desaturation alarms involves distinguishing patients who may develop Type II respiratory failure, using supplemental oxygen judiciously and providing training regarding the possibility of alarm fatigue and the consequences of complacency. Multiple monitors should be considered in very high-risk patients, such as super morbid obesity, OSA and high-dose continuous opioid treatment to prevent late desaturation alerts. Individualizing alert thresholds may be necessary to provide adequate alert time without increasing false alarms.

*Figure 4: Type II Pattern of Unexpected Hospital Death ($CO_2$, Narcosis)*



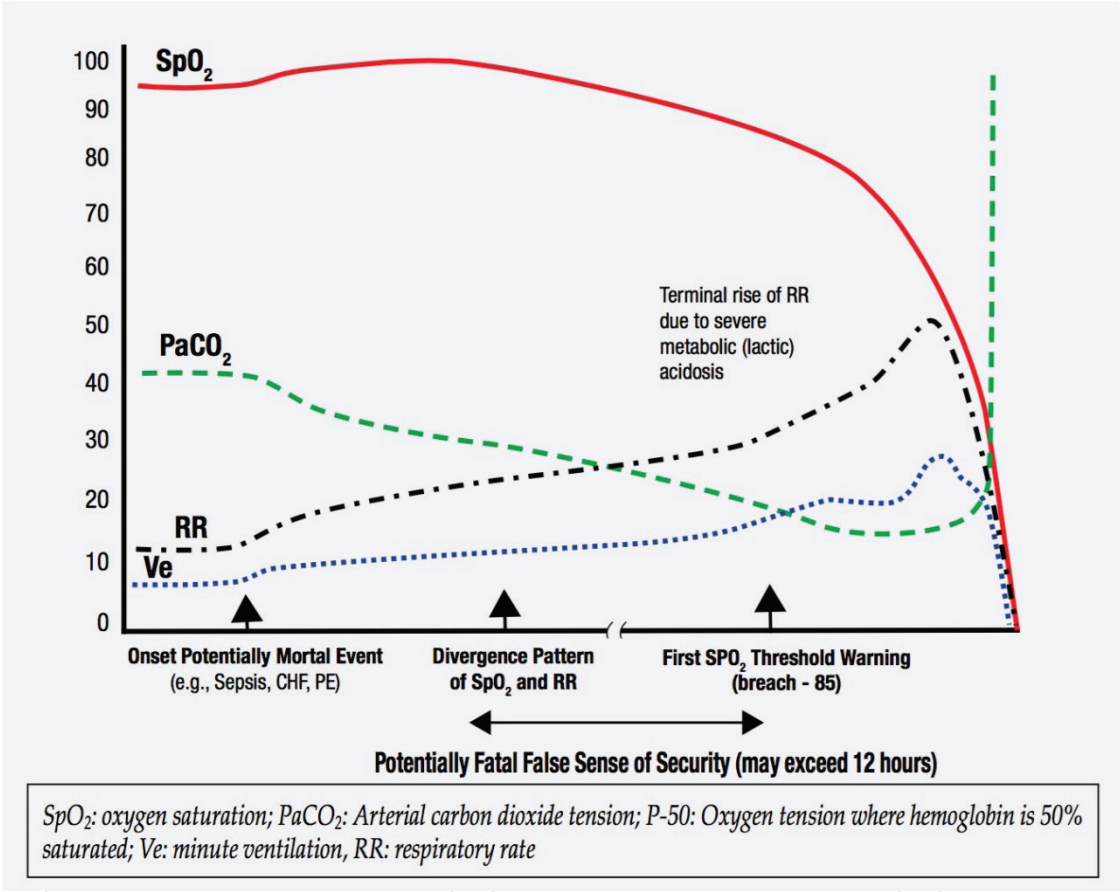

*(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)*

**Thresholds for respiratory rate**

In Type I unexpected hospital death events, desaturation can be a significantly late finding of impending respiratory failure (see Figure 5).[99] Rapid respiratory rate, instead, is a hallmark of impending respiratory failure. High respiratory rate thresholds (often above 30/min) are commonly used to trigger a rapid response team and represent the eventual development of metabolic acidosis in these patients. Even though this is a late finding, the rapid respiratory rate often maintains an elevated $SpO_2$ giving the clinicians a false sense of security in the early stages of this process. In addition, supplemental oxygen is often given to these patients and this again increases the false sense of security provided by the $SpO_2$.

Low respiratory rate thresholds can be useful to detect hypoventilation due to Type II or Type III unexpected death patterns. Frequently respiratory rate monitors are calculated from changes in chest impedance alarms and have poor sensitivity and reliability, are prone to frequent false alarms, but do provide a moderate level of responsiveness when true respiratory depression occurs. Newer respiratory rate monitoring systems are often attached with the capnography monitors using sampling from nasal cannulas to detect airflow. These provide higher sensitivity and fairly good response systems, but are also prone to errors.

*Figure 5: Type I Pattern of Unexpected Hospital Death*



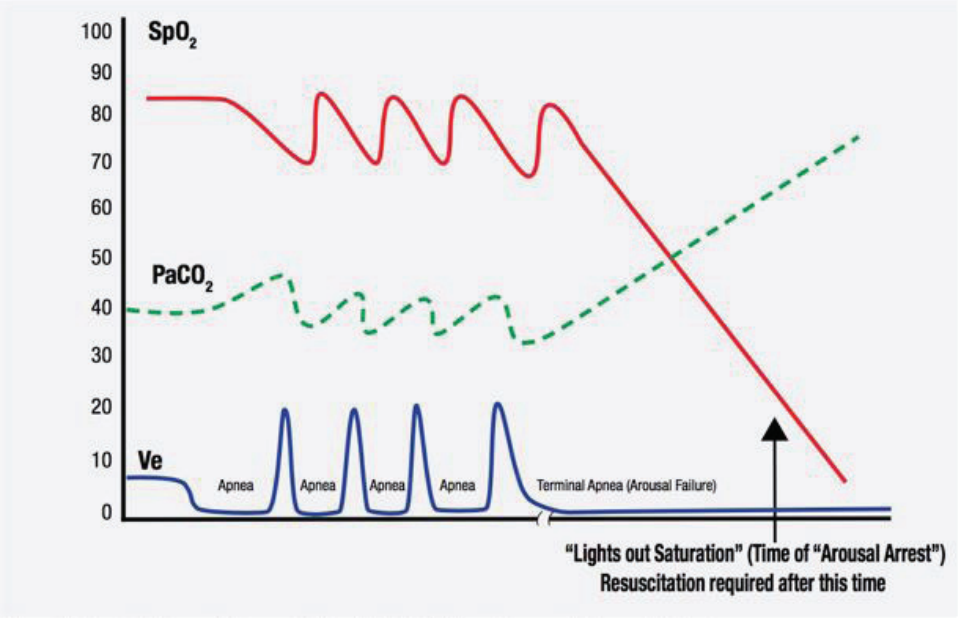

*(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)*

**Thresholds for capnography**

Quantitative analysis of capnography can be challenging in a patient who is not intubated since dead space ventilation during tidal volume breathing and ambient dilution can reduce the absolute amount of $CO_2$ detected during sampling. Threshold alarms geared toward absolute $CO_2$ elevations or reductions as used in the ICU or operating room will have significant false alarm rates on the general care floors. However, capnography monitors can be very useful as an additional monitor for respiratory rate since the periodic nature of $CO_2$ exhalation and the drop to zero during inhalation provide a clear demarcation of respiratory cycling. The same thresholds for respiratory rates can be used with capnography to detect hyperventilation as in Type I events or hypoventilation as in Type II or III events.[99]

Capnography is imperfect, though. Sampling errors, significant dilution from room air and the patient's ability to tolerate the sampling line can all lead to inconsistent results with capnography. In addition, in Type III (see Figure 6) phenomenon where arousal failure is the precipitating event, capnography changes, just like pulse oximetry, can be a late finding.

*Figure 6: Type III, Pattern of Unexpected Hospital Death (Sleep Apnea with Arousal Failure)*

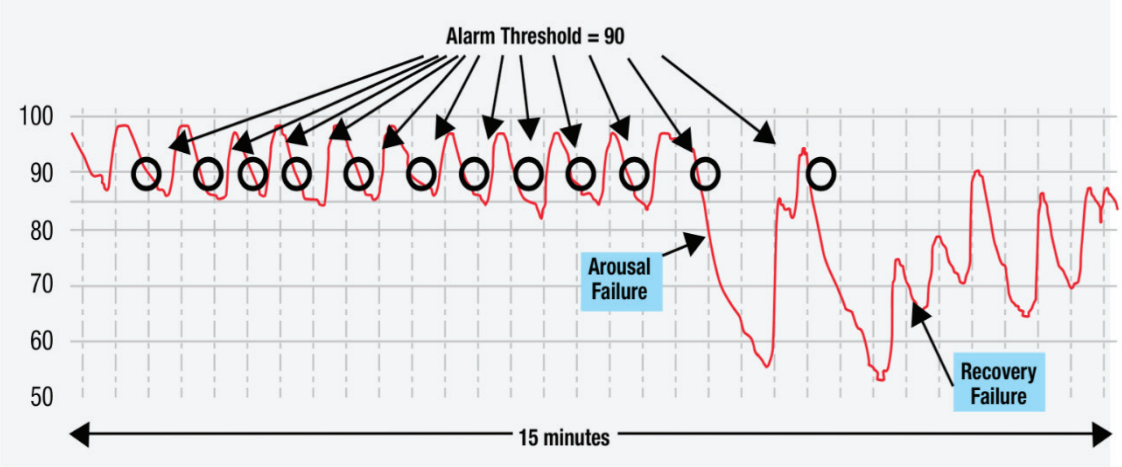



*(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)*

**Concern for alarm fatigue**

Alarm fatigue is the process where the patient or the care provider responds to a threshold alarm multiple times in a short time frame. In each episode, no significant clinical event is noted, and the alarm is reset. After a certain number of events, complacency sets in and the response to an alarm is delayed or ignored. However, as can be seen in Figure 7, in patients with OSA and respiratory depression from opioids, alarm fatigue can lead to a respiratory event. Initially, there can be frequent brief desaturations that trigger a low threshold alarm that may arouse the patient. However, after alarm fatigue sets in due to these multiple alerts, eventually the patient may develop a terminal arousal failure and develop significant respiratory depression. Knowing when this episode will occur is difficult. Developing a policy for reasonable alarm thresholds, utilizing multiple monitors for corroborating alerts and training staff to recognize alarm fatigue can help prevent these events from occurring as frequently.[99]

*Figure 7: Type 3 Pattern: Note the Potential for Alarm Fatigue Preceding Arousal Failure*




*(Curry JP, Lynn LA. Threshold Monitoring, Alarm Fatigue, and the Patterns of Unexpected Hospital Death. Anesthesia Patient Safety Foundation Newsletter. 2011;26(2):32-35.)*

## 4.4 Interventions for Patients with Excess Sedation and Adverse Drug Events Related to Opioid Use

The previous sections helped to guide your RADEO team through risk assessment, safe administration and prescribing, and rational monitoring of patients on opioids. A well-crafted program will decrease, but not eliminate, the need for rapid interventions such as medical emergency team activation in order to prevent the progression to respiratory failure or arrest. Guidance is also provided on how to avoid or address other bothersome and sometimes dangerous adverse reactions to opioids such as delirium, constipation and urticaria.

### 4.4.1. Rapid Response and Escalation of Care

Optimal pain management in the hospitalized patient is necessary in order to achieve appropriate recovery. Even though the use of a multimodal approach to pain management is advocated and recommended, opioids are still the most frequently used medication. Whether used alone or in combination with other drugs, opioids are associated with the

development of disturbing side effects including respiratory depression, especially in high-risk patients. When excess sedation or respiratory depression complicates care, patients require evaluation for potential transfer to a higher level of care. This often involves activation of a rapid response system (RRS).

The need for higher level of care is usually based on the presence and identification of symptoms and signs (vital signs abnormalities, decreased urine output, changes in mental status, respiratory depression, etc.) that should alert the clinical provider (nurse, physician) of the possible deterioration of the patient's clinical status. The ability of the clinical provider to recognize signs of deterioration as early as they manifest is essential in this process. Direct communication between the nurse taking care of the patient and the treating physician is paramount. A careful assessment of the patient's status will allow the provider(s) to make appropriate decisions. If doubts persist, it may appropriate to consider activating a rapid response.

Rapid response systems have been created in the attempt to improve recognition of and response to the deterioration of patients' clinical conditions on general hospital wards, and reduce the incidence of hospital morbidity and mortality. The concept of an RRS has been developed in order to detect such clinical deterioration early, and eventually trigger a rapid response by staff with appropriate skills, knowledge and experience.[100] Since their initial description, there has been a worldwide adoption of the concept and RRSs have been supported by a growing number of influential patient safety organizations.[101-106]

A RRS generally comprises three components:[107]

1. **Criteria and a system for notifying and activating the response team (known as the "afferent limb" – the mechanism by which team responses are triggered):**

   Activation criteria usually include vital signs abnormalities, decreased urine output, changes in mental status and/or significant concerns about the trajectory of the patient's clinical course expressed by a clinician (e.g., nurse, physician) or a family member.[78] The afferent limb defines the variables that indicate deterioration and empowers bedside clinicians to trigger the response team when there is suspicion that a patient is deteriorating. Most RRSs rely on clinicians to proactively identify deteriorating patients rather than on continuous monitoring technology, which is common in the ICU.

2. **The response team (efferent limb):**

   The response team most frequently comprises ICU-trained personnel and equipment. Team composition should vary on the basis of local needs and resources but one of the following models is generally used:

   a. Medical emergency teams (METs): they usually include a physician (e.g., the code blue team)

   b. RRTs: usually they do not include a physician (e.g., ICU and ED registered nurse and a respiratory therapist)

   c. Critical care outreach teams: they follow up on patients discharged from an ICU but can also respond to critical care situations involving all ward patients

Perhaps, more important than team configuration, is the novel concept of individual unit managers (i.e., charge nurse) regularly rounding on their own most "at risk" patients. That may add a layer of familiarity and increased likelihood of identifying even subtle changes associated with eventual decompensation. The implementation of such strategy may result in the decrease of the incidence of non-ICU cardiopulmonary arrests and overall hospital mortality.[109,110]

3. **An administrative and quality improvement component:**

   This group/team collects and analyzes event data and provides feedback, coordinates resources and ensures improvement or maintenance over time.

Despite the widespread implementation and the increasing evidence that they may help reduce morbidity and mortality, RRS effectiveness still remains controversial. Experts have suggested that the variation in effectiveness may be attributable to barriers that usually prevent staff from calling and activating the rapid response team in a timely fashion.

Three barriers have been identified:[111]

1. **Self-Efficacy:**

   Self-efficacy is described as "the perception that one has the necessary skills and abilities to perform a behavior, even in the face of specific barriers and obstacles."[112]

   Self-efficacy in recognizing clinical deterioration and activating the RRS is a strong determinant of whether care is escalated in a timely fashion for patients whose condition is deteriorating.

2. **Perceptions of Hierarchy:**

   Existing hierarchical norms among nurses and physicians can contribute to delays in RRS activation, as clinicians may wait to activate the RRS in order to seek the approval of others who are above them in the hierarchy.

3. **Expectations of the Outcomes of the RRS Activation:**

   Expectations of the outcome of the RRS activation and related interaction with the RRS team and, possibly, other teams (e.g., ICU) can strongly shape behavior due to previous experiences. Some attending physicians seem to be hesitant to send their patients to the ICU for fear of inappropriate management. On the other hand, some nurses and physicians (residents in particular but attending physicians as well) fear resistance and criticism from the RRS team. Those with positive previous experiences report that they are more likely to activate the RRS quickly.

By recognizing and addressing these barriers, hospital leaders may be able to improve the RRS safety culture and eventually enhance the impact that RRS may have on morbidity and mortality rates outside the ICU.

Finally, it is likely that high-quality implementation plans and organizational "buy-in" may be more important than the structure of the system. The focus of most reports, the content of the afferent and efferent limbs, may not be as important as initially thought. Instead, ignored administrative and quality limbs (education, culture change, modifying the process to improve outcome) may be in the end the most important factors. Making sure that the organization is prepared to respond to these needs may be more important than who responds or what criteria trigger the call. RRSs have become a reality in the daily medical landscape and are here to stay because of the regulatory requirements and because they have become, de facto, standard of care. How the RRSs are implemented, however, may be as, if not more, important than what the intervention is.[113]

RRSs as mechanisms for preventing opioid-related respiratory events are necessary but not sufficient. Because activation is based on the periodic monitoring of patients by staff and family, it is an unreliable means to monitor for respiratory depression. It is should be counted on as part of your opioid safety program only as an adjunct to risk assessment, safe prescribing and administration, and continuous monitoring of selected patients.

### 4.4.2 Naloxone Use

As an opioid antagonist, naloxone may be administered to reverse opioid sedation and respiratory depression, to determine the cause for a change in level of consciousness, to treat other opioid side effects as a continuous infusion and, at times, has been used to rule out cause for hypotension.[115]

Examination of naloxone events may be useful to uncover deficits in processes and targets for improvement in opioid safety. However, caution must be provided not to interpret a higher incidence of naloxone use simply to imply over-treatment or errors. A very low rate of administration of naloxone may reflect under-dosing of opioids. The use of naloxone to reverse opioid-induced respiratory depression in the postoperative setting is reported to be <1 percent. Some patients, despite proper execution of appropriate orders, develop significant respiratory depression requiring reversal.

Root cause analysis of naloxone events may uncover:

- Improper prescribing and administration of multiple opioids (e.g., parenteral dosing and inappropriate use of long-acting opioids)
- Lack of knowledge about potency differences in opioids
- Deficits in sedation monitoring
- Excess use of supplemental CNS depressants (e.g., benzodiazepines, sedating antiemetics, antihistamines)
- Breakdowns in communication regarding medication reconciliation and opioid tolerance
- Overreliance on opioids for pain control with limited use of multimodal analgesia

Over-sedation in adults may be reversed with as little as 80 to 100mcg. Overaggressive naloxone administration could in and of itself lead not only to uncontrolled pain but also acute abstinence syndrome in patients who are physically dependent and to other adverse events such as massive sympathetic discharge resulting in pulmonary edema.[116]

### References

Lin RJ, Reid MC, Chused AE, Evans AT. Quality assessment of acute inpatient pain management in an academic health center. *American Journal of Hospice.* 2014; Aug 8. pii: 1049909114546545. [Epub ahead of print]

### Guidelines for Naloxone Administration and Patient Monitoring

1. **Patients should meet at least two of the three criteria before naloxone (Narcan) is administered:**
    - Sedation Scale = 3 (Somnolent; Difficult to arouse)
    - RR <8
    - Pinpoint pupils

    Documented exceptions to the criteria may be accepted based on physician assessment and clinical judgment.
2. **If the criteria listed above are met, stop the administration of the opioid and benzodiazepines,** if prescribed. Maintain IV access.
3. **Provide oxygen via facemask STAT.**
4. **Stay with the patient.** Continue to attempt to arouse the patient. **Request help from a coworker.**

5. **Notify the primary physician and/or house staff of the need to immediately evaluate the patient.**

   If the house staff does not arrive within 5 minutes or if the nurse assesses the need, a "Condition C" should be called. **House staff should contact the appropriate consult services** following the patient (i.e., Pain Service, Palliative Care Service, UPCI Pain Program or the Toxicology Treatment Program).

6. **Obtain a physician's order for naloxone administration: Naloxone 0.04mg IV q 1 minute until a change in alertness is observed.** Dilute 0.4mg naloxone (one ampule) with NSS to a total volume of 10mL (1 mL = 0.04mg) in a 10mL syringe.

7. **Titrate the prescribed naloxone until the patient is responsive.** At that point, stop naloxone dosing and reassess the patient. **Naloxone administration should not cause pain to return or precipitate opioid withdrawal.**

8. If the patient does not respond, continue to titrate naloxone at the same rate. **If a response is not obtained after one ampule of naloxone** (10 cc of diluted solution) **is administered, examine the patient for alternate causes of sedation and respiratory depression.**

9. **Keep the naloxone syringe readily available.** The duration of action of naloxone is considerably shorter than the duration of action of most narcotics. A second dose of naloxone may be needed in as early as 30 minutes. **House staff or a consult service should assess the need to administer naloxone by continuous infusion.** For assistance with further naloxone dosing, please contact the UPCI Pain Program or the Toxicology Treatment Program.

10. **House staff or a consult service should determine what additional monitoring is necessary.**

    Patients receiving long-acting opioid products (i.e., OxyContin, MS CONTIN, fentanyl patch or methadone), epidural morphine analgesia, higher-than-expected opioid doses or concomitant benzodiazepine therapy may require additional monitoring. **Partial reversal of respiratory depression via naloxone does not prove that the narcotic was the primary cause.** The patient should be evaluated to determine if other disease states might have exacerbated the effects of the opioid. **Patient-specific evaluation should be performed and monitoring needs should be determined, as well as the site of continued monitoring.** Patients who have refused intensive care interventions and monitoring may remain in their current setting with approval by the physician or as per their advanced directives.

    **Minimal Monitoring Requirements: Monitor vital signs (RR, BP, HR), pulse-oximetry, and pain score every 15 minutes for 2 hours; then every 30 minutes for the next 4 hours.**

11. **Re-evaluate the events leading to the need for naloxone administration.** In cases where the prescribed opioid dosing was too high, reassess the therapeutic plan for pain management. Consider decreasing the opioid dose by 50 percent. Resume opioid administration when the patient is easily aroused and after the RR increases to >9.

12. **Physicians, nurses and therapists should document their actions.**

## 4.5 Other Opioid-Related Side Effects

There are a number of other side effects that can be seen in the patient receiving opioids. A full description of all of the possible side effects is outside the scope of this *Guide.* Below is a discussion of some of the more common problems: delirium, constipation, nausea and vomiting, allergic reactions and pruritus.

### 4.5.1 Central Nervous System Effects

Opioids are known to cause many adverse effects in the CNS. These CNS depressants are well known to reduce the level of consciousness, causing sedation and sleep disturbances (**see Section 4.4.1** for discussion of sedation, assessment and management of opioid-related sedation). They also cause cognitive impairment, psychomotor slowing, delirium, hallucinations and abnormal dreams. In the realm of toxicity, they are known to cause myoclonus, seizures and hyperalgesia.[117]

#### Cognitive and psychomotor impairment

In hospitalized cancer patients receiving opioids, up to 77 percent have cognitive impairment, increasing to 80 to 90 percent in palliative care patients just prior to death. It is unknown how much of this is caused by opioids, pain, organ system failure or the disease process itself. In healthy volunteers, parenteral opioids have been shown to cause greater impairment in cognition than oral agents.[118] On the other hand, morphine has been shown to improve cognition by reducing pain, which also impairs executive functioning.[119] The effects of opioids may, however, be less problematic than benzodiazepines. The cognitive effects of opioids are unknown as the results of studies have been mixed in the chronic non-cancer population. A review by Lawlor showed that meperidine caused more psychomotor and cognitive effects than hydromorphone and morphine.[118] Bruera found that during times of dose escalation, patients had more difficulty than stabilized patients. He hypothesized that tolerance may develop to the cognitive effects in stabilized patients.[120]

Psychomotor impairment due to opioids is largely unknown. There have been studies showing impairment (e.g., driving) but just as many that show no impairment. Sedation caused by opioids can certainly affect psychomotor function and is additive with other CNS depressants such as benzodiazepines or alcohol.

Treatment of the psychomotor and cognitive effects of opioids is largely trial and error. Some providers use stimulants to improve higher executive function, but there is little literature support for this. Others will employ an opioid rotation. Reducing the opioid dose and using adjunctive non-sedating therapies such as NSAIDs may be useful.

#### Delirium

Delirium is defined as an acute onset of cerebral dysfunction with a change or fluctuation in baseline mental status, inattention and either disorganized thinking or an altered level of consciousness. It is thought to be caused by an imbalance in the dopamine and acetylcholine systems. Opioids are known to cause anticholinergic effects in the CNS, including impairment of cortical arousal and information processing as well as cognitive awareness and focus. There is conflicting data with regard to opioids being an independent cause of delirium, as delirium is just as likely to be caused by uncontrolled pain, underlying disease processes or other medications (particularly anticholinergics). Because there are so many factors involved, it is almost impossible to determine how often opioid-induced delirium occurs. The incidence of delirium is estimated as 60 percent in the general population, with greater occurrence in older age groups. The incidence of delirium is as high as 70 percent in mechanically ventilated patients in the ICU, with dementia patients having a 40 percent greater risk, and is reported in 28 to 88 percent of the terminally ill.[119,121]

The diagnosis of delirium is clinical as no laboratory test can diagnose delirium. *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* diagnostic criteria for delirium are as follows[122]:

- Disturbance in attention (e.g., reduced ability to direct, focus, sustain and shift attention) and awareness.
- Change in cognition (e.g., memory deficit, disorientation, language disturbance and perceptual disturbance) that is not better accounted for by a pre-existing, established or evolving dementia.
- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
- There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use or more than one cause.

The most reliable and validated delirium screening tools are the Confusion Assessment Method (CAM), CAM-ICU (for the ICU setting) and the Intensive Care Delirium Screening Checklist (ICDSC), the latter two being the assessment tools of choice for the ICU setting.[123-125]

It is paramount that providers be aware of the most common settings for delirium to develop. This includes emergence delirium after procedures in healthy young adults, usually males. There is a higher risk of delirium in patients with pre-operative anxiety, pre-operative benzodiazepine use or lengthy invasive surgery. Postoperative delirium occurs more frequently in patients undergoing orthopedic procedures and other major surgeries, particularly in patients over the age of 60. Patients are also more likely to have nightmares, hallucinations and bizarre dreams in the postoperative settings. Other settings where delirium is more prevalent are those where there is cognitive decline, intensive care admission and in the terminally ill.

A recent systematic review of delirium in the ICU found strong evidence that age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mechanical ventilation, metabolic acidosis, delirium on the prior day and coma are risk factors for delirium. They did not list gender as a risk factor for ICU-related delirium, though this is listed as a risk factor for emergence delirium. There is moderate evidence that multiple organ failure is a risk factor for delirium as mentioned above.[126] Multiple other risk factors across settings have been reported, including CNS pathology, organ failure, metabolic abnormalities, psychiatric illness, infection, constipation, substance withdrawal (including opioids, benzodiazepines, alcohol, nicotine and psychotropics) and medications including opioids, alcohol, steroids, anticholinergics, anticonvulsants, antidepressants, antiemetics, antihistamines, antiparkinsonians, antipsychotics, anxiolytics, hypnotics and stimulants.

Delirium is often described as *hyperactive* (agitated, associated with hallucinations and delusions) or *hypoactive* (calm or lethargic, associated with confusion and sedation) or some fluctuation between these. Opioids may contribute to either of these types of delirium if given in inadequate doses to relieve pain or if given in excessive doses. Agents such as morphine, hydromorphone and meperidine have active metabolites (3- and 6-morphine glucuronides, 3- and 6-hydromorphone glucuronides and normeperidine, respectively) that are renally excreted. If any renal compromise occurs (due to dehydration, diuretic use, antibiotics, contrast dye or other toxins), the metabolites are not excreted and they accumulate. The 3-glucuronides and normeperidine cause CNS excitation and may cause symptoms consistent with hypo and/or hyperactive delirium. This occurs quite commonly and sometimes is not obvious (no acute change in serum creatinine) so providers must be diligent.

*Preventing delirium*[127]

| |
|---|
| Regular orientation to place, time, person |
| Early mobilization and rehabilitation |
| Access to glasses/hearing aids |
| Avoid unnecessary catheters/manipulation |
| Reduce modifiable risk factors (e.g., infection, pain, metabolic imbalance) |
| Reduce/avoid anticholinergics, benzodiazepines, propofol |
| Consider use of dexmedetomidine for sedation |
| Monitor older patients more closely |
| Monitor patients with dementia more closely |
| Minimize opioid needs by applying multimodal analgesic regimens with non-opioids (NSAID, acetaminophen, etc.) |
| Avoid opioids that have active metabolites that are renally cleared (e.g., morphine) in patients at risk. Hydromorphone is also affected with markedly impaired renal function. Use opioids like fentanyl (for acute or chronic pain) or methadone (for chronic pain) whose clearance is not affected by renal function. |
| Avoid rapid escalation of long-acting opioids |
| Avoid opioids like meperidine, pentazocine |

**Neurotoxicity**

Neurotoxicity, or damage to neurons or the nervous system, is increasingly reported with opioids. The neuroimmunomodulatory activities of glial cells is one of the key areas of research at this time. Glial cells make up 70 percent of the CNS. They are activated by injury, infection and medications like opioids. Once activated, they release inflammatory cytokines and excitatory neurotransmitters like glutamate into the CNS. Glutamate, in turn, activates NMDA receptors, increasing neuroplasticity in the CNS.

Myoclonus is a centrally mediated symptom. It has been reported to occur in as many as 87 percent of cancer patients and is commonly associated with chronic and high-dose opioid use.[128] It is caused by an imbalance in excitatory and inhibitory neuronal activity. It is hypothesized that opioids may inhibit glycine activity (which is an inhibitory neurotransmitter), or increase the activity of glutamate and its effects at the NMDA receptor, or even dopamine antagonism, causing myoclonus via the extrapyramidal pathway. Myoclonus has been associated with accumulation of opioid metabolites (normeperidine and the 3-glucuronides of morphine and hydromorphone).

Opioid-induced hyperalgesia is a controversial adverse effect. Hyperalgesia is a lowering of the firing threshold of action potentials due to repeated stimulation. It is hypothesized that opioid use, particularly with chronic use (e.g., repeated stimulation) and higher doses, causes GABAergic cell apoptosis, leading to neuroplasticity in the spinal cord. Opioids also inhibit glycine, as mentioned above, and increase glutamate activity, leading to activation of the NMDA receptors.

Treatment and prevention of neurotoxicity is focused on reducing opioid exposure, blocking the NMDA receptor (possibly with NMDA receptor antagonists like ketamine) and inhibiting glutaminergic activity at the spinal level (with gabapentinoids and other anticonvulsant medications) or rotating to an opioid that does not have active neurotoxic metabolites.

### 4.5.2 Constipation

#### Definition

There is no single definition of opioid-induced constipation, and definitions of constipation are not specific to opioid use. Definitions of constipation include infrequent bowel movements, hard stools and incomplete emptying. Unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both are considered in the definition provided by The American College of Gastroenterology.[129]

#### Incidence

The majority of patients taking opioids suffer gastrointestinal side effects including nausea, vomiting, bloating and abdominal pain. The most common complaint of patients taking opioids is constipation. The incidence ranges from about 50 to 80 percent in patients taking opioids.[130,131] Gastrointestinal side effects often do not resolve over time with continued exposure to opioids. Patients may elect to discontinue treatment or reduce the opioid dose. A severe form of opioid-induced constipation is *narcotic bowel syndrome* that may occur in approximately half of patients receiving opioids. This syndrome is described by chronic or frequently recurring abdominal pain, worsening with continued or escalating dosages of opioids.[132]

#### Mechanism of action

The action of opioids on the enteric nervous system (ENS) is directly responsible for this unwanted side effect. The ENS is the native network of the GI tract. These organizations of nerves regulate the sensory, motor, electrolyte secretion and immune functions in the GI system.[99] Opioids affect these neurons throughout the GI tract by decreasing colon water and electrolyte secretion, ultimately leading to diminished bowel motility.[133] Opioids also affect the action of the three G-couple protein receptors: alpha (a), kappa (k) and mu (μ)[131] that modulate neurotransmitter release within the bowel.

The mu and kappa receptors are primarily responsible for blunting pain perception in the CNS. Opioids interact prominently with mu receptors to produce analgesia. These same receptors are also found in abundance in the stomach and lower GI tract of the colon. Opioids inhibit the μ G-couple protein receptors. This inhibition limits expulsion and excitatory effects of acetylcholine on GI mucosa, which creates constipation.[129]

#### Predisposing factors

Predisposing factors of opioid-induced constipation include gender and age with females and older patients having a higher incidence of this problem. Other risk factors are reported to be higher education levels, simultaneous use of aspirin and not smoking tobacco. The incidence is not affected by the route of opioid administration.[134]

#### Measurement scales

A number of measurement scales have been described to evaluate opioid-induced constipation as well as to assess response to treatment. These include the Bowel Function Index, bowel function diary and the Patient Assessment of Constipation (PAC-SYM). The simple, three-item Bowel Function Index is administered by the clinician evaluating ease of defecation, feeling of incomplete bowel evacuation and patient judgment of constipation. The bowel function diary includes outcomes reported by the patient where he or she immediately reports movement characteristics such as straining, emptying and consistency of the bowel movement along with daily reported items such as bloating, gas and lack of appetite. Patients also report what they did to help relieve the symptoms such as taking extra fiber or laxatives. The PAC-SYM is a 12-item instrument that assesses stool characteristics, rectal symptoms and abdominal symptoms. The reliability and validity of these tools has been assessed in various patient populations.[129]

### Clinical evaluation of constipation

The clinical evaluation of the patient with opioid-induced constipation includes taking a thorough history, physical examination and targeted laboratory and other diagnostic tests.

The history should include

- Medication history
- Start of constipation in relation to beginning opioid use
- Diet and lifestyle
- Defecation patterns
- Abdominal symptoms
- Additional gastrointestinal symptoms

The physical examination includes an abdominal examination. A digital rectal examination should be done to assess the anal sphincter and pelvic floor relaxation on straining. Laboratory tests include a complete blood count, basic metabolic panel and thyroid function tests. Patients with family history of colorectal cancer, unexplained weight loss or rectal bleeding may require further testing such as colonoscopy. Other tests that may be warranted based on these findings include anorectal manometry/balloon expulsion and defecography.[129]

### Nonpharmacologic interventions

Nonpharmacologic interventions that may be considered are proper hydration, encouraging mobility, regular timing of bowel movements and dietary changes. Unless the patient is dehydrated, increasing fluid intake is not likely to relieve constipation. Moderate physical activity has been suggested to improve bowel symptoms and decrease colonic transit times. If the patient assumes a regular pattern of defecation by recognizing and responding to the urge to defecate it may help relieve constipation.[129]

Unfortunately, fiber has not been shown to be efficacious in relieving opioid-induced constipation as well as constipation induced by other drugs. However, due to the low risk of intervention, it may be considered as part of a treatment regimen. Soluble fiber (found in barley, flax and supplements such as psyllium) is usually better tolerated and more effective than insoluble fiber (sources include skins of fruits and vegetables, seeds, whole grains). Patients may complain of bloating when starting fiber, which may be reduced if the fiber is taken initially once per day and titrated up to three times per day. [129]

### Pharmacologic interventions

Opioid rotation

Reducing the dose of the opioid is not usually effective in relieving opioid-induced constipation. Opioids vary in their likelihood to cause constipation. In addition, the dose of an opioid that is efficacious as well as the dose-causing side effects varies between patients. Opioids can be switched (opioid rotation) to reduce constipation while maintaining analgesia. This must be done carefully with the provider consulting equianalgesic tables to reduce the risks of under- or overdosing.[129] There are few studies supporting the use of one opioid over another to reduce constipation but one study suggested transdermal fentanyl may cause less constipation compared with oral sustained-release morphine.[135] Another study indicated that tapentadol, dual μ-opioid agonist and norepinephrine reuptake inhibitor, may offer some advantages over other opioids. Compared with oxycodone, the results of one study suggested it caused less opioid-induced constipation in subjects with lower back pain or osteoarthritis.[136]

Stool softeners

Stool softeners are often prescribed for patients with opioid-induced constipation, however support is lacking.[137] The addition of docusate to sennoside was not beneficial in relieving constipation for hospice patients taking opioids.[138]

Stimulant and osmotic laxatives

Authors of a Cochrane Review reported there was little evidence supporting the use of laxatives in palliative care patients.[139] Many of these patients were probably taking opioids. Also, they found no difference between osmotic and stimulant laxatives.[129] However, authors of another systematic review suggested there is evidence supporting the use of stimulant and osmotic laxatives in treating chronic idiopathic constipation, and these findings may offer some information in using these agents in patients with opioid-induced constipation.[140]

Lactulose and polyethylene glycol, osmotic laxatives, have been found to be effective in preventing constipation in subjects with chronic idiopathic constipation. Perhaps osmotic lactulose is more effective compared with polyethylene glycol.[141]

Senna

Investigators administered senna and lactulose to the subjects who had undergone a neck-of-femur surgery with postoperative opioid pain control. They defined constipation as a failure to defecate for three consecutive days. The researchers examined the frequency of opioids and laxatives and incidence of constipation, and compared demographics of each group (including nutritional status). There was no difference in the incidence of constipation, perhaps due to the inadequate sample size. The researchers pointed out statistically significant factors that were associated with constipation included nutritional status and age, whereas the choice and dose of opioid did not indicate significance.[142]

Opioid receptor antagonists

Naloxone

Naloxone is a nonspecific opioid antagonist. There is no oral formulation in the U.S. because it has very poor bioavailability. It is possible to use the injectable formulation orally. It blocks opioid intestinal receptors and has been used to treat morphine-induced constipation. However, it has a narrow therapeutic index and must be titrated carefully to avoid opioid withdrawal symptoms.

Naltrexone

This is a nonspecific opioid antagonist available orally. It is currently available as a single entity or in combination with long-acting morphine to prevent abuse and diversion but the naltrexone is sequestered and not released. This combination product was studied, however approximately 25 percent of subjects did not complete the study due to side effects, 3 percent of whom had constipation.[143] As a single entity it is not used for treating constipation as it is readily absorbed and may precipitate withdrawal.

Methylnaltrexone

Methylnaltrexone is a selective, peripherally acting μ-opioid receptor antagonist (PAMORA). Due to its quaternary structure it does not cross the blood-brain barrier. It is available for subcutaneous administration in patients who have opioid-induced constipation and where a bowel obstruction has been ruled out. This drug was designed to decrease the peripheral adverse effects of opioids without interfering with the centrally mediated analgesia. Subjects given methylnaltrexone had a bowel movement within two and four hours of first dose. Subjects receiving methylnaltrexone had a significantly shorter time to defecation than those given placebo.[144]

Alvimopan

This is another PAMORA. It reverses opioid-induced slowing of the GI tract and opioid-induced constipation but does not antagonize the analgesic effect of opioids and is available for oral administration. It also does not precipitate withdrawal in opioid-dependent patients. It is not approved for treatment of opioid-induced constipation but the results support its use.[145]

Naloxegol

Naloxegol is a PAMORA supplied as an oral preparation. It is a derivative of naloxone but due to pegylation, has difficulty crossing into the CNS. The results of a multicenter trial suggested naloxegol significantly reduced the incidence of constipation without decreasing analgesia. There was an increased incidence of gastrointestinal side effects including diarrhea, abdominal pain and nausea with higher doses but the incidence of these side effects was less than 5 percent.[146]

**Other medications**

**Lubiprostone**

Lubiprostone is a locally acting type-2 chloride channel activator that increases intestinal fluid and electrolyte secretion, and thus increases intestinal mobility. This agent bypasses the antisecretory effects of opioids. A study comparing senna (control group) and lubiprostone utilized the patient assessment of constipation (PAC) tool that described symptoms (PAC-SYM) and quality of life (PAC-QOL) for the subjects in each group. There were no significant differences between groups in regard to scores related to PAC-SYM and PAC-QOL. Variables that were examined included completeness of bowel movement and reduction in abdominal pain. The control group had a better result in bowel movement completeness and a reduction in abdominal pain as compared to lubiprostone. Rescue laxatives were administered in 75 percent of the lubiprostone and 78 percent of the senna subjects, which was not a clinically significant difference. Gastrointestinal symptoms were the most common side effects reported. The researchers concluded that both medications were equally effective and it is likely that more than one type of laxative will be used in preventing constipation. Senna can be administered in a generic form, which proves to be more economical compared to lubiprostone.[147]

Misoprostol

This agent has been used off label to treat opioid-induced constipation. A synthetic prostaglandin E1 agonist, misoprostol is administered to prevent gastric ulcers in patients taking NSAIDs. A side effect of misoprostol is diarrhea. This action has been used to treat patients with severe constipation and has found to be effective in small studies. Its use is limited due to side effects. Its use in pregnancy is limited due to its potential to cause harm to the fetus.[148,149]

### 4.5.3 Nausea and Vomiting

**Incidence**

Nausea and vomiting has reportedly occurred in ~30 percent of all patients taking opioids.[150-151] Sixty percent of patients with advanced cancer report nausea, while 30 percent report vomiting. Thirty-two percent of patients with chronic non-cancer pain also report nausea, with 15 percent reporting vomiting.[150] The higher incidence in cancer patients may reflect multiple additional factors including chemotherapy, surgery and radiation-induced emesis. There is a great deal of variability in patient response, though nausea and vomiting may be more common with phenanthrenes that have a 6-OH group (e.g., morphine), and less problematic for compounds without this hydroxyl group (e.g., hydromorphone).

**Pathophysiology of nausea and vomiting**[152]

Nausea is the feeling of the impending need to vomit. It is associated with salivation, repeated swallowing, tachycardia and pallor. Vomiting, on the other hand, is a very complex process mediated by a "vomiting center" in the brain. This may be activated by 1) visceral afferent input from the GI tract (like with GI distention or mucosal irritation), 2) the cerebral cortex and thalamus (possibly related to previous experiences, sights, smells that caused nausea), 3) the vestibular region (as with motion sickness) and 4) the chemoreceptor trigger zone (CRTZ). Once activated, motor neurons descend to the upper GI tract, vagal and sympathetic nerves descend to the lower GI tract, and spinal nerves activate the diaphragm and abdominal muscles.

Opioid-induced nausea and vomiting (OINV) is thought to occur through both central and peripheral mechanisms. One of the pathways is through the vestibular system. There are opioid receptors in the vestibular epithelium (mu receptors) and the inner ear (delta and kappa receptors) that trigger the vestibular apparatus, which in turn, sends input to the vomiting center via histaminergic and cholinergic pathways.

The blood-brain barrier at the CRTZ is more permeable to drugs, toxins, etc., and opioid receptors (mu, delta, kappa) within the CRTZ may be activated directly by opioids.

Delayed gastric emptying is a key mechanism of OINV. There are opioid receptors in the myenteric plexus and submucosal plexus in the gut (mu, kappa). Constipation caused by opioids leads to gastric distention and prolonged GI emptying time, which in turn, stimulates the visceral mechanoreceptors and chemoreceptors, sending the message to the vomiting center.

**Predisposing factors**

There are several factors that may predispose someone to OINV including route of administration, dose, pharmacokinetics and variations in gene expression. The different responses between patients may be related to polymorphisms in the opioid pathways (e.g., cross membrane transport of opioids through the blood-brain barrier) or in the neural pathways affecting the vomiting center.[153]

Some believe that these receptors exhibit tolerance to some extent, with repeated dosing causing less nausea and vomiting, though others found that up to 33 percent of study patients showed no attenuation of symptoms despite at least four months of opioid therapy with stable doses and sufficient analgesia, regardless of the opioid employed.[154]

**Pharmacologic interventions**

OINV is not necessarily something that can be predicted, and antiemetics are preventive therapies. Once a patient has already started vomiting, these are useless. Systematic reviews of antiemetics have demonstrated that there are no agents that have strong literature support. The most evidence with the highest-quality studies includes metoclopramide in a continuous infusion or in high doses. Lower-quality studies support phenothiazines like prochlorperazine and olanzapine. There is very little support for 5HT3 antagonists like ondansetron, antipsychotics like perphenazine or risperidone, antihistamines, corticosteroids, mirtazapine or cannabinoids. This does not reflect what is recommended in various guidelines, however, very few guideline recommendations are supported by evidence (see Table 16).

For some types of nausea (postoperative, chemotherapy-induced) a combination of antiemetics are recommended and have some literature support, however, antiemetic combinations have not been shown to be beneficial for OINV. Switching classes has not been shown to be beneficial either.[155]

*Table 16: Pharmacologic Interventions for Opioid Induced Nausea and Vomiting*

| Target | Associated Receptors | Antiemetic |
|---|---|---|
| Vestibular apparatus | M1, H1 antagonist | Scopolamine<br>Promethazine |
| CRTZ | Mu, Kappa, Delta opioid receptors | Naltrexone, Naloxone |
| | D2 | Promethazine,<br>Olanzapine,<br>Metoclopramide,<br>Prochlorperazine |
| | NK-1 | Aprepitant |
| Periphery/GI tract | 5-HT3 | Palonosetron,<br>Ondansetron |
| | Mu opioid receptors | Naloxone,<br>Naltrexone |

### 4.5.4 Allergic Reactions

Patients often refer to opioid side effects as "allergies." While opioids are associated with many adverse effects, most are not associated with an immunologic response.

Pseudoallergic reactions include mild itching, urticaria, bronchospasm and hypotension. These symptoms are usually caused by mast cell activation and subsequent histamine release, but are not a true immunologic reaction. Histamine release is commonly seen with administration of morphine and to a lesser degree other opioids. It is thought that the natural opioids cause a more pronounced histamine release, while synthetic compounds cause a more mild reaction, however this hasn't been definitively proven. These reactions may be idiosyncratic and may or may not recur with re-challenge of the same opioid. Hypotension can occur due to vasodilation, negative inotropic effects and/or vagal-mediated bradycardia.

Immunologic reactions may present as an allergic dermatitis (erythroderma, scarlatina, eczema or exudative vesicular eruptions) related to a type IV (delayed) hypersensitivity reaction. Patients can undergo diagnostic patch testing for confirmation.

Anaphylactic reactions are systemic immunoglobulin E (IgE)-mediated reactions with release of potent mediators. Anaphylactoid reactions are clinically the same, but not IgE-mediated. Symptoms include nasal congestion, flushing, pruritus and angioedema. If the process worsens, patients can develop nausea, diarrhea, urinary urgency, bronchospasm, hypotension and death. These reactions are very rare.

### Management

If a patient has a true anaphylactic reaction to an opioid, he or she may be switched to another structural class; however, there is no guarantee that the patient will not have the same type of reaction. This is a very individualized effect. Anaphylactoid reactions require urgent treatment with epinephrine and histamine blockers. For milder histamine-related symptoms, opioid rotation to a different pharmacologic class (see below) along with use of antihistamines or steroids is recommended.

*Table 17: Opioid Structural Classes*

| Opioid Structural Classes | Drugs |
|---|---|
| Phenanthrenes | morphine; codeine; hydrocodone; oxycodone; oxymorphone; hydromorphone; levorphanol |
| Phenylpiperadines | fentanyl; meperidine; sufentanil; remifentanil |
| Diphenylheptanes | methadone |

## 4.5.5 Pruritus

### Incidence

Opioid-induced pruritus (OIP) affects 10 to 50 per cent of patients receiving IV opioids and 20 to 100 percent of those receiving epidural or intrathecal opioid therapy.[156] The frequency of OIP increases with increasing opioid dosages and seems to be more common with long-acting opioids due to their prolonged activation of the opioid receptor.[157]

### Pathophysiology of opioid-induced pruritus

Historically, it was thought that OIP was exclusively due to histamine release from mast cells. However, research has shown that central mu-opioid receptors also play a significant role in the pathophysiology of OIP.[158] This is particularly applicable in the scenario of intraspinal opioid administration. In addition, itching may be mediated by the peripheral effects of opioid peptides.[159] Even though some of the histamine-related reactions (pruritic rash and flushing) may be amenable to antihistamines, the pruritus associated with mu-receptor activation is only relieved by a mu-receptor antagonist.

### Predisposing factors

The most susceptible groups of patients are women receiving intraspinal opioids for labor and patients undergoing major orthopedic surgery. Morphine appears to be the agent most commonly associated with pruritus. Intrathecal administration (directly into the CSF) causes the fastest onset of pruritus, followed by epidural administration.

**Prevention and treatment**

Ideally we would like to avoid OIP. Using the minimal effective dose is the best strategy to avoid any of the opioid-induced adverse effects, including OIP. Opioid rotation to an agent with less histamine release (e.g., switching morphine to a semi-synthetic like hydromorphone or oxycodone) occasionally provides relief but does not consistently relieve OIP. Changing the route of administration/dosage form is another option and, of course, utilizing antagonists is a possibility as well. Commonly used antagonists include naloxone and naltrexone, as well as mixed agonist/antagonists like nalbuphine.[160-163]

Antihistamines are commonly used for OIP, though, as discussed above the role of histamine release is likely minimal. They are ineffective for mu-receptor mediated pruritis. Other agents that are often mentioned but lack strong evidence for efficacy include serotonin (5HT3) antagonists, promethazine, droperidol, propofol, mirtazapine, NSAIDs and gabapentin.

Naloxone, a synthetic derivative of oxymorphone, antagonizes the pharmacologic effects of opioid analgesics. It competitively antagonizes all opioid-receptor sites, including the mu, kappa and delta sites. Naloxone has no opioid agonist effects and, unfortunately, with larger doses, also antagonizes the analgesic effects of opioids. It has been used in everything from intermittent injections to continuous infusions to reduce pruritus without compromising analgesia. The most effective dose appears to be in the range of 0.25-1mcg/kg/hr as a continuous infusion, due to the very short half-life of naloxone.

Naltrexone, an analogue of naloxone, has a longer half-life than naloxone (four hours versus 55 minutes) and twice the potency.[164] It has historically been used in addiction medicine to competitively displace opioid molecules at the opioid receptors as well as block opioid receptor sites. Naltrexone is considered to have no agonist effects, but some studies have reported adverse effects such as miosis, dysphoria and respiratory depression in healthy non-addicted recipients, suggesting that naltrexone has some degree of partial agonist activity.[165] Naltrexone is more difficult to titrate as it is given orally. Studies report the most effective dose seems to be 9mg.

Nalbuphine is a mixed agonist/antagonist. At low doses it does not cause reversal of analgesia, though this is seen with higher doses. A typical dose of nalbuphine is 1-3 mg intramuscularly.

*Table 18: Drug Dosing*

| Drug | Dosing | Mechanism | Advantages | Disadvantages |
|---|---|---|---|---|
| Naloxone | 0.25-1mcg/kg/hr IV continuous infusion<br>(<2 mcg/kg/hr) | Mu receptor antagonist | Rapid onset, effective | $T_{1/2}$ 1 hr<br>May reverse analgesia |
| Naltrexone | 6-9mg orally | Mu receptor antagonist | $T_{1/2}$ 4-5 hrs | Only comes in 50mg tablets<br>May reverse analgesia |
| Nalbuphine | 1-3mg IM | Mixed mu-receptor agonist/antagonist | Less likely to cause reversal of analgesia | May cause sedation |

### 4.5.6 Other Opioid-Related Adverse Effects

**Serotonin syndrome**

Serotonin syndrome is a rare, but potentially life-threatening, iatrogenic complication from therapeutic use or overdose of serotonergic drugs alone or in combination via postsynaptic stimulation of 5-hydroxytryptamine (5-HT) 2A and 1A serotonin receptors in the central and peripheral nervous system. Serotonin syndrome presents as a constellation of hyper-metabolic symptoms including mental status changes (confusion, anxiety, hypomania, restlessness), neuromuscular over-activity (muscle rigidity, tremor, myoclonus) and autonomic instability (hyper/hypotension, tachycardia, tachypnea, hyperthermia).[165,166]

Proposed mechanisms for opioids' serotonergic action include weak serotonin reuptake inhibition, and/or increased release of intrasynaptic serotonin through inhibition of pre-synaptic GABAergic transmission on serotonin neurons.[167,168] Synthetic piperidine opioids (fentanyl, methadone, meperidine, tramadol) are serotonin reuptake inhibitors. The phenanthrene opioids (oxycodone, hydromorphone, oxymorphone and buprenorphine) may increase intrasynaptic serotonin levels, either through increased release of neurotransmitter or some unknown mechanism.[135],[139],[140],[165],[169-170]

This complication can be prevented by increasing provider awareness and provider (physician, pharmacist) vigilance with regard to analgesic choices and drug interactions. Treatment of serotonin syndrome consists of discontinuing the offending drugs and implementing supportive measures.

**Urinary retention**

One of the most uncomfortable and potentially dangerous complications seen with opioids in hospitalized patients is urinary retention. In addition to discomfort, urinary retention has clinical implications on perioperative outcomes such as prolonged length of stay, iatrogenic infection from catheterization with the potential risk of systemic infection, and possible long-term bladder dysfunction. In the orthopedic population the greater risk of urinary retention is deep joint sepsis.

The incidence of urinary retention in orthopedic patients is estimated at 60 percent for males and 5 percent for females with use of intraspinal morphine.[171] Patients receiving spinal anesthesia with a 0.5 percent hyperbaric solution of bupivacaine combined with intrathecal morphine were demonstrated to have a higher incidence of urinary catheterization, longer time to urinary catheterization and longer time to micturition compared to patients receiving only local anesthetic.[172] Risk factors include male gender, total hip arthroplasty (compared to knee arthroplasty) and intrathecal morphine use.[173] Risk factors include medical comorbidities, surgical type, anesthetic type and long-acting neuraxial opioids. The risk is also greater with bladder overdistention lasting more than four hours.[174]

## Step 5: Choose Metrics and Develop a Data Collection Plan

Consider choosing metrics that address structure, process and outcomes[175] related to the specific aims of reducing serious harm related to opioid use. Structure is defined as the physical and organizational properties of the setting where care is delivered. Processes include communication and practice patterns. Pertinent outcome variables include opioid-related adverse events. Although interest is high on outcomes, data on outcomes does not usually illuminate how the outcomes were achieved or how processes might be changed to improve them.

Examples of structure measures can be the presence of electronic opioid safety alerts, opioid medication administration guidelines, and nursing assessment policies and rapid response protocols. Adherence to best practices and policies and other process measures may be more enlightening than structure or outcome measures.

Consider what evidence can be gathered in a reliable and practical way to answer questions such as:

- Did staff explain to the patient and/or the patient's representative the assessment and monitoring process including that it might be necessary to awaken the patient to assess the effects of the opioid medication?
- Were patients and their families educated to alert staff to breathing problems or other reactions that may be related to medication?
- Are patients assessed by nursing and/or other staff, per hospital policy, for their risk of opioid-related adverse events?
- Are patients who are at higher risk and/or receiving opioids monitored for adverse effects?
- Is staff knowledgeable about intervention protocols when patients experience opioid-related events?

Data can be obtained by a variety of methods including patient surveys and medical record audits, rapid response team and incident event reports (e.g., Patient Safety Net and adverse drug reaction reports), drug utilization reviews of opioids and root cause analysis of naloxone events, reviews of flowcharts detailing how pain is currently managed, and systematic observation of current practice including documentation of patient assessments.

Joint Commission (JC) Sentinel Event Database

Sentinel events are defined as adverse events that result in death or permanent harm to patients. Opioids are among the most common type of medication-related sentinel events. The sentinel event-related data, reported to JC from JC-accredited organizations, can be accessed at the link below to help identify causes, trends, settings and outcomes of sentinel events nationally.
http://www.jointcommission.org/sentinel_event_statistics_quarterly/default.aspx

Patient Safety Net (PSN) or Incident Event Reports

Voluntary reporting such as Patient Safety Net (PSN) or other electronic incident databases, adverse drug reports and naloxone events can be used to highlight individual cases of safety issues. These reports can be examined individually or aggregated to analyze trends and factors related to overtreatment and misuse or technology-related problems (e.g., analgesic pump, computer physician order entry). Root cause analysis can reveal opportunities to enhance interdisciplinary communication and other processes affecting continuity of care (e.g., medication reconciliation, patient handoffs).

**Examples of Potential Measures**

Process
Patient and family opioid safety education/counseling
Drug utilization reviews (e.g., high-dose opioids, supplemental oxygen, naloxone)
Screening and documentation of opioid risk factors
Documentation of nursing serial sedation assessments, respiratory rate and vital signs

Structure
Computer opioid order guardrails and best practice alerts
Staff and patient/caregiver education program/resources
Opioid administration guidelines
Pain management policies
Rapid response teams and protocols

Outcomes
Trends in rapid response calls
Naloxone events
Incidence of opioid-related side effects including nausea and sedation requiring higher level of monitoring

Opioid-related adverse event ICD-10 codes can be found at:

http://www.icd10data.com/ICD10CM/Codes/S00-T88/T36-T50

# Step 6: Implement Interventions and Procedures, and Monitor Impacts

## 6.1 Implementing Your Guideline

After you have identified your metrics for your RADEO quality improvement program and determined your baseline performance on those metrics, your QI team will need to develop solutions and intervention strategies at various points of the patient encounter.

This section will provide possible strategies to improve the documented assessment of risk for opioid-related adverse events (ORAEs) in the inpatient care record and documentation of steps taken to reduce this risk.

We recommend the following three-step approach to the patient at risk for ORAEs:

- First, assess a patient's risk for ORAEs as outlined in the earlier sections of this *Guide* during every hospital admission and record it in the chart or EMR to ensure that changes in ORAEs are updated every time.
- Second, whenever a patient is prescribed an opioid (for those patients receiving an opioid) or the patient's condition changes, the patient is reassessed for risk of an ORAE.
- Third, if feasible, address the risks and benefits of opioid use with the patient and family.

As you evaluate opportunities for systems change, consider incorporating key patient safety principles in your efforts:

- Reduce reliance on memory. Systems combining clinician education with additional strategies that do not depend primarily on clinician memory to do all the necessary QI steps will provide the most comprehensive results.
- Use fail-safe systems and forcing functions. By using methods integrating provider workflow with fail-safe systems and forcing functions, your initiative will have a greater likelihood of success. Thus, provider-based point-of-care alerts within the EMR that require completion will ensure that the appropriate assessments will be done. Of course, electronic alerts will need to be well integrated into workflow so the requirements are easy to complete.
- Standardize and simplify processes. Assessments need to be standard across the care continuum so the same risk stratification tools are used every time. Clinicians will more likely accept processes that are simple, well designed and not redundant. Assessments done on admission should not need to be completed again on discharge if clinical risk does not change.
- Enhance access to complete and timely information. To assist clinicians in completing assessments, access to a fully updated medical record will ensure that the information that is being entered is correct. For example, pop-up alerts,

if within the EMR, should allow clinicians to close the alert, access clinical information and then return to the content of the reminder rather than forcing the clinician to complete the information with no opportunity to re-access the patient chart.

- Improve quality and cycle time. The goal of any QI project will be to obtain the desired results to improve the outcome of interest in a timely manner. Thus, your systems changes should lead to an increase in the percent of patients who are assessed for risk of ORAEs over a defined period.
- Once you have determined your baseline rates of ORAEs, you can develop specific interventions.
- Layering multiple interventions to allow for process change rather than focusing on one particular intervention will improve the effectiveness of any QI initiative. The relative efforts placed on each intervention will depend on the infrastructure, the barriers to change and the resources at your institution.
- One approach to structuring your project with the layering of multiple interventions is to consider the points in the patient encounter that are opportunities for intervention.

## 6.2 Electronic Medical Record-Based Triggers in the Computer Physician Order Entry Environment

In hospitals that have an EMR and CPOE, systems change can occur by leveraging the technological capabilities of your IT systems. As you consider how the EMR can trigger an ORAE assessment to appear for completion, one starting point would be to use the admission order entry process or the initial nursing assessment physician to trigger an ORAE risk assessment when patients meet certain parameters. Your QI team will need to have an understanding of the capabilities of your individual hospital's IT systems and how order entry and documentation are structured. For example, how you incorporate the ORAE assessment will partly depend on the scope of the admission order sets that are being used at your institution. Some hospitals use disease-specific order sets, while others use generic admission order sets. This is an important distinction as you consider how to trigger assessments.

If your institution has disease-specific admission order sets for certain primary diagnoses, then the ORAE assessment can be written into every order set that has an option of ordering an opioid. Or, the risk assessment can be triggered anytime an opioid is ordered for the patient.

In situations when the ORAE assessment is not written into the initial order set, your QI team will need to develop methods to trigger ORAE risk assessments, a process that will greatly depend on the capabilities of your EMR. One strategy employed in many EMRs is to use the concept of problem lists at time of order entry to assist in triggering the assessments for patients at risk for ORAE. Although the notion of a problem list has typically been associated with a list that is written by the physician as part of his or her clinical note, problem lists can be developed in EMRs that are entered by the physician at time of admission order entry. Some EMR systems have a list of the most common medical diagnoses appearing at time of admission order entry and require the physician to place a checkmark next to all applicable diagnoses a patient may have. If a diagnosis such as chronic pain is checked, then the EMR can recognize this discrete data point. EMR-based code language can then be written such that if opioid or pain is in this list, it will trigger an ORAE-specific risk assessment. This process, however, will rely on the physician accurately completing the problem list. Another approach is to use ICD-9/10 diagnosis codes from prior admissions and link them to all future patient encounters. Lastly, some integrated EMRs link a risk assessment to the medication administration record (MAR), or directly to CPOE any time an initial or increased dose of opioid is ordered.

Thus, the approach of how to trigger the ORAE risk assessment will differ based on your EMR and will require you to partner with your IT department in writing EMR code language to assist you in this process. In fact, many hospitals currently trigger reminders for a variety of quality metrics. The process used for deep venous thrombosis (DVT) prophylaxis is one example of such a reminder triggered in many EMRs. However, unlike this metric that requires risk assessment on all admitted patients, the ORAE risk assessment would only trigger if the EMR recognizes that the patient in question has a diagnosis that places the patient at risk for an ORAE. You will need to individualize your approach based on your specific institution's EMR. The strategies noted below on alerts during the hospitalization and upon discharge will also depend on your EMR recognizing that the particular patient in question is at risk for an ORAE.

The results of the risk assessment should result in described data in the EMR that in turn triggers potential safety protocols such as a pharmacy consult for medication review, specific monitoring protocols and associated documentation for nursing staff, or implementation of continuous monitoring technology. Your EMR in the hands of a skilled IT department should make implementing the policies and processes your RADEO designs easier to implement with less reliance on provider memory and knowledge.

Ensuring ORAE risk assessment protocols are used in hospitals with paper-based medical records faces similar hurdles to those hospitals in the EMR world. If paper-based disease-specific order sets are being used, then the ORAE risk assessments can be incorporated into those order sets and will capture patients at risk for an ORAE. Strategies will need to be developed at time of discharge if ORAE assessment has not been done and if an opioid is being given.

## 6.3 Interventions to Reduce ORAEs

### 6.3.1 Intervention 1: Focus on Provider Education

A significant number of patients who receive opioids are at risk for an ORAE. A significant contribution to this quality gap is a clinician knowledge gap in assessing benefit and risk of opioids and the principles of safe opioid prescribing. Addressing this knowledge gap must be accompanied by other strategies – such as alerts, hard stops and reminders – in order to ensure a RADEO project is successful.

The first step in a successful initiative to reduce ORAEs is to ensure that you have educated all providers at your institution on the tools for assessing the patient for ORAEs. Your QI team should engage providers in educational seminars and lectures and increase visibility on the need for evidence-based assessments. Some approaches to address this knowledge gap include:

- Educational programs
- Grand rounds, noon conferences or division meetings
    - The focus of these sessions should be to review current guidelines to reduce ORAEs as well as methods to assess patients for risk of ORAEs
- Distribution of educational materials (e.g., pocket cards with opioid equivalency chart, OSA scoring)
- Links to educational materials within order sets in the EMR environment. At the time of completion of an admission order set, links to the literature would be an excellent opportunity to provide valuable references that would assist in education of ORAEs.

- Creation of visibility of ORAEs initiative on patient floors. Posters, signs and project boards at your institution provide visible reminders of the key concepts of your QI project to all constituents in the hospital.
- Development of RN education campaign that could involve all members of the interdisciplinary team. By focusing education efforts on all members of the healthcare team, your ORAE prevention efforts would be potentiated, as team members could work in conjunction with providers.
- Use of Web-based education tools that can be incorporated into the credentialing and re-credentialing process. Requirements to complete a Web-based program on common QI metrics could include methods to decrease ORAEs.
- Development of a continuing medical education (CME) program led by physician leaders with expertise in ORAEs. Frontline hospitalists, academic leaders and anesthesiologists and nurse anesthetists can provide education in structured CME formats.
- Identification of a physician champion to lead hospital-wide education efforts. An individual with visibility and respect within your institution can be used to effectively communicate the quality gap and discuss tools available to assist in provider decision-making.
- Development, promotion or dissemination of mobile applications that could be used by providers.
    - OSA scoring
    - Opioid equivalency chart
    - Identify medical-based calculators incorporating ORAEs assessments that can be used in the decision-making process.
- Dissemination of information about quality initiatives at medical staff meetings.
- Incorporating data on the ORAEs quality initiative at staff meetings amongst other topics most often discussed such as value-based purchasing, patient satisfaction, readmission rates and adverse events will assist in the staff education process.
- Social media such as Twitter

By educating providers about the importance of the use of ORAE tools and guidelines on opioid use, outcomes will be positively impacted as providers become self-compliant. However, other interventions will need to be layered into your QI project to optimally reduce ORAEs.

### 6.3.2 Intervention 2: Development of a Process to Identify Patients at Risk for ORAEs

These patients include those of extreme age, having comorbidities, with OSA and those receiving drugs that may enhance the respiratory depression caused by opioids. **(See Section 4.1.)**

### 6.3.3 Intervention 3: Real-Time Decision Support for Preventing ORAEs

Your EMR alerts and triggers should capture patients at higher risk for ORAEs at admission and throughout the hospital stay as the patients' risk profiles change. Identifying patients at risk for ORAEs within the EMR will remain the most difficult challenge. As high-risk patients are identified, alerts can then be written that trigger safety interventions such as nurse monitoring protocols, continuous monitoring through technology or pharmacy reviews.

The approach addressed in this intervention can lead to a decrease in ORAEs during the hospital stay and subsequently at discharge. These alerts would remind providers within the CPOE environment to be aware the patient is at risk for an ORAE.

An important consideration for your QI project may be the notion that repeated alerts for risk assessment may lead to the phenomenon of "alert fatigue," where the frequency of alerts would be a barrier to effective clinician workflow. Thus, involving an interdisciplinary team in QI strategy development will be essential to ensure that there is frontline provider buy-in to your process changes and that there is judicious use of CPOE-based alerts. Your team should track and analyze the sensitivity and false negative rates of alerts. Alerts with high false negative rates will lead to alert fatigue. This, of course, has to be weighed against the sensitivity of the alert (with a low false negative rate leading to a less sensitive alert) as well as the seriousness of the event that the alert is designed to prevent. With the aid of a data analyst, frontline clinicians are the best judges of which alerts are at risk of causing alarm fatigue, and thus can be ignored.

### 6.3.4 Intervention 4: Discharge-Based Alerts for Transitioning Patients on Opioids

Similar to alerts on admission at the time of initial order entry and during hospitalization in situations when an opioid is added or the dose changed, EMR based alerts at the time of discharge within the CPOE environment represent another opportunity to do the appropriate risk assessments and to assess the patient for risk of ORAE. Thus, your QI team may choose the discharge as an additional point in the patient encounter to initiate risk assessment. Once again, opioid use would have to be a discrete field within the EMR for it to recognize the need to trigger the alert, and there would need to be a cross-reference to ensure the lack of an order to assess for ORAEs. Your IT department can provide guidance on the capabilities of your individual IT systems.

### 6.3.5 Intervention 5: Feedback of Performance to Providers

Feedback to providers regarding the progress in achieving your ORAE QI project outcomes can be an effective method to support the change process. Reports detailing results can be hospital, unit or provider specific. This will largely depend on the capabilities of data collection, the type of metric being reported and your hospital's culture. In addition, the results can be in real time or upon audit after discharge. To obtain real-time reports, your EMR would have to abstract patients at risk for ORAEs and report if an ORAE risk assessment was completed. In addition, the report could also outline if an opioid was started and if the ORAE assessment was started.

Real-time information is actionable and can improve your desired outcomes metrics. For example, a real-time report generated based on a particular physician's census would allow that physician to see a list of his or her patients at risk for ORAEs while in the hospital with corresponding completion or pending status of assessment of ORAE risk assessment. Real-time reports can also be generated per unit that would allow one to see the same information for the entire unit rather than only for one physician. Interdisciplinary rounds with members of the care team could incorporate a discussion on the assessment of risk for an ORAE and if safety policies and monitoring procedures are in place. A unit medical director or RADEO QI team member could also use the real-time report to encourage the completion of tasks to better adhere to your process and outcomes measures. The generation of this type of real-time data is more difficult for hospitals that are not EMR based but could be completed with chart reviews if focused on areas in the hospital where patients are likely to be receiving opioids, such as surgical floors. The process chosen and methods to extract such data would need to be individualized to the resources available at your particular institution.

Similarly, post-discharge data could be obtained looking at the same metrics. Thus, reports could be generated monthly or for any specified time range within your chosen measures. The results can then be conveyed to a particular unit and its leadership or individual physicians or physician groups. Transparency can further motivate groups or individual physicians to improve their results. Benchmarking the top performers can lead to a positive modeling effect for lower-performing providers. It is critical that your QI team determine the best approach in providing feedback based on your institution's norms and culture.

### 6.3.6 Intervention 6: Patient and Family Education

Ensuring patient compliance with the plan to reduce the patient's risk for ORAEs is critical for your QI project to succeed. Although the patient is administered the ordered doses of opioids in the hospital, the likelihood of patient compliance post-discharge is much greater if education is started while patients are in the hospital. In addition, focused education to patients at increased risk for ORAEs can be a motivator for patient involvement in their care. Patient education can take the form of pamphlets, educational handouts or even media-based education such as a closed-circuit television program in patient rooms.

To ensure that all patients receiving opioids have education regarding ORAE risk, a task requirement could be sent directly to an RN through the EMR-based on a physician order or could automatically be triggered within the EMR. Visibility of the tenets of your QI project on hospital floors and common areas where patients may ambulate will reinforce the other patient educational strategies that your QI team uses.

While a complete review of patient and family education in the inpatient setting is beyond the scope of this *Guide*, important principles include education throughout the hospital stay, involving family members and caregivers, using language at the fifth-grade level, proper use of qualified medical interpreters, using visual clues and using the teach-back method. The **project RED website** is an excellent resource on patient education in the inpatient setting.

### 6.3.7 Intervention 7: Organizational and Operational Change

As noted in Section II of this *Guide*, creating a shared need for your QI project with important constituencies in the hospital and obtaining institutional support from all hospital stakeholders will be critical to your QI group's success. Your team will need to procure resources and infrastructure to allow you to operationalize your project. In addition, you will need to develop new roles to support the functions necessary to reduce ORAEs. In hospitals that are paper-based, new administrative support personnel may be needed for concurrent monitoring to ensure compliance with newly implemented tools. For hospitals that are EMR-based, the RADEO teams will ensure that this project gets the necessary IT resources to ensure that the steps outlined in this *Guide* are developed and operating as planned. Frequent overview and fine-tuning of the processes developed by your team will be an ongoing task. Physician, nurse and pharmacy leaders currently dedicated to ensuring other QI metrics are met can potentially incorporate RADEO into their work flows.

### 6.3.8 Intervention 8: Monitoring the Effect of Your Interventions

Tracking and trending data over time will be important to monitor the progress of your RADEO project. Robust data collection strategies will be needed to track your performance over time. Strategies include electronic abstraction through the EMR or by random sample abstraction of paper charts. Your RADEO team may choose to track a variety of different outcomes, such as the percentage of patients who have risk assessment completed or the percentage of patients receiving the appropriate opioid drug and dose per the policies set forth by your team. The duration of data collection, especially if it is manual and labor intensive, will need to be determined by your work group, keeping in mind that processes that are not monitored will less likely become hard wired. Visual methodologies, such as graphs or run charts, may enhance your ability to understand and communicate your results. You will need to analyze any possible variation from your protocol to determine methods to improve your outcomes rates. In addition, you will need to develop a control phase of your project. The control phase ensures the solution is sustained and the process will not revert to the original state. It also shares the lessons learned across the organization if interventions are piloted in only one part of the organization. The key components of a control plan include a strategy for maintaining the improved process performance over time and definition of specific actions and tools required for sustaining the process improvement or gains.

## Step 7: Safe Transitions of Care for Patients on Opioids

The period following discharge from the hospital is a vulnerable time for patients because they have not fully recovered from the event that required them to seek medical attention and often continue needing acute care.

For patients who are discharged on low- or moderate-dose opioids and who are expected to be on those medications for a short period of time, providing clear instructions on how to use and eventually taper them off is sufficient; the risk of dependence and withdrawal is usually low. However, patients who have had a complicated hospital course may require opioids for a prolonged period of time.

The goals of the pain treatment plan following discharge include:

- effective pain relief to help facilitate the rehabilitation plan
- prevention of drug misuse, abuse and withdrawal
- minimization of medication side effects
- avoiding inadvertent overdose and reducing oversupply of medications that may potentially lead to harm

Medication complications after discharge are common; 19 percent to 23 percent of patients suffer an adverse event after discharge from the hospital, most commonly related to the inappropriate use of medication.[176]

Approaches to promoting effective transitions of care include the following:[177-179]

1. **Detailed communication** between the medical team managing the patient in the hospital and the provider responsible for management after discharge. Inform the patient and family which provider will be responsible for managing postoperative pain, and prescribing opioids and other analgesics.[180]
2. **Reconciliation** of all prescribed pain medications (opioids and other adjuvant analgesics) as well as other medications.
3. **Education** of patients and families about safe medication storage and disposal. Remind the patient of the dangers of prescription opioid diversion and the importance of secure storage of their medications. Sharing medications with others is never appropriate and is illegal. Instruct the patient and family on prompt disposal of controlled substances either through a DEA-approved take-back program or FDA guidelines for safe disposal of medications. Leftover medications can become a potential source of danger for children or any family members or others with a personal history of substance abuse who visit the home.[181] See **Section 6.3.6** for more information on patient and family education.
4. **Involvement of a family member** or other caregivers is important for patients who may not be able to safely dispense medications themselves. This will minimize the possibility of misuse and withdrawal.[180]
5. Proper counseling regarding the risk of using **alcohol and other CNS depressants** in combination with opioids.
6. **Medical follow-up** shortly after discharge and engagement of social support systems when necessary. A follow-up visit with the provider identified as the one prescribing opioids after discharge should be scheduled as soon as possible. The patient's medical condition and the need for continuing opioid therapy should be discussed at that time with patients and their families. Based on that initial assessment, a tapering-off plan could be discussed and eventually initiated.

7. **Avoid adding additional opioids or adjusting the dose of opioids and other CNS depressant medications without appropriate medical follow-up.** If pain becomes difficult to manage, consider investigating for the presence of possible new sources of pain (infection, surgical/trauma late complications, evidence of new pathology, etc.). Communication with the medical team who managed the patient in the hospital is crucial for appropriate guidance.[180]

8. **The provider responsible for managing the patient's pain and prescribing further pain medications must always be identified before discharge.** Ideally, the patient's primary care provider should be that provider. However, primary care providers may not feel prepared to manage patients who have been discharged on high doses of opioids and other medications, or who have had a prolonged postoperative pain. Identification of these patients early in their hospital stay and involvement of a pain specialist willing to manage the patient upon discharge will facilitate discharge for high-risk patients. The pain specialist may help the primary team and the patient by focusing on the goals of the treatment plan, reassuring the patient and family that the patient's needs will be adequately met and implementing a plan.

9. It is important to remember that for some **minor surgeries** it may be appropriate to discharge patients on acetaminophen or NSAIDs only or with only a very limited supply (e.g., two to three days) of short-acting opioids — even if the patients were taking opioids preoperatively.

10. Instruct the patient and family on the **planned tapering off** of postoperative opioids, including a timeline for return to preoperative or lower dosing for those on chronic opioids.

Patients on high dosages of opioids or on opioids for a prolonged period of time need a tapering-off plan. Tapering off would continue after discharge and should lead to the discontinuation of all the medications initiated while the patient was in the hospital. The tapering-off plan should proceed in parallel with the patient's recovery process.

For opioid-tolerant patients on pain medications prior to their admission to the hospital, clear instructions on how to use their medications and taper back to the baseline dose should be provided. Follow-up visits with their usual opioid prescriber to discuss a tapering-off plan are recommended.

Most patients, including those who have undergone major surgical procedures or are recovering from trauma, can taper off opioids. Follow through with the agreed-upon preoperative plan to taper off opioids added for surgery as surgical healing takes place. The goal is always the shortest duration and lowest effective dose.

Most patients with major surgeries should be able to be tapered to preoperative doses or lower within six weeks. The tapering goal is often approximately 20 percent of dose per week although tapering may be slower in the first seven to 10 days and then become more rapid as healing progresses.

Most patients do not need further management after they have fully recovered from the event that brought them to seek medical attention. If further pain management is necessary after any possible reason for residual or continuing pain has been excluded, a referral to a Pain Management Center will be the most appropriate next step.

# Section III: Conclusion

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As you can see from this *Guide,* RADEO will not necessarily be an easy task. There will be challenges, and some of the potential challenges have been discussed in this *Guide.* They include garnering broad support from all levels of the organization, creating an environment where your organization is ready to move forward with significant change, facing competing priorities, obtaining resources, overcoming barriers and wading through the evidence, which is not always completely clear cut. So, why should you take on this challenge? We offer the following Top 10 list of reasons, some of which we suspect will be compelling enough to move your institution to adopt RADEO:

10 – RADEO will help your frontline clinicians become more familiar with the tools of QI.

9 – RADEO will provide your facility with experience in multidisciplinary QI projects.

8 – RADEO will help you prepare for Joint Commission surveys.

7 – RADEO will help your institution gain more experience with continuous monitoring, teach you about alert and alarm fatigue, and show you how to make your alerts and alarms more meaningful.

6 – RADEO will help you learn how to leverage your EMR for better patient safety.

5 – RADEO will protect and enhance your institution's reputation.

4 – RADEO will help decrease the incidence of delirium in your facility.

3 – RADEO will be part of your hospital's approach to managing opioid-habituated patients.

2 – RADEO will decrease postoperative respiratory failure in your hospital.

1 – RADEO will save the lives of high-risk patients in your hospital.

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## Notes