VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

Veterans Health Administration
Department of Defense

Prepared by:

THE MANAGEMENT OF **POSTOPERATIVE PAIN**
Working Group

with support from:

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INTRODUCTION

Version 1.2

Postoperative Pain Management

Acute postoperative pain is a significant issue for surgical patients in the Veterans Health Administration (VHA) health care system, the Department of Defense (DoD) health care system, and in the nation at large. In 2000, more than 360,000, combined inpatient and outpatient, surgical procedures were performed in the VHA (VHA Patient Care Services, 2001), and approximately 475,000 procedures were done in the DoD system (TRICARE, 2001). Effective pain management is associated with patient satisfaction, earlier mobilization, shortened hospital stay, and reduced costs (AHCPR, 1992). Despite these benefits, there are substantial numbers of patients who suffer from postoperative pain. To address this problem, the Agency for Health Care Policy and Research (AHCPR) Acute Pain Management Clinical Practice Guideline (CPG) was released in 1992. The VHA added pain as a fifth vital sign as of October 2000 (VHA, 2000). Since then, therapeutic advances, outcome studies, and the publication of the Joint Commission on Accreditation of Healthcare Organizations' (JCAHO) Pain Management Standard for 2001 have refined the practice of pain management, (2001). It is therefore essential that the VHA and DoD develop a systematic approach to pain management that assures that pain is recognized and treated promptly and effectively. This guideline is part of a system-wide approach to pain management that is designed to reduce pain and suffering for patients experiencing acute and chronic pain.

Alleviation of pain and suffering, especially when it occurs as a consequence of treatment, is a priority for all health professionals. The subjective nature of the pain experience requires flexibility, compassion, and understanding on the part of the health care practitioner. This acute postoperative pain guideline was written from a specific procedural perspective and is intended as a tool to enhance the practitioner's clinical skills by presenting therapeutic options with supporting information. It does not dictate one approach, but provides principles and guidance to effective, safe, and timely pain management. As a web-based guideline, it can be used in a variety of ways—providing information on algorithms, assessment, special needs, interventions, and planning for pain management at the chosen level of detail. In addition, as improvements in pain management are realized, they can be rapidly disseminated.

Surgical procedures inevitably produce tissue trauma and release potent mediators of inflammation and pain (NHMRC, 1999). New treatment techniques and drugs, and the increased attention to pain management in general, have led to opportunities to improve the care of patients with pain. The VHA/DoD Guideline for the Management of Postoperative Pain is intended to improve the quality of care and facilitate the management of patients with postoperative pain. The guideline focuses on the assessment, diagnosis, treatment, management, and follow-up of these patients.

Goals of the Guideline

The VHA/DoD Clinical Practice Guideline for the Management of Postoperative Pain is intended to assist medical care providers in all aspects of care for patients with postoperative pain. The system-wide goal of using evidence-based guidelines is to improve the patient's outcome. In general, the expected outcome of successful implementation of this guideline is to improve the postoperative experience, and to reduce the morbidity that is associated with unmanaged pain. To achieve this goal, the guideline addresses the following critical points:

- Efficient and effective initial preoperative assessment.
- Developing a collaborative pain management plan with the patient.
- Providing appropriate education for the patient and family.
- Optimizing the use of therapeutic techniques to control pain .
- Reducing the incidence and severity of postoperative pain.
- Minimizing preventable postoperative complications and morbidity.

The current guideline represents a major step toward achieving this goal for patients in the VHA and DoD. However, as with other CPGs, challenges remain to develop effective strategies for guideline implementation and evaluation of the effect of guideline adherence on clinical outcomes.

This guideline is not intended as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advances and patterns evolve. The ultimate judgement regarding a particular clinical procedure or treatment course must be made by the individual clinician, in light of the patient's clinical presentation, patient preferences, and the available diagnostic and treatment options. The guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment, in the care for an individual patient.

For the Future

The inability of consumers and health care purchasers to determine if medical care is appropriate and effective has given rise to the concept that the health care system should be held accountable for what is done and what outcomes are achieved. The quality and cost of care are being scrutinized at every level of the health care system. CPGs have been introduced in many settings as one way to reduce variations in the delivery of care, thus improving the quality of the care. However, experience has demonstrated that it is difficult to affect clinicians' behavior through the use of practice guidelines. The VHA and DoD are developing a variety of tools for implementing the guidelines and a set of indicators to measure the impact of guidelines on the quality of the care.

Modifications to the guideline are anticipated as lessons are learned and new research and practice-based evidence become available. The developers believe that this guideline should always be considered "a work in progress."

KEY POINTS OF THE PAIN MANAGEMENT GUIDELINE

The experts concluded the guideline process by summarizing the key points:

- An effective pain program is based on an understanding of the scientific foundation of postoperative pain and pain management options.
- Preprocedural patient evaluation is necessary to provide safe and effective pain management.
- Medical or surgical stabilization must be provided prior to or in conjunction with effective pain management.
- Pain management requires systematic patient assessment postoperatively, at scheduled intervals, in response to new pain, and prior to discharge.
- The components of a good assessment will vary depending on the patient's situation, but should include both severity of pain and its impact on functioning.
- Education of the patient and those involved in patient care is a central component of effective pain management:
  - Pain management education should provide the patients with realistic expectations about pain, the postoperative and discharge treatment plan, and expected outcomes.
  - Pain management education decreases emotional distress, enhances coping skills, and enables the patient to participate in treatment.
- Postoperative pain management should be multimodal and individualized for the particular patient, operation, and circumstances. Understanding the range of available interventions and considering the type of surgery are essential to safe and effective pain management.
- Selection of a pain management option should be determined by balancing the advantages, disadvantages, contraindications, and patient preference. In most patients, more than one modality will be needed for successful pain management.
- Interventions for postoperative pain management include both pharmacologic (using the main classes of medication: opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics) and non-pharmacologic (cognitive and physical modalities).
- Evaluation of the balance between pain control and side effects should be routine, timely, and specific. The management plan should be modified, if indicated.
- The discharge plan should include a plan for continued pain management. It should be in place prior to discharge and be effectively communicated to the patient and their caregiver if appropriate.

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ALGORITHM AND ANNOTATIONS

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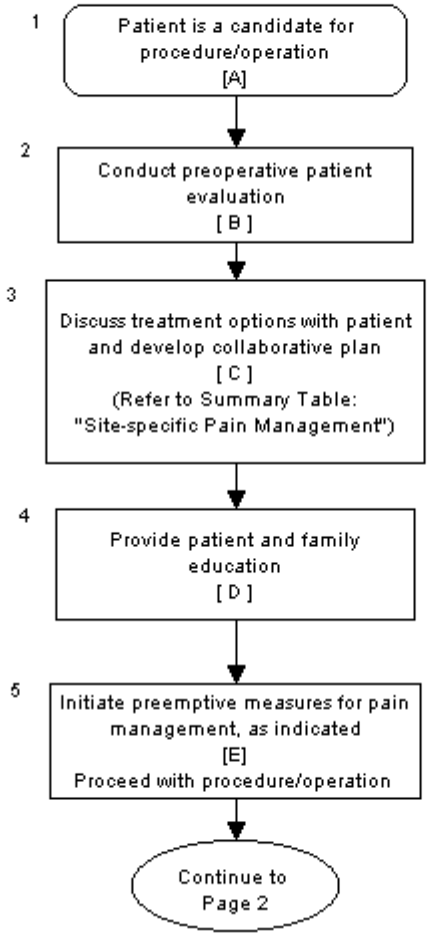
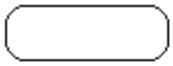
Preoperative Management

Page 1





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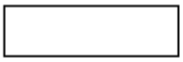

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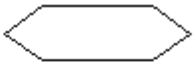

Hexagon
A decision point in the process
Answer Yes or No

Oval
A link to another section in the guideline

A letter within a box refers to the corresponding annotation.

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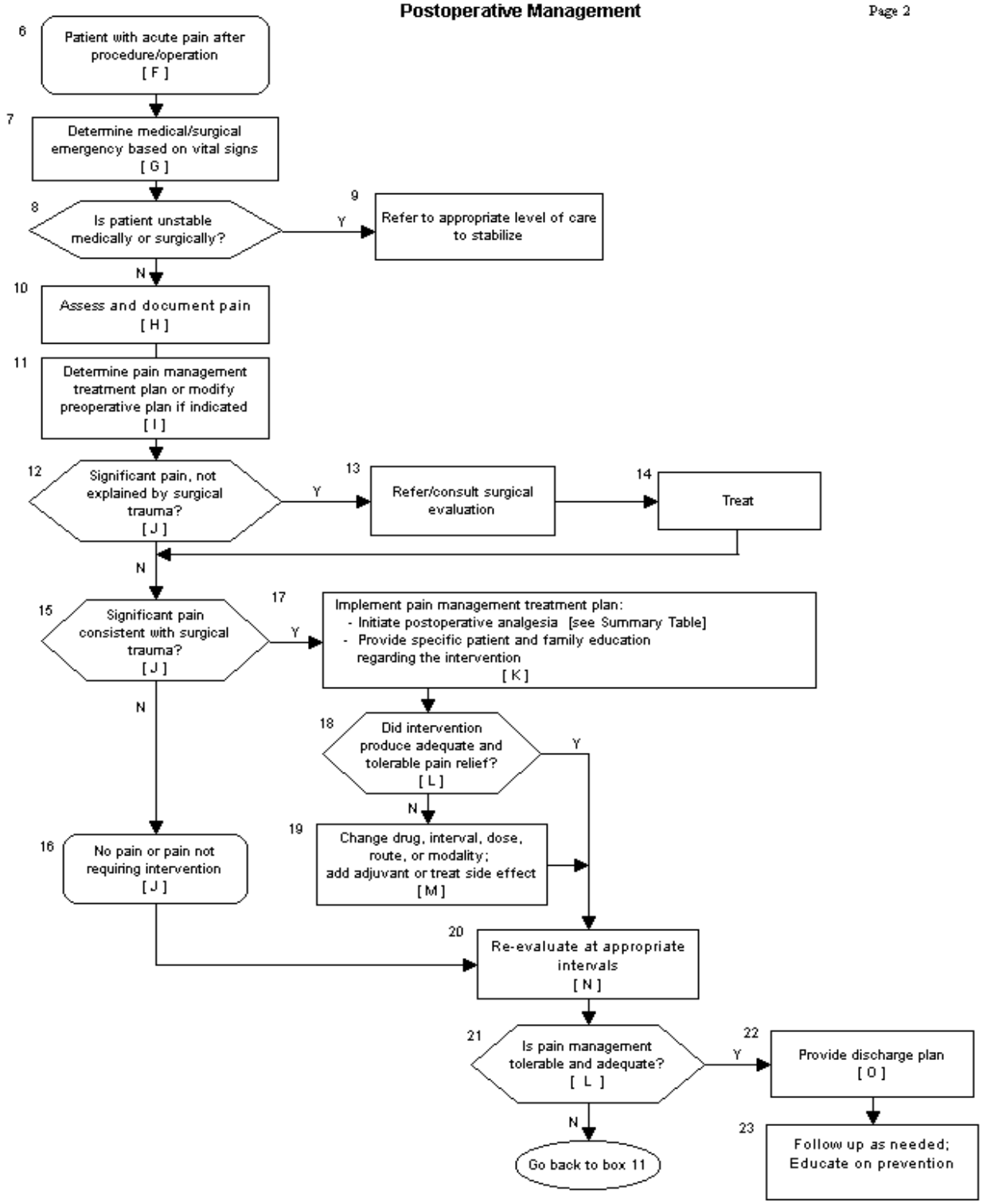


ANNOTATIONS

A. Patient is a Candidate for Procedure/Operation

Patients managed by this guideline are adults (age ≥ 17) within the VHA and DoD health care systems who are undergoing a procedure or operation and for whom pain management is warranted. In an emergency procedure, implementation is determined by the time available and patient status.

B. Conduct Preoperative Patient Evaluation

OBJECTIVE

Identify factors, both clinical and psychosocial, that may impact the postoperative pain management plan.

ANNOTATION

Most of the information needed to develop a postoperative pain control plan is contained in a routine history and physical examination. In order to provide effective pain control, the clinician should pay particular attention to the following specific questions:

Chief Complaint—What is the planned surgical procedure? What are the circumstances under which the procedure is being performed? Is the procedure elective or emergent? Does the patient have acute pain?

Past Medical History—What concurrent medical problems are present? Are there any known problems with coagulation? Are there congenital abnormalities? Are there concurrent neurologic diseases such as multiple sclerosis, muscular dystrophy, stroke, mental dysfunction, amyotropic lateral sclerosis or peripheral neuropathy, among others? Is there a history of prior trauma to the proposed surgical site? Is there a history of infection or respiratory difficulty?

Past Surgical History—Is there any history of surgery (e.g., spine surgery)?

Medications—What medications is the patient currently taking? Is the patient taking any anticoagulants that would alter choices for postoperative pain control? Is the patient taking opiates on a chronic basis? Is the patient taking any monoamine oxidase inhibitors (MAOIs) medications?

Allergies—Is the patient allergic to any of the opiates, local anesthetics, NSAIDs, agonist-antagonists, corticosteroids or any other medications commonly used to provide postoperative pain control?

Psychosocial History—Is there any history of drug or alcohol abuse or addiction?

Past Pain History—Does the patient have chronic pain? How is the chronic pain currently being treated? What postoperative pain control methods were used successfully or unsuccessfully? Did the patient develop side effects from the chosen method?

Physical Examination—Are there patient characteristics (i.e., physical or mental abnormalities) that preclude the use of certain postoperative pain control techniques? Will the surgical procedure involve the insertion areas for regional or neuraxial analgesia techniques? Are there signs of infection at the site of proposed needle insertion?

Imaging Studies—Are there physical anatomic abnormalities, either congenital or acquired, that involve the proposed site for a pain control technique?

Pain Assessment:
If the patient reports any pain, a pain assessment needs to be completed. This assessment may help in evaluation of postoperative pain. See the "Pain Assessment" section of this guideline for detailed information on pain assessment.

C. Discuss Treatment Options with Patient and Develop Collaborative Plan

OBJECTIVE

Establish a collaborative approach for pain management based on the patient's understanding about, and acceptance of, available treatment options.

ANNOTATION

- Review with the patient the available options for pain prevention and control including physical and cognitive non-pharmacologic interventions, as well as pharmacologic management (i.e., PO, IM, IV/PCA, regional, epidural, and spinal). Consider a *multimodal* approach.
- Answer the patient's questions and provide patient education material (see section "Education For Pain Management").
- Patient refusal is a contraindication to any treatment option.
- The treatment plan must be acceptable to the surgeon as well.

For a review of the options, refer to the Summary Table in the section "Site-Specific Pain Management."

D. Provide Patient and Family Education

OBJECTIVE

Prepare the patient for treatment interventions that promote postprocedural comfort.

ANNOTATION

One of the primary concerns of patients and their significant others is the pain and discomfort following surgery. Patients respond differently to pain depending on their prior experience, emotional state, and level of anxiety. Individualized preoperative education may favorably alter this experience by reducing anxiety and allaying preconceived fears (Voshall, 1980).

Information to be included in pain education preoperatively should address the following:

Expectations:

- Effect of pain management on healing and reducing complications after surgery
- Expectation of pain and individual nature of pain experience. Review the expected severity and duration for specific type of surgery. See Table ED-1: Patient Education Trajectory Table in the "Education for Pain Management" section.
- Expectation that pain can be controlled following surgery
- Goals for pain relief

Assessment:

- Ways of assisting in the measurement of pain
- What patients should report regarding pain and its treatment

Postoperative plan:

- Postoperative pain management plan (i.e., specific information about the interventions)
- Importance of patient involvement in the plan (e.g., controlling PCA)

Interventions:

- How quickly the pain intervention should work
- When to ask for pain medication
- Patient concerns about the intervention (e.g., side effects, addiction, and complications)
- Non-drug measures for pain relief (explain those applicable)
  - Relaxation
  - Physical modalities
  - Distraction
  - Hypnosis

DISCUSSION

Information should be presented to patients more than once, and in more than one way (e.g., pamphlets, videos, and discussion) in order to achieve the desired effect. The information provided in the "Education for Pain Management" section of this guideline is comprehensive. The clinician should apply the relevant sections to the individual patient's needs.

Opinions of respected authorities support the efficacy of preoperative education for pain control. One article (Owen et al., 1990) included a patient survey.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Individualized preoperative education may favorably alter the pain experience.	Voshall, 1980 Owen et al., 1990	III III	B A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

E. Initiate Preemptive Measures for Pain Management, as Indicated

OBJECTIVE

Initiate interventions prior to operation in order to prevent or enhance postoperative pain control.

ANNOTATION

Some procedures/interventions will be more beneficial if the patient had prior experience or training (e.g., hypnosis and relaxation technique) prior to the operation. For certain procedures, specific interventions need to be undertaken before the procedure (e.g., see amputation in the "Site-specific Pain Management" section). Detailed information on interventions can be found in the "Site-specific Pain Management" section and in the "Pharmacologic Management" sections of this guideline.

F. Patient with Acute Pain after Procedure/Operation

Patients managed by this algorithm are those who have undergone a procedure or operation with analgesia or anesthesia.

DISCUSSION

Understanding pain physiology and the mechanism by which treatment can prevent or control pain, may help the clinician in choosing the optimal therapy and providing appropriate care.

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Mersky & Bogduk, 1994). The three major 'types' of pain can be defined as nociceptive, non-nociceptive (neuropathic), and idiopathic.

Nociceptive Pain:
Starting with the site of actual tissue damage and ending with the perception of pain is an extremely complex series of events collectively known as nociception, which can be divided into four processes:

1. Transduction
2. Transmission
3. Modulation
4. Perception

Transduction refers to the process in which noxious stimuli are translated into electrical energy at sensory nerve endings and then transmitted to the spinal cord.

Transmission refers to propagation of the impulse through the sensory nervous system by primary afferent fibers (Meeker & Rothrock, 1999) which synapse in the dorsal horn of the spinal cord and second-order neurons in the lamina of the dorsal horn, ascending neurons projecting to brain stem, thalamus, and thalamocortical projections (Moser et al., 1997).

Modulation denotes the alteration of nociceptive information by endogenous mechanisms. This modulation may result in attenuation or amplification of the initial signal. Perhaps the most important is the dorsal horn of the spinal cord.

Perception reflects the effect of the nociceptive information on the existing psychological framework. Perception is the emotional and physical experience of pain. This experience can alter the way subsequent pain experiences are perceived.

The most effective postoperative pain management plan attempts to attack all four phases of nociception. For example, NSAIDs can decrease the tissue inflammatory response (transduction); neural blockade inhibits signals from reaching the CNS (transmission); opiates can enhance the central inhibitory input at the spinal cord (modulation); and thorough pre- and postoperative teaching can help prevent and manage anxiety (perception).

Nociceptive pain results from activation of the physiologic processes mentioned above in somatic or visceral structures. It often is related directly to the extent and location of tissue damage. Nociceptive somatic pain is often described as sharp, aching, throbbing, and/or pressure-like, whereas nociceptive visceral pain is poorly localized; cramping or gnawing if a hollow viscus is involved or aching and sharp if a capsule or mesentary tissue is involved. Most postoperative pain falls into this category.

Non-nociceptive Pain:
Non-nociceptive pain (neuropathic) results from abnormal function in the central or peripheral somatosensorysystem. This pain may occur when the normal physiologic process of nociception has been altered, producing different subjective and objective findings. Usually, the subjective presentation is of burning, stabbing, or lancinating (lightning bolt) pain.

Idiopathic Pain:
Idiopathic pain is pain that can not be explained with organic pathology.

G. Determine Medical/Surgical Emergency Based on Vital Signs

OBJECTIVE

Rapidly determine, in the immediate postoperative period, whether a medical and/or surgical emergency exists, and whether the patient is medically or surgically unstable.

ANNOTATION

The postoperative evaluation must begin with a determination of whether there is need for emergency action, including immediate life-saving measures and/or immediate referral to an intensive level of care. This assessment consists of two levels:

1. Immediate assessment of the patient's vital signs:
   - Temperature
   - Pulse
   - Blood pressure
   - Respiratory status
   - Initial assessment of pain

2. More thorough but expeditious assessment:
   This phase of the assessment focuses on problems that may occur in a postoperative patient. It is important to convey to the patient and/or significant others the rationale and steps to be taken in this phase of the assessment.
   - Respiratory
     - Airway obstruction (e.g., problems with positioning of an endotracheal tube, poor positioning of the neck by obstruction by the tongue, and hemorrhage in the neck following such procedures as thyroidectomy)
     - Laryngospasm
     - Bronchospasm
     - Hypoxemia, from a variety of causes – including sedation, intrapulmonary shunting, inadvertent administration of oxygen-poor inspired gases, pneumothorax, pulmonary edema, pulmonary embolism, pain causing decreased thoracic and/or diaphragmatic excursion, and failure of reversal of neuromuscular blocking agents. Pulse oximetry is critical to assessment for hypoxemia.
   - Circulatory
     - Hypotension from a variety of causes
     - Surgical bleeding/pneumothorax-including hypovolemia, cardiogenic shock, and septic shock. Prompt identification is essential to prevent hypoperfusion of vital organs.
     - Tachycardia
     - Hypertension—may be secondary to preexisting hypertension or may be related to the surgical procedure because of pain, hypercapnea (from hypoventilation), hypoxemia, or excessive intravascular fluid volume.
     - Dysrhythmias—predisposing factors include electrolyte imbalance (especially hypokalemia), hypoxia, dysphoria, hypercapnia, metabolic alkalosis and acidosis, and preexisting heart disease.
   - Neurologic:
     - Failure to regain consciousness is most commonly due to the continued effect of anesthesia agents, sedatives, and preoperative medications. However, the clinician must consider other causes, such as hypothermia, hypoglycemia, hyperglycemia, hypoxia, and cerebrovascular event. Agitation may be from pain, but may also be due to hypoxia, metabolic causes, or intracerebral events.
   - Pain:
     - Evaluate any new, acute unexpected reports of pain that are not related to the operation.

- Nausea and vomiting:
  - Nausea and vomiting are the most common postoperative complications, reported to occur in 90 percent of inpatient surgeries and 4 percent of outpatient surgeries. This problem is influenced by choice of anesthetic, antiemetic, and the type of surgery, and may lead to aspiration complications.

DISCUSSION

Rapidly assessing the patient's clinical status following a surgical procedure is of extreme importance in ensuring a successful outcome. There are guidelines, which have been developed by national organizations, that may be helpful in organizing the approach to this process. The American Society of Anesthesiologists has promulgated Standards for Postanesthesia Care, available on the Internet at http://www.asahq.org/ (ASA, 1994). The Association of Perianesthesia Nurses (ASPAN) developed protocols and standards for the responsibilities of postanesthesia care unit (PACU) nurses. These guidelines are also available on the Internet at www.aspan.org.

Studies of the relative frequency of occurrence of postoperative complications have shown the following for inpatient surgical patients (Hines, 1992).

- Nausea and vomiting—42%
- Airway problems—30%
- Cardiovascular complications—25%
- Central nervous system—3%

Respiratory Complications:
The major respiratory complications encountered in the PACU are airway obstruction, hypoxemia, hypercapnea, and aspiration. Rose defined these events as critical respiratory events (CREs). Out of 24,157 consecutive PACU admissions, the incidence of CREs in patients who had received general anesthesia was 1.3 (Rose, 1994). Factors which increased this risk included increased age, obesity, long or emergency operations, use of opioids, and choice of anesthesia agent. Patients with CREs were more likely to require ICU admission.

Circulatory Complications:
Over half of the patients who develop hypertension postoperatively have had preexisting hypertension and experience an increase secondary to discontinuation of their antihypertensive agent in the perioperative period (Gal & Cooperman, 1975). If hypertension occurs postoperatively, it usually does so within 30 minutes of the end of the procedure (Gal & Cooperman, 1975).

Pain:
Note the major impact that pain can have in causing or worsening postoperative complications. Studies have shown that up to 75 percent of postsurgical patients are undertreated for their pain (Frost, 1992). Of course, pain in the postoperative state may be difficult to evaluate. If the patient is not fully conscious and verbal, it may be manifested by more subtle signs, such as agitation, or hypoventilation secondary to splinting of the chest or abdomen.

H. Assess and Document Pain

OBJECTIVE

Evaluate and document postoperative pain as a guide to intervention.

ANNOTATION

In order to accomplish adequate pain control, it is necessary to assess pain on a regular schedule as well as following any new pain control intervention.

- Assess pain intensity using a 0 to 10 numeric rating scale
- Ask patient to describe the pain (quality, duration and onset)
- Determine pain location from patient's report
- Document intensity, quality and location
- As time permits and as indicated by patient's condition, perform a more comprehensive pain assessment including description of behavior and impact
- Assess adverse effects associated with inadequate or intolerable interventions (sedation, inadequate respiration, nausea, vomiting, pruritis, numbness and weakness)

DISCUSSION

The initial postoperative assessment of pain evaluates the effectiveness of the pain management that occurred intraoperatively and establishes a new baseline for continuing pain management. Systematic pain assessment should occur at regular intervals.

The important domains included in the assessment of pain are:

- Pain attributes (Intensity, onset, duration, location and description)
- Behavior manifestation of pain
- Impact of pain
- Current and past treatments for pain
- Patients' expectations for pain relief

The extent and nature of pain assessment will depend on several factors including time available, medical status of the patient, and whether the surgery is elective or emergent.

Detailed instructions, including examples of specific questions and assessment measures, are included in the "Pain Assessment" section.

I. Determine Pain Management Treatment Plan or Modify Preoperative Plan If Indicated

OBJECTIVE

Provide safe, effective, and timely pain control.

ANNOTATION

Pain management is a complicated, multimodal process. To obtain adequate pain control, a systematic comprehensive treatment plan should be established. The treatment plan should be collaborative in nature and approved by the patient. The plan should be developed and documented as early in the perioperative course as possible.

The documented plan should address the following:

- Education
- Choice of treatment options:
  - Pharmacologic (includes route and dose)
  - Cognitive intervention
  - Physical intervention
- Discharge plan

Information regarding the components of the plan is included in this guideline in several sections:

- Treatment Options—select the appropriate treatment using the Summary: "Site-specific Pain Management"
- Type of Surgery—discussion of the evidence-based recommendation for the specific type of surgery
- Patient Education—general education for the patient and those taking care of the patient
- Specific Pharmacologic and Non-Pharmacologic Therapy—specific information regarding route and dosage for the specific intervention

J. Significant Pain Not Explained by Surgical Trauma? Significant Pain Consistent with Surgical Trauma?

OBJECTIVE

Identify patients who may have a significant complication and need surgical re-evaluation.

ANNOTATION

After the initial pain assessment, and before initiating the postoperative treatment plan, the clinician needs to determine if the pain is consistent with the recent surgical trauma.

Questions the provider should consider include:

- Is the pain level that which would typically be expected after a particular operation? Pain experience is individualized and dependent on a number of factors (see the "Site-specific Pain Management" section for discussion of typical expected pain).
- Is the location of the pain appropriate for this operation?
- Are measures that are normally used to control pain after this operation failing to provide relief?

The clinician should have a low threshold for consultation/evaluation. If the answers indicate a potential significant complication or an atypical postoperative course, then consultation is warranted.

K. Implement Pain Management Treatment Plan: Initiate Postoperative Analgesia

Please refer to the Summary Table in the section "Site-specific Pain Management" and the "Options for Postoperative Pain Management" section.

L. Provide Specific Patient and Family Education Regarding the Intervention

OBJECTIVE

Provide the patient with education about treatment interventions that promote postprocedural comfort.

ANNOTATION

Information to be included in pain education postoperatively should address the following:

Expectations:

- Expectation that pain can be controlled following surgery
- Goals for pain relief

Assessment:

- Ways of assisting in the measurement of pain
- What patients should report regarding pain and its treatment

Postoperative plan:

- Postoperative pain management plan (i.e., specific information about the interventions)
- Importance of patient involvement in plan (e.g., controlling patient controlled analgesia)

Interventions:

- How quickly the pain intervention should work
- When to ask for pain medication
- Patient concerns about the intervention (e.g., side effects, addiction, complications)
- Non-drug measures for pain relief (explain those applicable)
  - Physical modalities
  - Cognitive modalities

One of the primary concerns patients have in the preoperative setting is postoperative pain and discomfort.

DISCUSSION

In the immediate postoperative period, uncontrolled pain is a major concern and focus that increases a patient's anxiety. Preoperative concerns about the outcome of the surgery may interfere with the patient's learning about postoperative care. It is therefore important to simply reinforce basic pain management principles to help the patient better cope with the pain during this period (Moore and Estey, 1999).

See the "Education for Pain Management" section for specifics on postoperative pain education material.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Reinforcing pain management principles helps the patient cope with postoperative pain.	Moore and Estey, 1999	III	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

M. Did the Intervention Produce Adequate and Tolerable Pain Relief?

OBJECTIVE

Determine whether the patient had an adequate response to interventions provided for pain relief.

ANNOTATION

Initial pain assessment should include the patient's goal for pain relief measured as an intensity score (e.g., 0-10 scale) and function (e.g., what pain rating would be acceptable or satisfactory to him or her, considering the activities required for recovery or for maintaining a satisfactory quality of life?). Efficacy of pain relief should focus on the location of pain for which the patient received analgesia. If pain is located at another site, a complete initial pain assessment should be completed for that different site.

Adequacy of pain relief is then measured by the following:

1. Met patient's goal for pain relief, which included current pain intensity (e.g., <4 on 0-10 scale) and function (activity).

2. Pain control at a level that allows the patient to perform the functional requirements necessary for recovery (activity)
3. Duration of pain relief (e.g., did analgesia last between doses)
4. Patient satisfaction with pain relief

Possible function (activity/quality of life) from which to select appropriate measure of postoperative functioning:

1. Interference with the ability to cough and deep breathe
2. Interference with the ability to ambulate
3. Interference with mood
4. Interference with sleep
5. Interference with activities of daily living
6. Interference with ability to work (include work inside and outside the home)
7. Interference with relations with other people (interactions)
8. Interference with enjoyment of life

DISCUSSION

The findings of several studies of different cultures have found that, on a 0–10 pain rating scale, pain ratings of 5 or more interfere significantly with daily functions (Cleeland, 1984; Cleeland et al., 1994; Serlin et al., 1995). Further research suggests that 4, rather than 5, is the point at which pain significantly interferes with function. The results of using the Brief Pain Inventory to assess 111 patients with pain and advanced cancer showed that, on a 0-10 scale, pain ratings of 4 or greater interfered markedly with activity, and interference with enjoyment increased markedly between scores of 6 and 7 (Tycross et al., 1996). This study and others, combined with clinical experience, has led many clinicians to the conclusion that a pain rating greater than 3 signals the need to revise the pain treatment plan with higher doses of analgesics or different medications and other interventions (Cleeland & Syrjala, 1992; Syrjala, 1993).

One practice implication of these studies is that, when patients and staff are determining the comfort/function goal, pain-rating goals greater than 3 should be avoided. Thus, pain ratings of 4 or more are not appropriate unless they are temporary or intermediary goals. In other words, for a patient with a pain rating of 10, achieving a pain rating of 5 within 8 hours might be a way to make progress toward a lower pain rating, such as a 3 within the next 24 hours. Achieving a pain rating of 5 may be appropriate for a brief procedure. However, patients who set ongoing goals greater than 3 need to be reminded that recovery or quality of life requires that they easily perform certain activities. Emphasize to the patient that satisfactory pain relief is a level of pain that is noticeable but not bothersome. Also, explain that a pain rating equal to or less than the goal should be maintained as much of the time as possible. Once again, be specific about the activities that accompany the pain rating goal. Ask the patient what pain rating would make it easy to sleep, eat, or perform other physical activities.

Not only does setting a comfort/function goal help the entire team, including the patient and significant others, know what the pain treatment plan should achieve, but it also helps the patient see how pain relief contributes to recovery or improves the quality of life. By setting pain relief goals that correspond to function, patients learn that pain relief helps them recover faster from surgery. The patient's comfort/function goal should be visible on all records where pain ratings are recorded, such as a bedside flow sheet. Whether the goal has been achieved or not should also be routinely included at change-of-shift report, perhaps as the fifth vital sign along with other vital signs (McCaffery, 1999).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Pain ratings of 4 or greater interfered markedly with activity.	Cleeland & Syrjala, 1992	B	II

QE = Quality of Evidence; R = Recommendation (See Appendix A)

N. Change Drug, Interval, Dose, Route, Modality; Add Adjuvant or Treat Side Effects

OBJECTIVE

Modify treatment to achieve effective pain control with minimal harm and side effects.

ANNOTATION

Adverse effects associated with inadequate and or intolerable interventions for pain management are provided in Table 1 and described below:

Increased Pain
Reports of increased pain require pain assessments to ensure that no untoward events have occurred (see "Pain Assessment" section). In addition, the assessment will direct the therapy and alternatives selected.

Nausea/Vomiting

- Evaluation of postoperative nausea is to ensure stable vital signs and adequate control of pain.
- Unfortunately, opioids stimulate nausea and may require treatment (Cohen et al., 1992; Wang, 1996; Gan et al., 1997; Wang et al., 1998; Chung et al., 1999) or alteration of pain therapy to allow the patient to be nausea free with pain control.
- Because of high incidence of nausea, prophylactic antiemetic therapy is often given (Chen et al., 1996; Pitkanen et al., 1997; Helmy, 1999; Gan et al., 1997).
- The choice of antinausea agent is driven by patient factors and prior antinausea therapy. For example, if a dopamine antagonist was given for nausea earlier, the addition of a serotonin antagonist may be more helpful than a second dopamine antagonist.

Lethargy/Sedation/Respiratory Depression

- Evaluation is paramount to treatment of sedation.
- Respiratory depression secondary to opiates is preceded by lethargy and sedation; treatment is the same for this side effect.
- After causes of sedation other than analgesics have been addressed, adjusting the selected pain therapy is required (Kenady et al., 1992; Eriksson-Mjoberg et al., 1997; Passchier et al., 1993).
- If significant overdose of analgesics is suspected, use of reversal agents is indicated (naloxone 0.4mg IM/IV). If respiratory depression persists, this dose may need to be repeated and other causes considered.
- If there is no medical emergency, small doses of naloxone (0.04-0.2 mg) are preferred.

Itching/Pruritis

- Once allergic reactions have been ruled out, treatment of pruritis in the presence of appropriate opioid therapy is with antihistamines and opioid antagonists (Cohen et al., 1992; Gan et al., 1997).
- With regional analgesia techniques, it may be possible to eliminate the opioid component.

Numbness/Weakness

- Numbness is not associated with analgesics other than local anesthetics and the cause should be sought.
- Numbness in the affected area in the presence of regional analgesia should be evaluated (possible subarachnoid hematoma, abscess) and the dose adjusted.
- Weakness can be seen with analgesics usually in conjunction with other signs of relative overdose.
- Weakness seen with regional techniques should be minimized to allow for ambulation with assistance if desired.

Myoclonus/Seizures

- Seizure-like activity in the postoperative setting should be evaluated and treated.

- Some opioids, meperidine in particular, are associated with seizures and myoclonus.
- While very high doses of local anesthetics can cause seizures, this is unlikely in the postoperative setting unless a large amount is actully given.

Hallucinations

- Hallucinations in the postoperative patient can be due to a variety of causes including change in surroundings, sleep deprivation and intraoperative medications (H2 blockers, anticholinergics, opiates).
- Evaluations of hallucinations are often decided by "trial and error" techniques.

Dysphoria

- Postoperative dysphoria is unsettling to the patient and family and difficult to evaluate. Sometimes reassurance can be all that is needed, but it may also require changing of pain management techniques.
- It is more common with mixed opioid agonists/antagonists and antidopaminergic medications.

Urinary Retention

- Urinary retention is a common side effect of pharmacologic pain management and is more common after neuraxial administration.

Hypotension

- Hypotension due to systemic analgesics is rare and is likely due to hypovolemia and loss of sympathetic drive with appropriate analgesia.
- Hypotension from neuraxial opioids alone is unlikely.
- Hypotension with regional analgesia techniques is common and treated by replenishing fluids and altering the local anesthetic dose.
- Short term therapy can be accomplished with vasopressors until the above can be addressed.

Table 1: Management of Adverse Effects of Therapies

SYMPTOM In order of frequency	Route					
	PO	IM/IV	PCA	REGIONAL	EPIDURAL/ SPINAL	OTHERS
Increased Pain	• Increase dose or potency. • Decrease interval. • Add adjuvant. • Change route or site.					
Nausea and Vomiting	• Evaluate (check vital signs). • Decrease dose. • Add anti nausea agent. • Change pain agent. • Change route.			• Evaluate (check vital signs). • Decrease opioid dose. • Add anti nausea agent. • Change pain agent. • Change route.		
Lethargy/ Sedation	• Evaluate to determine etiology. • Decrease dose/increase interval. • Stop medication. • Consider reversal agents (Narcan).					
Itching/ Pruritis	• Consider allergic reaction. • Decrease dose. • Consider antipruretic medication agent. • Change agent. • Change route.					

Table 1: Management of Adverse Effects of Therapies (continued)

SYMPTOM In order of frequency	Route					
	PO	IM/IV	PCA	REGIONAL	EPIDURAL/ SPINAL	OTHERS
Numbness/ Weakness	• Evaluate to determine etiology. • Decrease dose.			• Evaluate to determine etiology. • Decrease dose level. • Increase interval. • Adjust technique. • Change route.		Re-evaluate.
Hypotension	• Stop medication. • Evaluate (check vital signs). • Change position. • Check fluid status. • Change agent. • Change dose. • Change medication. • Change route.					
Urinary Retention	• Decrease dose. • Change agent. • Change route.					
Dysphoria	• Nonpharmacologic therapy/reassurance. • Add adjuvant. • Consider change of agent/route.					
Myoclonus	• Stop medication. • Evaluate to determine etiology. • Change agent. • Adjuvant.			• Stop infusion. • Re-evaluate.		Re-evaluate.
Hallucinations	• Stop medication. • Evaluate to determine etiology. • Change agent. • Add anti-psychotic.			• Evaluate to determine. etiology. • Decrease opioid. • Stop infusion. • Change route.		Stop agent. Re-evaluate.

O. Re-evaluate at Appropriate Intervals

OBJECTIVE

Evaluate pain as a guide to further intervention.

ANNOTATION

The timing for assessment of the efficacy of pain relief is dependent upon the situation. If the patient is in severe pain requiring upward titration of analgesics, pain assessment should be completed frequently (e.g., every 15 minutes). In general, pain should be assessed approximately 15-30 minutes after administering parenteral medication and 60 minutes after administering oral medication. During the initial 24-hour post-operative period, pain should be assessed at least every 2 to 4 hours. If pain is well controlled, the pain intensity should be assessed routinely with vital signs.

P. Provide Discharge Plan

OBJECTIVE

Promote continuity of pain management after discharge.

ANNOTATION

Provide the patient and family with a workable, effective and safe pain management program for use at home, foster continuity of pain management across the care continuum, and promote understanding of the treatment plan.

1. Discharge planning should begin at admission with an assessment of the home environment and support systems.
2. Pain management at home should be within the capability of the patient, significant others, and other home resources. Visiting nurses may serve as a valuable resource if a complex pain management plan is required.
3. The pain management plan should guide patients' expectations as to the likely time course of their pain and how to manage functionality and expected return to premorbid function.
4. A written pain management plan should be given to the patient. It should include:
   - Specific drugs to be taken
   - Dose and frequency of administration
   - Side effects management
   - Potential drug interactions
   - Methods to improve function while recovering
   - Precautions to follow when taking pain medication (e.g., activity limitations, dietary restrictions)
   - Contact person for pain problems and other postoperative concerns
   - Nonpharmacological methods
5. Potential use of over-the-counter medications and interactions with prescribed medication should be addressed.
6. Follow-up contact by day surgery staff regarding the procedure and pain management (for day surgery patients) should be scheduled.
7. Patients who will be discharged to a location other than home must have a comprehensive pain management plan in place and clearly communicated in the transfer orders.

DISCUSSION

Early discharge planning ensures continuity of care and pain management. It is important to assess the discharge environment to evaluate support for the pain management plan proposed for discharge and address the patient's ability to adhere to treatment procedures. It is desirable that, if possible, the effectiveness of a plan of care is evaluated before discharge.

It is important that discharge teaching include anticipated needs and problems, including possible use of over-the-counter medications for pain relief.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Assess the discharge environment to evaluate support for the pain management plan and address the patient's ability to adhere to treatment procedures.	Hughes et al., 2000 Jacobs, 2000	III III	B B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

PAIN ASSESSMENT

Version 1.2

PAIN ASSESSMENT

Assessment of pain should include the following domains:

A. Pain attributes
B. Behavioral manifestations of pain
C. Impact of pain
D. Current and past treatments for pain
E. Patients' expectations for pain relief

The assessment's comprehensiveness will depend upon:

- The timing of the assessment (e.g., immediately preoperative, immediately postoperative, routinely postoperative, several days following surgery).
- The amount of time available to perform the assessment (e.g., emergency versus elective surgery, routine postoperative pain versus pain identified as a persistent problem).
- Whether a new pain has developed.

It is desirable, during initial assessment, to inquire and record patients' descriptions of their pain, aggravating and alleviating factors, perceptions of the impact of pain, current and past treatment(s) for pain, and patients' ratings of acceptable pain relief. For routine pain screening, patients should be asked about the severity of their pain and its onset, duration, location and quality (description).

Time permitting, the assessment should be repeated at regularly planned intervals, when a new pain is reported and when any new interventions to control pain are initiated. It is not necessary, however, to ask about current and past treatments and patients' acceptable goals each time the pain is assessed. The use of standard methods on a routine basis is highly desirable, time permitting.

A. Pain Attributes

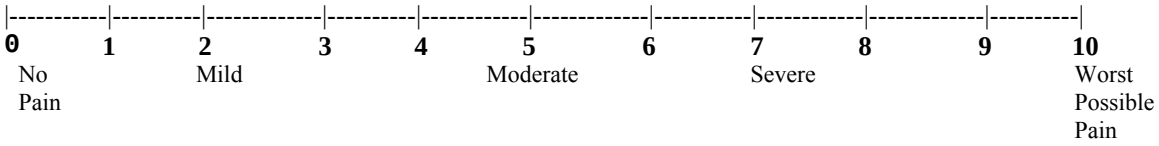
Pain Intensity

Assessment and documentation of pain scores in a systematic and consistent manner is an important mechanism for promoting identification of unrelieved pain at the individual patient care level. Availability of pain scores will provide an important index for monitoring improvement in the pain management.

Patients are asked to rate the intensity of their pain (e.g., current, worst, average) using the 0 to 10 Numeric Rating Scale (NRS) on which 0 equals no pain while 10 represents the worst possible pain (see Figure 1). The number reported by each patient is the pain score and should be documented in the medical record. The NRS may be used either verbally or visually.

When using the NRS for pain, the provider would ask, "On a scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is your current pain level?"

Figure 1. Numeric Rating Scale (NRS)



Self-report measures of pain intensity may not be appropriate for patients with problems communicating verbally (e.g., patients with strokes or coma). In these instances, the clinician should rely on behavioral observations (e.g., wincing, grimacing) and physiological indices (e.g., increase in respiratory rate or significant increases in heart rate or blood pressure).

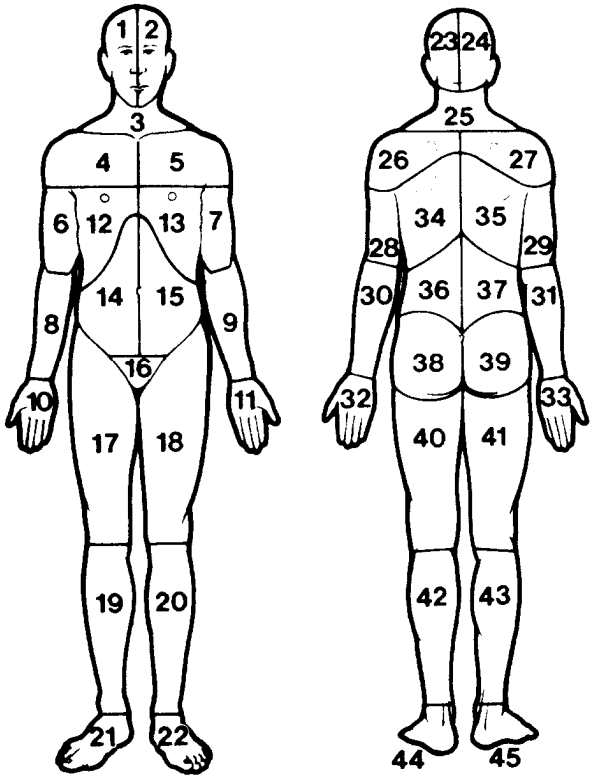
Onset and Duration of Pain

Onset and duration of pain should be determined by patient self-report or by someone who is familiar with the patient and his or her condition.

Pain Location

Pain location is important as it may provide useful information to help guide further assessment and treatment. Asking patients to indicate on their bodies where they feel pain can help to assess the distribution (location) of the pain. It is also useful to employ a standard pain drawing, consisting of a line drawing outline of the front and back of a human body (see Figure 2). Patients (or their significant others) should be asked to indicate the location of their pain on the drawing by marking or shading in the areas of the figure. Pain drawings may be more appropriate during the initial pain assessment, time permitting, when pain persists, or when a new pain develops, rather than on a routine basis.

Figure 2: Pain Drawing (Margolis et al., 1986)



A coding system based on a grid of regions has been established (Margolis et al., 1986). This system may be useful in detecting changes in multiple areas over time.

Pain Description

Patients should be asked to describe their pain. When time permits, the use of a standard form, such as the short form of the McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987), may be helpful as it provides patients with a list of frequently endorsed pain descriptors. The short form consists of 15 representative adjectival descriptors selected from the longer McGill Pain Questionnaire (Melzack, 1975). The descriptors were selected on the basis of their frequency of endorsements by patients with a variety of

acute, intermittent, and chronic pain syndromes (see Figure 3). Descriptors 1 to 11 represent the sensory dimension of pain and 12 to 15 represent the affective dimension.

Figure 3: McGill Pain Questionnaire – SF-MPQ (Melzack, 1987)

	Description	NONE	MILD	MODERATE	SEVERE
	Score	0	1	2	3
1	Throbbing				
2	Shooting				
3	Stabbing				
4	Sharp				
5	Cramping				
6	Gnawing				
7	Hot/Burning				
8	Aching				
9	Heavy				
10	Tender				
11	Splitting				
12	Tiring-Exhausting				
13	Sickening				
14	Fearful				
15	Punishing-Cruel				

Scoring:

- Each item should be scored: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
- Mean score of "sensory pain"=sum of scores for items 1 to 11, divided by 11.
- Mean score for "affective pain"=sum of scores for items 12 to 15, divided by 4.
- Mean overall pain score obtained by the sum of scores for all 15 items, divided by 15.

The MPQ may not be appropriate for use with all patients (e.g., patients unable to communicate). Someone who is familiar with the patient or the operative procedure may be used as a proxy, but with caution, as the subjective nature of pain makes it difficult for anyone to describe someone else's pain.

Factors that Alleviate/Exacerbate Pain

Patients (or significant others) should be asked to list factors that alleviate their pain ("What kinds of things make your pain feel better, e.g., heat, medicine,or rest?") and what factors exacerbate their pain (What kinds of things make your pain worse, e.g., coughing, walking, or sitting?"). Checklists are available to assist patients and may be used, time permitting.

B. Behavioral Manifestations of Pain

The healthcare professional should not only ask for patients' self-reports but also observe their behaviors for an indication of the severity of the pain and pain impact. The general areas to observe include the following:

- Facial/audible expression of distress (e.g., grimaces, moans, or crying)
- Ambulation and posture (e.g., movement in a protective or guarded fashion; limping, and frequent shifting of position; frequent stops when ambulating; and lying in fetal position)
- Avoidance of activities (e.g., frequent lying down), avoidance of specific movements and other behaviors believed to indicate pain, distress, or suffering (e.g., wringing hands, using a cane or wearing a cervical collar)

The nature, number, and frequency of these behaviors should be recorded when possible.

C. Impact of Pain

The 0 to 10 NRS can be used to assess the impact of the pain with the appropriate anchors (0=Does not interfere; 10=Completely interferes). Patients (or significant others) can be asked to rate how much pain affects or interferes with their general activity, sleep, ability to walk, interactions with other people, and personal care (e.g., washing and dressing).

The 0 to 10 NRS can also be adapted to assess the patients' moods. The two most important areas are anxiety and depression and may be assessed by using the appropriate anchor terms: 0=Extremely worried/anxious/upset; 10=Not at all worried/anxious/upset; 0=Extremely depressed; 10=Not at all depressed. There are a number of other measures available to assess patients' moods (Bradley & McKendree, 2000).

D. Current and Past Treatments for Pain

Patients (or significant others if a patient is unable to communicate) should be asked what pain management methods (e.g., pharmacological or non-pharamcological) have been used to treat their current and past pain and how effective these were for each pain event, using the 0 to 10 NRS.

E. Patients' Expectations for Pain Relief

When possible, the patient's (and or significant other's) goal for, or acceptability of, pain control should be rated using the 0 to 10 NRS defining the anchors as: 0=Absolutely no pain; and 10=Worst pain I can imagine.

Satisfaction with pain control should be assessed by asking patients (or significant others) to rate their satisfaction with their current and past pain control. The 0 to 10 NRS can be used to assess patient satisfaction, defining the anchors as: 0=Completely unsatisfied; and 10=Completely satisfied.

DISCUSSION

For pain evaluation, the patient should be asked about A through C and E above and observed for any pain-related behaviors (B above). Many clinicians and investigators have recommended the use of visual analog scales (VAS) to assess pain intensity. Several studies have reported that patients (especially older patients) have difficulty understanding the appropriate use of these scales (Jensen et al., 1986; Jensen et al., 1989; Jensen et al., 1992). The advantage of the VAS scale is the almost infinite number of intensity ratings. Such a large range will permit identification of very small changes. This may be important for research; however, it is not essential in the clinical situation. In addition to the difficulty patients have in using the VAS, it is cumbersome for clinical use as it requires someone to measure the very small units using a ruler. There are several devices available that can be used to assist the evaluator in measuring VAS scores; however, there does not seem to be sufficient need to use VAS in the clinical context. The numeric rating scale is easy to administer and to score, demonstrates high compliance rates, and has been shown to have good consistency over time (test-retest reliability).

Self-report measures of pain intensity may not be appropriate for patients with problems communicating verbally (e.g., patients with strokes or coma). Other methods are available to assess pain in these patients (Hadjistavropoulos et al., 2000).

The presence of pain affects multiple areas of patients' functioning and is not always directly correlated with pain intensity. It is important to assess not only pain description and ratings of pain intensity, but also patients' perceptions of how pain affects important areas of physical functioning, including the ability to engage in routine daily activities, sleep, interactions with others, and mood (Turk & Okifuji, 1999).

There are a number of measures designed to assess the impact of pain on functional activities; however, many of these are specific to the location of the pain (e.g., back pain). Some general measures also exist, most notably the SF-36 (Ware & Sherbourne, 1992). However, these measures tend to be quite long and may place too heavy a burden on patients in the preoperative setting. Brief measures of functional activities have been shown to be useful and proxy measures for more extensive and more specific activity measures (Daut & Cleeland, 1982).

Although there are a large number of extensive self-reports and interviews designed to assess the role of emotional factors and the present mood state of patients (Bradley & McKendree-Smith 2000 in press), such extensive measures may not be appropriate as an initial assessment. Self-report on a relatively few items assessing mood have been shown to be highly correlated with more extensive questionnaires (Daut & Cleeland, 1982; Kerns et al., 1985). These relatively brief measures of patient mood have been shown to have good reliability (i.e., internal consistency, stability), validity, and sensitivity to change.

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

SITE-SPECIFIC PAIN MANAGEMENT

Version 1.2

Summary Table: Site-specific Pain Management Interventions

	Pharmacologic Therapy (Route)							Non-Pharmacologic		
Type of surgery by body region	**PO**	**IM**	**IV**	**Epidural**	**Intrathecal**	**IV PCA**	**Regional**	**Physical**	**Cognitive**	**Comments**
1. Head and neck										
Ophthalmic	***OP***, ***NS***	OP, NS	OP, NS	--	--	RARELY	**LA**	C	X	If there is risk of or actual bleeding, avoid NS*
Craniotomy	OP, NS	***OP***, ***NS***	***OP***, ***NS***	--	--	OP	LA			If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Radical neck	OP, NS	OP, NS	OP, NS	--	--	***OP***	LA		X	
Oral-maxillofacial	***OP***, ***NS***, CS	OP, NS, CS	OP, NS, CS	--	--	OP	LA	**C, I**	X	
2. Thorax-noncardiac										
Thoracotomy	OP, NS	OP, NS	OP, NS	**OP, LA**	OP, LA	OP	**LA**	C, **T**	X	If there is riskof or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Mastectomy	OP, NS	OP, NS	***OP***, ***NS***	OP, LA	OP, LA	***OP***	LA	C, T	X	
Thoracoscopy	OP, NS	OP, NS	***OP***, ***NS***	OP, LA	OP, LA	OP	LA	C, T	X	
3. Thorax-Cardiac										
CABG	OP, NS	OP, NS	**OP, NS**	RARELY	OP	OP	RARELY			If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
MID-CAB	OP, NS	OP, NS	***OP***, ***NS***	RARELY	OP	OP	LA		X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
4. Upper abdomen										
Laparotomy	OP, NS	OP, NS	OP, NS	**OP, LA**	OP, LA	***OP***	LA	***E***, **T**	X	Opioids may impair bowel function If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Laparoscopic cholecystectomy	***OP***, ***NS***	***OP***, ***NS***	***OP***, ***NS***	RARELY	RARELY	OP	LA	***E***, ***T***	X	Opioids may cause biliary spasm
Nephrectomy	OP, NS	OP, NS	OP, NS	**OP** *LA*	OP, LA	OP	LA	***E***, T	X	
5. Lower abdomen/pelvis										
Hysterectomy	OP, NS	OP, NS	OP, NS	OP, LA	OP, LA	***OP***	LA	***E***,	X	Opioids may impair bowel function
Radical prostatectomy	OP, NS	OP, NS	OP, NS	**OP, LA**	OP, LA	OP	--	**E**	X	Opioids may impair bowel function If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Hernia	***OP***, ***NS***	OP, NS	OP, NS	RARELY	OP	RARELY	**LA**	C,	X	
7. Back/Spinal										
Laminectomy	OP, NS	OP, NS	***OP***, ***NS***	RARELY	RARELY	OP	--	C, **E**	X	
Spinal fusion	OP	OP	***OP***	RARELY	RARELY	***OP***	--	**E I**	X	Use of NS may be associated with nonunion
6. Extremities										
Vascular	OP, NS	OP, NS	OP, NS	**OP, LA**	OP, LA	OP	LA	***C***, **E**	X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Total hip replacement	OP, NS	OP, NS	***OP***, ***NS***	**OP, LA**	OP, LA	OP	LA	**C, E,** **T**	X	Use of NS is controversial
Total knee replacement	OP, NS	OP, NS	OP, NS	***OP***, ***LA***	OP, LA	OP	**LA**	**C, E,** **T**	X	Use of NS is controversial
Knee arthroscopy / Arthroscopic joint repair	OP, NS	OP, NS	OP, NS	RARELY	OP	OP	***LA***	**C, E,** **T**	X	
Amputation	OP, NS	OP, NS	OP, NS	***OP***, ***LA***	***OP, LA***	OP	***LA***	C, **E,** T	X	
Shoulder	OP, NS	OP, NS	OP, NS	--	--	OP	***LA***	**C, E, I, T**	X	

OP = Opioids; **NS** = NSAIDs; **CS** = Corticosteroid; **LA** = Local Anesthetics; **C** = Cold; **E** = Exercise; **I** = Immobilization; **T** = TENS; **X** = Use of cognitive therapy is patient-dependent rather than procedure-dependent

Indications for Use: **Bold/Red/Shaded**: Preferred based on evidence (QE=1; R=A); ***Italicized/Blue:*** Common usage based on consensus (QE=III); Plain Text: Possible Use; * = Bleeding is not contraindication for COX-2

How to Use this Table

1. Select operation from column 1, "Type of surgery by body region". If your operation is not exactly listed pick one that is close to it. For example, for a patient having a colon operation the appropriate choice would be "laparotomy".

2. Examine options on horizontal axis.
   Factors to consider:
   - Evidence rating—i.e., is it the best available?
   - Patient factors
     - patient motivation or desire
     - medical conditions (example: anticoagulation)
   - Institutional factors
     - Who will implement choice?
     - Is specialized equipment available?
     - Are the appropriate practitioners available (Example: Is physical therapy available for placement of TENS)

3. Additional considerations and suggestions can be found under the pharmacologic, non-pharmacologic and intervention sections.

HEAD AND NECK SURGERY

Type of Pain:
Operations involving the head and neck region are varied and result in both nociceptive and neuropathic pain (Sharf et al., 1977).

Severity/Duration:
Although the severity range for pain following head and neck surgery extends from mild to severe, most patients have mild to moderate pain of several days' duration (Bost et al., 1999; Mom et al.,1996; Cannon, 1990).

Interventions:
Oral agents are commonly used with or without adjuvant agents. Intraspinal medications are rarely indicated. Some larger procedures may preclude use of tablets or capsules.

Considerations:

- Pain relief regimens following neurosurgical procedures must not interfere with the ability to monitor neurologic status (MacKersie, 1993).
- Oropharyngeal and neck operations can interfere with swallowing and may preclude the use of oral agents.
- Operations involving the oropharynx and the neck may cause severe life-threatening airway compromise. As a result, postoperative analgesic techniques must be carefully selected to minimize the risk.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Pain relief regimens following neurosurgical procedures must not interfere with the ability to monitor neurologic status.	MacKersie, 1993	III-3	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HEAD AND NECK SURGERY

Ophthalmic Surgery

Type of Pain:
A wide variety of eye operations involve little nociceptive pain. The notable exceptions are enucleation and retinal surgeries, which produce pain that is both nociceptive and neuropathic (Fezza et al., 1999).

Severity/Duration:
Pain following ophthalmic surgery is mild to severe in intensity and lasts several days. Phantom eye pain of mild to severe intensity may develop following enucleation and last for months to years (Nicolodi et al., 1997).

Interventions:
Oral pain medications are a commonly used technique. Regional anesthetics used during surgery provide better analgesia in the immediate postoperative period (Calenda et al., 1999; Lai et al., 1999; Williams et al., 1995; Shende et al., 2000). Retinal operations or enucleations may be more painful and require more analgesia**.**

Considerations:
Nausea and vomiting following surgery may be detrimental to the surgical repair. Therefore, non-opiate pain medications postoperatively or regional anesthesia intraoperatively are preferred for mild to moderate pain (Williams et al., 1995; Shende et al., 2000).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Regional anesthetics used during surgery provide better analgesia in the immediate post-operative period.	Calenda et al., 1999 Lai et al., 1999 Williams et al., 1995 Shende et al., 2000	II-2 II-2 II-2 I	A B B A
2	Nausea and vomiting may be detrimental to surgical repair. Therefore, non-opiate pain medications postoperatively or regional anesthesia intraoperatively are preferred.	Williams et al., 1995 Shende et al., 2000	II-2 I	B A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HEAD AND NECK SURGERY

Craniotomies

Type of Pain:
Craniotomies are generally thought to be less painful than other operations (Atkinson et al., 1993; Conway, 1984; Dunbar et al., 1999; Bonica, 1990) except for frontal craniotomies (Dunbar & Lam, 1999). However, both of these assumptions have recently been challenged (DeBenedittis et al., 1996; Quiney & Cooper., 1996) and supported (Dunbar & Lam, 1999). Suffice it to say that, while craniotomy pain may be less severe than other operations, there is a growing consensus that it remains undertreated in the acute recovery phase for at least a minority of patients (Dunbar & Lam, 1999; Quiney et al., 1996; DeBenedittis et al., 1996; Stoneham & Walters, 1995). The pain that results is typically nociceptive in nature, and is secondary to the surgical incision and reflection of the muscle underlying the scalp (Quiney et al., 1996; DeBenedittis et al., 1996), but not of the brain tissue itself (Bonica, 1990; DeBenedittis et al., 1996).

Severity/Duration:
Craniotomy pain is mild to severe and decreases rapidly after the first 24 hours (DeBenedittis et al., 1996).

Interventions:
Postoperative pain control recommendations have been very conservative (Mackersie, 1993), with intramuscular codeine phosphate used as the most common postoperative analgesic (Stoneham & Walters, 1995). This approach has generally been accepted because of concerns about respiratory depression and altered mental status in postoperative craniotomy patients (Mackersie, 1993). Codeine may be the preferred narcotic analgesic because of its lesser effects on brain/blood flow. It has been shown to be superior to tramadol as a post-operative analgesic and not significantly different from IV PCA morphine (Stoneham et al., 1996). NSAIDs may be contraindicated in some settings due to concerns regarding intracranial bleeding (Palmer et al., 1994). Incisional bupivicaine is helpful in the immediate postoperative phase to achieve pain control (Bloomfield et al., 1998).

Considerations:
Analgesia needs to be balanced with the requirement for appropriate neurologic monitoring.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	While pain may be less severe than other operations, there is a growing consensus that it remains undertreated.	Dunbar & Lam, 1999 Quiney et al., 1996 DeBenedittis et al., 1996 Stoneham & Walters, 1995	II-3 II-2 II-2 I	B B B A
2	Post-operative pain control recommendations have been very conservative, with intramuscular codeine phosphate used as the most common postoperative analgesic.	MacKersie, 1993 Stoneham & Walters, 1995	III I	C A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

	Intervention	Sources of Evidence	QE	R
3	Codeine has been shown to be superior to tramadol as a postoperative analgesic and not significantly different from IV PCA morphine.	Stoneham & Walters, 1995	I	A
4	NASIDs may be contraindicated in some settings due to concerns regarding intracranial bleeding.	Palmer et al., 1994	II-2	A
5	Incisional bupivicaine is helpful in the immediate postoperative phase to achieve pain control.	Bloomfield et al., 1998	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HEAD AND NECK SURGERY

Radical Neck Surgery

Type of Pain:
Radical neck surgery may produce both nociceptive and neuropathic pain (Sharf et al., 1997).

Severity/Duration:
Pain from radical neck surgery is moderate to severe in intensity lasting days to years (Bost et al., 1999; Mom et al., 1996; Cannon, 1990; Chaplin & Morton, 1999; Sist et al., 1999).

Interventions:
Pain from radical neck surgery is typically controlled with IM, IV, or IV PCA opiates due to frequent limitations in oral intake (Bost et al., 1999; Mom et al., 1996). Intraspinal medications are almost never used for postoperative pain control in this setting (Tobias et al., 1990).

Considerations:
The choice of analgesia must consider the potential for airway compromise in patients without tracheostomy.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Pain from radical neck surgery is typically controlled with IM, IV, or IV PCA opiates due to frequent limitations in oral intake.	Bost et al., 1999 Mom et al., 1996	II-2 II-3	B A
2	Intraspinal medications are almost never used for postoperative pain control in this setting.	Tobias et al., 1990	III	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HEAD AND NECK SURGERY

Oral-Maxillofacial

Type of Pain:
Oral and maxillofacial procedures include a wide range of operations that result in both nociceptive and neuropathic pain.

Severity/Duration:
Pain from oral and maxillofacial procedures ranges from mild to severe. Outpatient procedures are associated with pain of short duration (1-3 days).

Interventions:

- Regional anesthesia is commonly provided intraoperatively by the surgeons to reduce both intraprocedural and early postprocedural pain (Robiony et al., 1999; Nicodemus et al., 1991). Oral opiates and nonsteroidal analgesia usually follow this. If the oral route is not available, effective pain control can be obtained using IM or IV opiate pain medications or IV or IM nonsteroidals.
- Extensive maxillofacial procedures, such as LE FORTE I maxillary osteotomies, may result in severe postoperative pain requiring IV or IM narcotics. In the setting of Internal Mandibular (IM) Fixation, opiates may be used in elixir form.

Considerations:

- Oral route may be unavailable.
- Potential airway compromise.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Regional anesthesia is commonly provided intraoperatively by the surgeons to reduce both intraprocedural and early postprocedural pain.	Robiony et al., 1999 Nicodemus et al., 1991	II-3 I	B A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

THORAX (NON-CARDIAC) SURGERY

Operative sites within the thorax include the heart, esophagus, and lungs, and somatically innervated structures such as the ribs, superficial chest wall, and breast. Procedures include thoracotomy, transhiatal esophagectomy, pneumonectomy, thoracoscopy and mastectomy.

Type of Pain:
Thoracic (non-cardiac) surgery produces nociceptive and neuropathic pain.

Severity/Duration:
Thoracic (non-cardiac) surgery produces pain that is moderate to severe in intensity lasting days to weeks. Patients may develop chronic post-thoracotomy or post-mastectomy pain syndromes lasting months to years (Katz et al., 1996).

Interventions:
There are a wide variety of analgesic techniques that have been used to provide pain control following surgical procedures involving the chest. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Paravertebral nerve blocks
- Intercostal nerve blocks
- Oral, intravenous, intramuscular, and IV PCA opioids
- Transcutaneous Electrical Nerve Stimulation (TENS)
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics

Considerations:

- Preexisting disease of thoracic organs (e.g., chronic obstructive pulmonary disease) or prior medical treatment (e.g., chemotherapy) is common. The presence of significant preoperative medical disease may contribute to postoperative morbidity through a variety of mechanisms, such as decreased pulmonary reserve or malnutrition.
- Assessing the optimal time for switching the care of patients with epidural catheters to oral analgesics is best accomplished by a specially trained team.
- Transition from intravenous PCA to oral opiates should be accomplished when the patient's bowel function recovers. If adequate opioid analgesia yields undesired side effects or the pain is not severe (e.g., when chest tubes are no longer in place), the patient can switch directly from epidural analgesia to oral analgesics using either opioids alone or a combination of opioid and acetaminophen or an NSAID.

THORAX (NON-CARDIAC) SURGERY

Thoracotomy

Type of Pain:
Thoracotomy produces nociceptive and neuropathic pain that is aggravated by respiration and coughing. Pain may be further exacerbated by the presence of chest tubes and drains.

Severity/Duration:
Thoracotomy pain is generally moderate to severe, lasting weeks. Patients may develop post-thoracotomy pain syndromes lasting months to years.

Interventions:

- There is good evidence that aggressive pain control in the form of epidural analgesia or neural blockade with local anesthesia following thoracic surgery improves pulmonary function, reduces morbidity, and reduces the length of stay in intensive care.

- Effective postoperative pain control may be achieved by delivering an opioid or a combination of an opioid and local anesthetic into the thoracic epidural space (Mahon et al., 1999; Miguel & Hubbell, 1993; Brichon et al., 1994). Mixing a local anesthetic with an opioid produces better and more prolonged analgesia, but randomized controlled trials indicate that there is a tendency toward more side effects when an opioid is added to a local anesthetic as compared to local anesthetic alone (Mahon et al., 1999). The addition of local anesthetics to epidural opioids allows a significant reduction in the total opioid required to produce equivalent analgesia (Burgess et al., 1994). However, reliance on local anesthetics alone to secure postoperative epidural analgesia in the thoracic region may be associated with hypotension due to sympathetic blockade. Epidural opioids may be delivered via either a lumbar or thoracic approach (Gaeta et al., 1995). Lumbar epidural opioids have been used successfully to provide analgesia but are less effective than thoracic administration. An example of a coordinated approach to postoperative analgesia following thoracic surgery is the placement of an epidural catheter prior to induction of anesthesia. This catheter may be used to deliver local anesthetic, either alone or mixed with an opioid for intraoperative analgesia. The catheter may then be left in place postoperatively for infusion of an analgesic solution containing either a local anesthetic, an opioid, or a combination of the two, delivered either as a continuous infusion or patient-controlled epidural analgesia. The patient is then switched to patient-controlled analgesia or oral analgesics if the epidural catheter ceases to function or is discontinued after several days.

- There is no significant difference between lumbar and thoracic epidural administration of the highly lipid-soluble opioids, fentanyl and sufentanil (Haak-van der Lely et al., 1994; Swenson et al., 1994). In addition, there is no significant difference between epidural and intravenous administration of these highly lipid-soluble opioids (Baxter et al., 1994; Sandler et al., 1992; Guinard et al., 1992).

- Preoperative initiation of a continuous local anesthetic epidural block has been associated with reduced long-term (at 6 months) post-thoracotomy pain (Obata et al., 1999).

- Paravertebral blocks performed as single shot or continuous techniques are also useful in providing postoperative analgesia following thoracic surgical procedures (Carabine et al., 1995). Continuous paravertebral blocks provide superior postoperative analgesia when compared to single shot techniques (Catala et al., 1996). Continuous paravertebral blocks are capable of providing equivalent or superior pain control when compared to epidural analgesia following thoracotomy (Richardson et al., 1999). Continuous paravertebral blocks are superior to interpleural blocks following thoracotomy (Richardson et al., 1995).

- Direct injection of a local anesthetic alone to block intercostal nerves has been performed as a means to provide postoperative analgesia and improve pulmonary function after thoracotomy. Since the analgesia from these blocks lasts only 6-12 hours, a single injection rarely suffices for the entire postoperative period. More prolonged relief can be obtained by performing cryoanalgesic blocks of the intercostal nerves (Bucerius et al., 2000). This may provide pain relief for several weeks. The brief duration of intercostal nerve blocks has been treated in some centers by administering interpleural local anesthetics. A catheter is placed between the parietal and visceral pleura, and a local anesthetic is injected at 4-6 hour intervals or infused continuously to produce continuous analgesia across several dermatomes (Barron et al., 1999; Raffin et al., 1994). Clinical use of this technique has not found widespread acceptance and it has been out of favor for many years (Gaeta et al., 1995; Solomon et al., 1980).

- Intrathecal administration of opioids has been used successfully to provide postoperative analgesia following thoracic surgical procedures. Intrathecal opiates may be used to provide postoperative analgesia following thoracotomy. This technique is associated with good analgesia at rest and a reduction in the need for opiates delivered via other routes during the first 24 hours. It may also be associated with a higher incidence of side effects when compared with epidural opioids or epidural local anesthetic and opioid combinations. The addition of intercostal nerve blocks to intrathecal opioids does not significantly improve postoperative pain control and has been associated with decreased pulmonary function after 24 hours (Liu et al., 1995).

- Administration of opioids via oral, IV, IM, or IV PCA routes can be an effective means of providing primary postoperative pain control or as an adjunct to regional or neuraxial analgesic techniques. The use of opioids to reduce postoperative pain after thoracotomy is well-documented. Because of potential side effects, clinicians have tried to optimize delivery and closely match the dose needed. In this context, IV PCA has resulted in incrementally improved analgesia, increased patient satisfaction, and tendency toward improved pulmonary function and earlier recovery or discharge.

- Drains and chest tubes inserted during surgery can cause intense irritation and pain at entry sites or deeper. The use of NSAIDs as an adjunct to other postoperative analgesics is beneficial for control of nonincisional pain following thoracotomy (Singh et al., 1997). Acetaminophen may be used as an adjunctive analgesic if an NSAID is contraindicated. These medications are rarely, if ever, sufficient to provide complete pain relief following thoracotomy.

- The use of TENS may serve as a useful adjuvant following minor thoracic surgical procedures.

Considerations:

- Pulmonary toilet is very important in ensuring a good outcome, so pain control is of paramount importance. Regional analgesic techniques provide better pulmonary toilet than IV PCA (Benzon et al., 1993).

- Opiates should be used cautiously in the setting of severe pulmonary disease due to the potential complication of respiratory depression. Therefore, in this group, regional analgesia may be strongly preferred (Benzon et al., 1993).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Effective postoperative pain control may be achieved by delivering an opioid or a combination of opioid and local anesthetic into the thoracic epidural space.	Mahon et al., 1999 Brichon et al., 1994 Miguel & Hubbell, 1993	I I I	A A A

	Intervention	Sources of Evidence	QE	R
2	Mixing a local anesthetic with an opioid produces better analgesia, but RCTs indicate that there is a tendency toward more side effects when an opioid is added to a local anesthetic as compared to local anesthetic alone.	Mahon et al., 1999	I	B
3	The addition of local anesthetic to epidural opioid allows a significant reduction in the total dose of opioid required to produce equivalent analgesia.	Burgess et al., 1994	I	A
4	Epidural opioids (hydrophillil) may be delivered via a lumbar or thoracic approach.	Gaeta et al., 1995	I	B
5	There is no significant difference between lumbar and thoracic epidural administration of the highly lipid-soluble opioids, fentanyl and sufentanil.	Swenson et al., 1994 Haak-van der Lely, 1994	I II-1	A B
6	There is no significant difference between epidural and intravenous administration of the highly lipid-soluble opioids.	Baxter et al., 1994 Sandler et al., 1992 Guinard et al., 1992	I I I	B A A
7	Pre-operative initiation of continuous local anesthetic epidural block has been associated with reduced long-term (at 6 months) pain.	Obata et al., 1999	I	A
8	Continuous paravertebral blocks are capable of providing equivalent or superior pain control when compared to epidural analgesia following thoracotomy.	Catala et al., 1999	I	B
9	Continuous paravertebral blocks are superior to interpleural block following thoracotomy.	Richardson et al., 1995	II-2	B
10	Direct injection of a local anesthetic alone to block intercostal nerves can be used. Analgesia only lasts 6-12 hours. More prolonged relief can be obtained by performing cryoanalgesic blocks of the intercostal nerves.	Burcerius et al., 2000	I	B
11	Interpleural local anesthetics can be delivered via catheter between the parietal and visceral pleura and a local anesthetic injected at 4-6 hour intervals or infused continuously to produce analgesia… …Clinical use of this technique has not found widespread acceptance and it has been out of favor for many years.	Barron et al., 1999 Raffin et al., 1994 Solomon et al., 2000 Gaeta et al., 1995	I I I I	A A A B

	Intervention	Sources of Evidence	QE	R
12	The addition of intercostal nerve blocks to intrathecal opioids does not significantly improve postoperative pain control and has been associated with decreased pulmonary function after 24 hours.	Liu et al., 1995	I	B
13	Opioids via oral, IV, IM, or IV PCA can provide postoperative pain control or be used as an adjunct to regional or neuraxial analgesia.	VHA/DoD Guideline working group	III	C
14	The use of NSAIDs as an adjunct to other postoperative analgesics is beneficial for non-incisional pain.	Singh et al., 1997	I	A
15	Regional analgesic techniques provide better pulmonary toilet than IV PCA.	Benzon et al., 1993	I	B
16	Opiates should be used cautiously in the setting of severe pulmonary disease due to the potential for respiratory depression.	Benzon et al., 1993	I	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

THORAX (NON-CARDIAC) SURGERY

Mastectomy

Type of Pain:
Mastectomy produces pain that is both nociceptive and neuropathic in nature.

Severity/Duration:
Pain from mastectomy is moderate to severe and lasts weeks. In rare instances, patients may develop post-mastectomy pain syndromes persisting for months to years.

Interventions:

- Paravertebral or intercostal blocks may be useful in providing postoperative analgesia for up to 24 hours for either inpatient or outpatient surgical procedures (Atanassoff et al., 1994; Klein et al., 2000).
- Thoracic epidural analgesia provides greater pain control and patient satisfaction, but is not frequently used because patients are discharged quickly (Yeh et al., 1999).
- Postoperative oral opioids are preferred because this may be done as an ambulatory surgical procedure.
- For hospitalized patients, an IV PCA is used for the first 24 hours followed by oral agents.
- NSAIDs may be used for postoperative pain (Chan et al., 1996).

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Considerations:
Patients may develop post-mastectomy pain syndromes involving the intercostal-brachial nerve that is often injured or resected during the performance of axillary lymph node dissection.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Paravertebral or intercostal blocks may provide postoperative analgesia for up to 24 hours.	Atanassoff et al., 1994 Klein et al., 2000	I I	A A
2	Thoracic epidural analgesia provides excellent pain control and patient satisfaction.	Yeh et al., 1999	I	A
3	NSAIDs may be used for postoperative pain.	Chan et al., 1996	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

THORAX (NON-CARDIAC) SURGERY

Thoracoscopy

Type of Pain:
Thoracoscopy pain is primarily nociceptive in nature.

Severity/Duration:
Pain from thoracoscopy is mild to severe and lasts from days to weeks (Kirby et al., 1995; Santambrogio et al., 1995). In most patients the pain is mild to moderate.

Interventions:

- Adequate analgesia can be readily obtained in most patients using oral, IV, IM, or IV PCA opiates.
- Supplemental treatment with NSAIDs or the use of TENS may allow a significant reduction in the use of postoperative opiate pain medications (Perttunen et al., 1999).
- Pain control in the immediate postoperative period may be enhanced by injection of a local anesthetic through the thoracoscope at the end of surgery (Lieou et al., 1996), incisional local anesthetic infiltration, or paravertebral or intercostal nerve blocks.
- In patients with extensive operations or poorly controlled pain, the use of epidural analgesia may be required.

Considerations:
Thorascopic procedures result in less postoperative pain and shorter lengths of stay as compared to thoracotomy.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Supplemental treatment with NSAIDs or the use of TENS may allow a significant reduction in the use of postoperative opiate pain medications.	Perttunen et al., 1999	II-1	A
2	Pain control in the immediate postoperative period may be enhanced by injection of local anesthetic through the thoracoscope at the end of surgery.	Lieou et al., 1996	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

THORAX (CARDIAC) SURGERY

Coronary artery bypass grafting (CABG), heart valve repair/replacement, and minimally invasive direct coronary artery bypass grafts (mid-CABS).

Type of Pain:
Thoracic (cardiac) surgery produces pain that is nociceptive in nature.

Severity/Duration:
Thoracic (cardiac) surgery produces pain lasting days to weeks. Because somatic nerves are not divided by the surgical incision, postoperative pain is usually less than after conventional thoracotomy. In rare circumstances, patients may have pain that persists for months to years related to sternal nonunion and suture or wire problems. Mid-CAB surgery produces mild to moderate pain lasting days to weeks.

Interventions:

- Most cardiac operations involve a median sternotomy and anesthetic induction using high doses of opioids.
- The pain of median sternotomy is frequently controlled with IV or IV PCA opiates. This is rapidly transitioned to oral opiates alone.
- Although it has been used successfully, epidural analgesia is uncommon in the setting of median sternotomy for cardiac surgery at the present time.
- Mid-CABs transition to oral medications very rapidly.

Considerations:
The frequent use of complete anticoagulation during thoracic cardiac surgery has resulted in significant concerns regarding the potential for complications associated with the use of epidural analgesia.

THORAX (CARDIAC) SURGERY

Coronary Artery Bypass Graft (CABG)

Type of Pain:
CABG produces pain from the sternum and drain sites that is nociceptive in nature.

Severity/duration:
Pain from a CABG is moderate to severe and lasts days to weeks.

Interventions:

- Pain control post-CABG is initially via IV PCA, IM, or IV routes. This rapidly changes to oral medication. In the first 24 hours, non-patient dependent routes (i.e. nurse administration) may be preferred to IV PCA (Tsang & Brush, 1999; Checketts et al., 1998; Munro et al., 1998; O'Halloran & Brown, 1997; Myles et al., 1994). After 24 hours, IV PCA transitioning to oral is preferred (Boldt et al., 1998).
- NSAIDs may be helpful for post-sternotomy pain.
- Neuraxial analgesia is rarely used but helps pulmonary function (Stenseth et al., 1996).
- Intrathecal opiates may be helpful in the first 24 hours, but may delay extubation (Chaney et al., 1999; Chaney et al., 1996; Shroff et al., 1997).

Considerations:
Because full systemic anticoagulation is necessary, epidural analgesia is rarely used.

EVIDENCE TABLE

	Interventions	Source of Evidence	QE	R
1	In the first 24 hours, non-patient dependent routes may be preferred (i.e., nurse administration).	Tsang & Brush, 1999 Checketts et al., 1998 Munro et al., 1998 O'Halloran & Brown, 1997 Myles et al., 1994	II-2 I I I I	A B A A A
2	After 24 hours, IV PCA transitioning to oral is preferred.	Boldt et al., 1998	I	B
3	Neuraxial analgesia is rarely used, but helps pulmonary function.	Stenseth et al., 1996	I	B
4	Intrathecal opiates may be helpful in the first 24 hours but may delay extubation.	Chaney et al., 1999 Chaney et al., 1996 Shroff et al., 1997	I I I	A B B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

THORAX (CARDIAC) SURGERY

Minimally Invasive Direct Coronary Artery Bypass (MID-CAB)

Type of Pain:
Mid-CAB surgery produces pain that is nociceptive and neuropathic in nature.

Severity/Duration:
Pain from mid-CABs is moderate to severe and lasts days to weeks.

Interventions:

- Pain control post MID-CAB is initially via IV PCA, IM, or IV routes. This rapidly changes to oral medication.
- NSAIDs may be helpful.
- Neuraxial analgesia is rarely used (Stenseth et al., 1996).
- Intrathecal opiates may be helpful in the first 24 hours (Chaney et al., 1999).
- Intraoperative cryoablation may improve postoperative pain control (Bucerius et al., 2000; Pastor et al., 1996).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Intrathecal opiates may be helpful in the first 24 hours.	Chaney et al., 1999	I	A
2	Neuraxial analgesia is rarely used.	Stenseth et al., 1996	I	B
3	Intraoperative cryoablation may improve postoperative pain control.	Bucerius et al., 2000 Pastor et al., 1996	II-1 II-1	B B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

UPPER ABDOMINAL SURGERY

Operative sites in the upper abdomen include the visceral and vascular structures, such as the stomach, gallbladder, pancreas, bowel, and aorta. Both somatic and visceral structures generate postoperative pain after intra-abdominal procedures such as laparotomy, cholecystectomy, nephrectomy, gastrectomy, gastric bypass, pancreatectomy, splenectomy, and abdominal aortic aneurysm repair.

Type of Pain:
Upper abdominal surgery results in nociceptive (somatic and visceral) and neuropathic pain.

Severity/Duration:
Upper abdominal surgery produces pain of mild to severe intensity lasting days to weeks. Laparoscopic procedures produce mild to moderate pain lasting several days. Non-laparoscopic procedures, including flank incision, clam-shell incision, and midline laparotomy all produce pain of moderate to severe intensity lasting days to weeks.

Interventions:
Many analgesic techniques are used to provide pain control after upper abdominal surgery. The decision to use one over another should consider both the expected postoperative pain and the patient's underlying medical condition. Multimodal analgesia using local anesthetic, NSAIDs, and opiates provides improved pain control, decreased nausea, and faster discharge following laparoscopic cholecystectomy (Michaloliakou et al., 1996). Adequate pain relief following upper abdominal surgery helps to reduce postoperative respiratory complications (Vassilakopoulos et al., 2000). Interventions include:

- *IV/IM Opiates*

Adequate analgesia at rest can be readily obtained with IV, IM, or IV PCA opiates (Wheatley, 1992; Passchier et al., 1993). Patients receiving IV PCA opiates tend to have better pain relief and to use more morphine than those limited to IM morphine on demand. Due to the potential for side effects, clinicians have tried to optimize delivery and match the dose to that required by the patient. In this context, IV PCA has resulted in incrementally improved analgesia, increased patient satisfaction, and a tendency toward improved pulmonary function, bowel function, and earlier discharge. These pain treatments frequently do not provide good pain control during movements, such as coughing, deep breathing, or ambulation. This route may serve as a bridge between interventions, e.g., a patient coming off of epidural analgesia but not yet ready for oral analgesics.

- *Epidural Analgesia*

Epidural analgesia, incorporating the use of local anesthetics or local anesthetic with opiates (Wiebalck et al., 1997; Schug et al., 1995) provides better pain control during activity while allowing a reduction in the total dose of opiates and fewer side effects (Mulroy et al., 1996; George et al., 1994). The net effect of this combination allows improved pain control at rest and with movement, improved pulmonary function, decreased side effects, and faster recovery of bowel function (Mann et al., 2000; Liu et al., 1995). Epidural analgesia after upper abdominal surgery has also been associated with less postoperative myocardial ischemia (deLeon-Casasola et al., 1995). In order to produce optimal analgesia, the thoracic epidural route should be used for upper abdominal surgery, especially if local anesthetics are to be used (Wiebalck et al. 1997; Chisakuta et al., 1995; George et al., 1994). Patient-controlled epidural analgesia (PCEA) is another effective intervention in this population (Komatsu et al., 1998). Epidural analgesia is the treatment of choice for pain following upper abdominal surgery. Once bowel function has recovered, patients can readily be switched to oral opiates and NSAIDs.

- *Intrathecal Opioids*

Intrathecal administration of opioids has been used successfully to provide analgesia following upper abdominal surgery. This technique is associated with good analgesia at rest for up to 24 hours. A drawback is the inability to re-dose without repeating the injection. Therefore, the effects are time-limited. Intrathecal opioids may be associated with a higher incidence of side effects when compared to the epidural route.

- *Intercostal Nerve Block*

The use of intercostal nerve blockade in combination with opiates has been shown to be more effective than opiates alone after subcostal incisions. They are not effective after midline laparotomy incisions (Engberg et al., 1985). However, given the limited duration of their effects (6-12 hours) and their need to be repeated, various authors have suggested means of prolonging the duration of the block. These recommendations have included cryoanalgesia and phenol in combination with local anesthetic (Maidatsi et al., 1998). Some centers have used interpleural catheters to provide prolonged intercostal neural blockade after upper abdominal surgery. This technique has not found widespread use and is not recommended as an initial therapy.

- *Local Anesthetic Injection into Wound/Incision*

Infiltration of the incision and/or wound by the surgeon with local anesthesia is a technique that has been used widely for many years. Preoperative infiltration of the wound with local anesthetic in addition to postoperative analgesia with epidural bupivicaine and morphine produced improved analgesia during mobilization and reduced the need for supplemental intramuscular morphine (Bartholdy et al., 1994).

- *NSAIDs*

Ketorolac has been shown to be a valuable adjuvant in the treatment of pain after laparoscopic upper abdominal surgery and facilitates the transition to oral pain medications (Lane, 1996).

Considerations:

- Pain relief is crucial because pain following upper abdominal surgery produces significant respiratory dysfunction (Vassilakopoulos et al., 2000). Effective analgesia and aggressive pulmonary toilet produce a speedier return of respiratory function and reduce postoperative respiratory complications.

- Aggressive management of the entire perioperative experience following laparoscopic abdominal surgery using epidural local anethetics, NSAIDs, complete avoidance of opiates, early feeding, and ambulation has been associated with improved pain control, reduced complications, and decreased length of stay (Kehlet et al., 1999; Bardram et al., 1995; Bardram et al., 2000).

- Use of laparoscopic procedures leads to less postoperative pain and shorter lengths of stay (McMahon, 1994). Many laparoscopic procedures are done on an outpatient basis, so pain control needs to be obtained expeditiously, prior to discharge.

- Previous treatment of simple laparoscopic procedures was limited to oral and IV analgesics. With the advent of complicated laparoscopic procedures, advanced strategies for pain management such as intraspinal analgesics (as a part of an aggressive pain management approach) have been associated with more rapid discharge and improved outcomes.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Multimodal analgesia using local anesthetic, NSAIDs and opiates provides improved pain control, decreased nausea, and faster discharge following laparoscopic cholecystectomy.	Michaloliakou et al., 1996	I	A
2	Pain following upper abdominal surgery produces inspiratory muscle dysfunction. This dysfunction is reduced with analgesia.	Vassilakopoulos et al., 2000	I	A

	Intervention	Sources of Evidence	QE	R
3	IV PCA morphine produces better analgesia than IM morphine, without any increase in postoperative hypoxemia.	Wheatley et al., 1992	I	A
4	Patients using IV PCA morphine used more morphine and had better analgesia than patients receiving IM morphine on demand. IV PCA patients also experienced more fatigue and had less vigor than patients receiving IM morphine.	Passchier et al., 1993	I	A
5	Epidural analgesia, with a combination of opiates and local anesthetic, provides better pain control during rest and activity, and is the treatment of choice. It is also associated with more rapid recovery of bowel function.	Mulroy et al., 1996 George et al., 1994 Mann et al., 2000 Liu et al., 1995	III I I I	A A A A
6	Epidural analgesia is associated with less postoperative myocardial ischemia (than IV PCA with morphine).	deLeon-Casasola et al., 1995	II-2	A
7	For optimal analgesia, the thoracic epidural route should be used for pain relief after upper abdominal surgery.	Wiebalck et al., 1997 Chisakuta et al., 1995 George et al., 1994	I I I	A A A
8	Pain control with intercostal nerve block in combination with opiates is more effective than opiates alone after subcostal incisions. Intercostal nerve blocks do not significantly improve analgesia following midline incisions.	Engberg et al., 1985	I	B
9	Phenol with local anesthetic has been shown to increase the duration of intercostal block and improve analgesia following cholecystectomy.	Maidatsi et al., 1998	I	B
10	Infiltration of the incision/wound with local anethesia improved postoperative analgesia provided by epidural bupivicaine/morphine during mobilization and reduced the need for supplemental intramuscular morphine.	Bartholdy et al., 1994	I	B
11	Ketorolac given before or after laparoscopic cholecystectomy reduced postoperative pain and facilitated the transition to oral pain medication.	Lane, 1996	I	A
12	Pain relief promotes return of respiratory function.	Vassilakopoulos et al., 2000	I	A

	Intervention	Sources of Evidence	QE	R
13	Aggressive perioperative management with epdural, NSAIDs, early feeding, and ambulation is associated with improved recovery and rapid discharge after laparoscopic colonic surgery.	Kehlet et al., 1999 Bardram et al., 1995 Bardram et al., 2000	II-3 II-3 II-3	B B A
14	Laparoscopic cholecystectomy is associated with less pain than open cholecystectomy.	McMahon et al., 1994	I	A
15	Patient-controlled epidural analgesia with a background infusion is more effective than patient-controlled epidural analgesia alone after gastrectomy.	Komatsu et al., 1998	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

UPPER ABDOMINAL SURGERY

Laparotomy

Type of Pain:
Produces pain that is nociceptive (somatic and visceral) and neuropathic in nature.

Severity/Duration:
Pain from laparotomy is moderate to severe and lasts from days to weeks.

Interventions:

- Analgesia at rest can be readily obtained with IV, IM, or IV PCA opiates.
- Thoracic epidural analgesia with a combination of opiates and local anesthetic produces improved pain control during activities such as coughing, deep breathing, and ambulation. It is also associated with better satisfaction, more rapid recovery of bowel function and more rapid return to normal mental status in the elderly (Liu et al., 1995; Mann et al., 2000).
- Adjuvant techniques, such as TENS and acupuncture, have not demonstrated great usefulness.
- Regional analgesic techniques such as intercostal or paravertebral nerve block may be useful in the first 24 hours postoperatively.
- Aggressive management of the entire perioperative experience following laparoscopic abdominal surgery using epidural, local anethetics, NSAIDs, complete avoidance of opiates, early feeding and ambulation has been associated with improved pain control, reduced complications, and decreased length of stay (Kehlet, 1995; Bardram et al., 1995; Bardram et al., 2000).

Considerations:
Laparotomy may be associated with reductions in forced expiratory volume (FEV) ranging from 25 to 75 percent and produce significant pulmonary complications.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Epidural analgesia produces better pain control at rest and with activity. It is also associated with earlier return to normal mental status in the elderly, better satisfaction, and more rapid recovery of bowel function.	Liu et al., 1995 Mann et al., 2000	I I	A A
2	Aggressive perioperative management with epidural, NSAIDs, early feeding, and ambulation is associated with improved recovery and rapid discharge after laparoscopic colonic surgery.	Kehlet, 1999 Bardram et al., 1995 Bardram et al., 2000	II-3 II-3 II-3	B B A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

UPPER ABDOMINAL SURGERY

Laparoscopic Cholecystectomy

Type of Pain:
Laparoscopic cholecystectomy produces pain that is nociceptive (somatic and visceral) and neuropathic in nature.

Severity/Duration:
Pain from laparoscopic cholecystectomy is mild to moderate lasting days (McMahon, 1994).

Interventions:
Analgesia can be readily obtained with IV, IM, or oral opiates. Multimodal analgesia using local anesthetic, NSAIDs, and opiates provides improved pain control, decreased nausea, and faster discharge following laparoscopic cholecystectomy (Michaloliakou, 1996). Suprahepatic suction drains placed by the surgeon have been shown to reduce shoulder tip pain from retained carbon dioxide (CO_2) following laparoscopic cholecystectomy (Jorgensen, 1995).

Considerations:
Laparoscopic cholecystectomy involves peritoneal insufflation of CO_2 gas. Invariably, residual CO_2 causes postoperative abdominal pain that may refer to the shoulder secondary to continued diaphragmatic irritation. It has been shown that active aspiration of insufflating gas at the conclusion of the operation results in less discomfort postoperatively (Fredman et al., 1994).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Multimodal analgesia using local anesthetic, NSAIDs, and opiates provides improved pain control, decreased nausea, and faster discharge following laparoscopic cholecystectomy.	Michaloliakou, 1996	I	A
2	Active removal of residual pneumoperitoneum reduces postoperative pain following laparoscopic cholecystectomy.	Fredman et al., 1994	I	A
3	Suprahepatic suction drains placed by the surgeon have been shown to reduce shoulder tip pain following laparoscopic cholecystectomy.	Jorgensen, 1995	II-3	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

UPPER ABDOMINAL SURGERY

Nephrectomy

Type of Pain:
Nephrectomy produces pain that is nociceptive (somatic and visceral) and neuropathic in nature.

Severity/Duration:
Pain from nephrectomy is mild to severe lasting days to weeks.

Interventions:

- Nephrectomies are usually performed through one of three possible incisions: flank, subcostal, or thoracoabdominal (Whalley & Berrigan, 2000). Laparoscopic nephrectomy is also an accepted technique that may be less painful (Nicol et al., 1994). Each type of incision will invariably have different levels of pain/discomfort and discussion with surgeons preoperatively is warranted, so that an appropriate pain management plan is in place.
- Thoracic epidural analgesia with a combination of opiates and local anesthetic produces improved pain control during activities such as coughing, deep breathing, and ambulation and is the superior technique. Oral/IV/IM opiates are also acceptable and efficacious, especially in the laparoscopic procedures.
- Interpleural local anesthetics have been shown to be effective in reducing opiate requirements post-operatively (Greif et al., 1999).
- Regional analgesic techniques such as intercostal or paravertebral nerve block may be useful in the first 24 hours postoperatively.

Considerations:
Renal function and drug clearance must be considered in developing a postoperative analgesia plan. NSAIDs may not be appropriate for use in patients with decreased renal function. In addition, opiate compounds requiring renal elimination may accumulate and produce undesirable side effects in patients with poor renal clearance.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Interpleural local anesthetics have been shown to be effective in reducing opiate requirements post-operatively.	Greif et al., 1999	III	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

LOWER ABDOMINAL AND PELVIS SURGERY

Type of Pain:
Operations of the lower abdomen and pelvis can produce both nociceptive (somatic and visceral) and neuropathic pain.

Severity/Duration:
Pain from lower abdomen and pelvic procedures generally ranges from moderate to severe in intensity lasting weeks to months.

Interventions:
Effective pain control can be obtained using IM, IV, IV PCA, or intraspinal drug administration (see specific operations). Epidural opiates provide better postoperative analgesia with fewer side effects than intravenous PCA opiates. Intraspinal opiate administration may not be the optimal technique for patients scheduled for rapid discharge from the hospital. Intraspinal analgesic techniques provide better postoperative pain control in patients undergoing major lower abdominal or pelvic surgery. Once bowel function has been recovered, oral administration of combination opiate preparations or NSAIDs can be used to effectively control pain for the remainder of the admission and following discharge.

Considerations:
- Epidural morphine provides better pain relief than patient-controlled intravenous morphine after hysterectomy (Eriksson-Mjoberg et al., 1997).
- Decreased bowel motility may be further exacerbated by opiate administration.
- Ambulation in the perioperative period is associated with a decreased risk of thromboembolic complications and more rapid recovery of bowel function (Bardram et al., 2000).
- In the absence of significant motor block with intraspinal drug administration, patients should be encouraged to ambulate with assistance.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Epidural opiates in the postoperative period provide better analgesia with fewer side effects than IV PCA morphine.	Eriksson-Mjoberg et al., 1997	I	A
2	Ambulation in the perioperative period is associated with a decreased risk of thromboembolic complications and more rapid recovery of bowel function.	Bardram et al., 2000	II-3	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

LOWER ABDOMINAL AND PELVIS SURGERY

Hysterectomy

Type of Pain:
Hysterectomy produces both nociceptive (somatic and visceral) and neuropathic pain.

Severity/Duration:
Hysterectomy pain can range from mild to severe and may last days to weeks. In the event of a nerve injury, the pain may last weeks to years.

Interventions:

- Wound infiltration with local anesthetic does not reduce opiate requirements following abdominal hysterectomy (Cobby & Reid, 1997).
- IV PCA opiates result in better analgesia with fewer adverse effects than intermittent IM opiates and result in higher patient satisfaction (Egbert et al., 1990; Ballantyne et al., 1993).
- Epidural morphine provides better pain relief with fewer side effects than intravenous PCA morphine following hysterectomy (Eriksson-Mjoberg et al., 1997).
- NSAIDs do not produce preemptive analgesia following abdominal hysterectomy (Danou et al., 2000; Rogers et al., 1995). However, they are associated with significant reductions in opiate administration when used as a part of the postoperative pain treatment regimen (Cobby et al., 1999; Varrassi et al., 1999; Gabbott, 1997).
- TENS units may be effective (Hamza et al., 1999; Chen et al., 1998).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Wound infiltration with local anesthetic does not reduce morphine requirements after abdominal hysterectomy.	Cobby & Reid, 1997	I	A
2	IV PCA opiates result in better analgesia with fewer adverse effects than intermittent IM opiates and result in higher patient satisfaction.	Egbert et al., 1990 Ballantyne, 1993	I I	A A
3	Epidural morphine provides better pain relief with fewer side effects than IV PCA morphine.	Eriksson-Mjoberg et al., 1997	I	A
4	TENS units may be effective.	Hamza et al., 1999 Chen et al., 1998	I I	B B
5	NSAIDs do not produce preemptive analgesia.	Danou, 2000 Rogers et al., 1995	I I	D B
6	NSAIDs reduce postoperative opiate requirements.	Cobby et al., 1999 Varrassi et al., 1999 Gabbott, 1997	I I I	A A A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

LOWER ABDOMINAL AND PELVIS SURGERY

Radical Retropubic Prostatectomy

Type of Pain:
Radical retropubic prostatectomy produces postoperative pain that is primarily nociceptive in nature.

Severity/Duration:
Radical retropubic prostatectomy produces pain that is moderate to severe in intensity lasting weeks.

Interventions:

- IV PCA opiates result in better analgesia with fewer adverse effects than intermittent IM opiates, and result in higher patient satisfaction (Egbert et al., 1990; Ballantyne et al., 1993).
- Postoperative administration of ketorolac instead of IV PCA morphine is associated with earlier recovery of bowel function, shorter hospitalization, and lower overall costs (See et al., 1995).
- Epidural analgesia provides superior pain control and may be associated with reduced postoperative pain for several weeks following surgery (Shir et al., 1994; Gottschalk et al., 1998).
- Postoperative administration of ketorolac is an effective adjuvant for improving postoperative epidural analgesia (Grass et al., 1993).
- Intraoperative administration of ketorolac does not decrease postoperative pain or improve analgesia (Fredman et al., 1996).
- FasTENS is an effective adjuvant for postoperative analgesia following retropubic prostatectomy (Merrill, 1989).

Considerations:
See general statement above.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	IV PCA opiates result in better analgesia with fewer adverse effects than intermittent IM opiates and result in higher patient satisfaction.	Egbert et al., 1990 Ballantyne et al., 1993	I I	A A
2	Epidural analgesia may be used to provide superior pain control and may be associated with reduced postoperative pain for several weeks.	Shir et al., 1994 Gottschalk et al., 1998	I	A
3	Postoperative administration of ketorolac instead of IV PCA morphine is associated with earlier recovery of bowel function, shorter hospitalization, and lower overall costs.	See et al., 1995	II-3	B
4	Postoperative administration of ketorolac is a useful adjuvant to epidural analgesia to improve postoperative pain control.	Grass et al., 1993	I	A
5	Intraoperative administration of Ketorolac does not decrease postoperative pain or improve analgesia.	Fredman et al., 1996	I	D
6	FasTENS is an effective adjuvant for postoperative analgesia following retropubic prostatectomy.	Merrill, 1989	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

LOWER ABDOMINAL AND PELVIS SURGERY

Inguinal Hernia

Type of Pain:
Inguinal herniorrhaphy produces both nociceptive and neuropathic pain. Certain types of hernia repair are more painful (Wellwood et al., 1998).

Severity/Duration:
Pain produced is generally mild to severe lasting weeks. Neuropathic pain following inguinal herniorrhaphy may last weeks to years.

Interventions:
Regional anesthesia (local field block, nerve block, spinal, or epidural) may have advantages in preventing postoperative pain and can be associated with fewer postoperative side effects such as nausea and vomiting, which can lead to delayed discharge (Song et al., 2000; Moiniche et al., 1998; Ding & White, 1995). Regardless of the choice of anesthesia for the case, regional analgesia, including local field block or peripheral nerve block, may be used to provide prolonged postoperative analgesia (Wassef et al., 1998; Ding & White, 1995). Preoperative administration of ketorolac reduces postoperative pain following inguinal herniorrhaphy and the need for additional postoperative analgesic medication. There is no advantage to delivering the medication within the wound or giving IV over IM drugs (Ben-David et al., 1996).

Considerations:
See general considerations.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Regional anesthesia may have advantages in preventing postoperative pain and can be associated with fewer postoperative side effects.	Song et al., 2000 Moiniche et al., 1998 Ding & White, 1995	I I I	A B A
2	Regional analgesia, including local field block or peripheral nerve block, may be used to provide prolonged postoperative analgesia.	Wassef et al., 1998	I	A
3	Preoperative administration of ketorolac reduces postoperative pain following inguinal herniorrhaphy and the need for additional postoperative analgesic medication. There is no advantage to delivering the medication within the wound or giving IV over IM drug.	Ben-David et al., 1996	I	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

BACK/SPINAL SURGERY

Type of Pain:
Back and spinal procedures produce nociceptive and neuropathic pain.

Severity/Duration:
Pain from back and spinal procedures is mild to severe in intensity and may last weeks to months. Back surgery is also associated with moderate to severe paraspinal muscle spasm. These patients may develop chronic pain syndromes lasting years (e.g., post-laminectomy pain syndrome).

Interventions:

- PO/IM/IV opioid medications are commonly used. IV PCA is the treatment of choice for moderate to severe pain. Placement of epidural catheters for postoperative analgesia can be accomplished preoperatively from a percutaneous approach, as well as by direct placement by the surgeon during the course of the operation.
- Operations on the spinal cord often involve laminectomy and bone grafting, and may include opening the dura around the spinal cord. These procedures may limit the role of intraspinal delivery of pain medications. The use of epidural or intrathecal opiates for control of pain after back surgery is not widespread.

Considerations:

- Operations on the spine at any level are frequently done for patients who have experienced chronic pain. Such patients may have typical complications of chronic pain, including depression, anxiety, irritability, and, if opioid analgesics were required preoperatively, a relative tolerance to opioid medications. All of these factors may complicate pain assessment and treatment in the postoperative period.
- As with any neurologic procedure, postoperative patients require careful monitoring of neurologic function, especially the assessment of sensory, motor, and autonomic functioning.
- NSAIDs may affect healing of spinal fusions (Glassman et al., 1998).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	NSAIDs may affect healing of spinal fusions.	Glassman et al., 1998	II-1	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

BACK/SPINAL SURGERY

Laminectomy

Type of Pain:
A laminectomy causes nociceptive and neuropathic pain.

Severity/Duration:
Laminectomy causes pain of mild to severe intensity lasting weeks.

Interventions:

- Laminectomy pain is treated with IV PCA, IV, IM (Colwell & Morris, 1995) and oral medication, as more of these procedures are done on an outpatient basis. Nonsteroidals may be effective (Rosenhow et al., 1998; Rowe et al., 1992).
- Regional techniques (epidural) can be used for superior postoperative pain control, but are not common (Ibrahim et al., 1986; Joshi et al., 1995; Kundra et al., 1997).
- Local infiltration of the incision may be helpful (Cherian et al., 1997).
- TENS is not helpful (McCallum et al., 1988).

Considerations:
This group of patients may be on significant doses of oral analgesics preoperatively and may need larger doses postoperatively than an opioid-naïve patient.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Laminectomy pain is treated with IV PCA, IV, IM, and oral medications.	Colwell & Morris, 1995	I	A
2	Nonsteroidals may be effective.	Rosenhow et al., 1998 Rowe et al., 1992	I I	A A
3	Regional techniques can be used for superior postoperative pain control.	Kundra et al., 1997 Joshi et al., 1995 Ibrahim et al., 1986	I I I	C B B
4	Local infiltration of the incision may be helpful.	Cherian et al., 1997	I	B
5	TENS is not helpful.	McCallum et al., 1988	I	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

BACK/SPINAL SURGERY

Spinal Fusion

Type of Pain:
Spinal fusion causes pain that is nociceptive and neuropathic in nature.

Severity/Duration:
Spinal fusion pain lasts months and is moderate to severe in intensity.

Interventions:

- Pain is addressed with IV PCA, IV, and IM medication with conversion to oral medication over a period of several days.
- Regional anesthesia is not used; pain relief is not superior to patient-controlled analgesia (Cohen et al., 1997; France et al., 1997).
- NSAIDs can provide analgesia, but there are concerns regarding increased rates of non-union following NSAID use (Glassman et al., 1998).
- Patients may use external braces.

Considerations:
Patients may be on preoperative analgesics and receive larger doses of postoperative medications.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Regional anesthesia is not used; pain relief is not superior to patient-controlled analgesia.	France et al., 1997 Cohen et al., 1997	I I	C A
2	NSAIDs are helpful.	Reuben et al., 1998	I	C
3	There are concerns regarding increased rates of non-union following NSAID use.	Glassman et al., 1998	II-1	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES/VASCULAR SURGERY

Type of Pain:
Extremities and vascular procedures may result in pain that is both nociceptive and neuropathic.

Severity/Duration:
Postoperative pain following extremity surgery may range from mild to severe in intensity and last days to weeks. If long-term anatomic abnormality or neuropathic injury results from the surgical procedure, pain may last from weeks to years.

Interventions:
There are a wide variety of techniques that may be used to provide anesthesia and postoperative analgesia for surgical procedures involving the extremities. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Interscalene brachial plexus blocks
- Supraclavicular brachial plexus blocks
- Infraclavicular brachial plexus blocks
- Axillary brachial plexus blocks
- Upper extremity peripheral nerve blocks
- Lumbar plexus blocks
- Femoral nerve blocks
- Fascia iliaca blocks
- Lateral femoral cutaneous nerve blocks
- Obturator nerve blocks
- Saphenous nerve blocks
- Ankle blocks
- Sciatic nerve blocks
- Popliteal nerve blocks
- Intra-articular injections
- Wound or joint infusions of local anesthetic
- Oral, intravenous, intramuscular, and IV PCA opioids
- TENS
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics
- Ice

Extremity surgery lends itself to the use of regional anesthesia/analgesia techniques. Epidural analgesia is particularly attractive in terms of establishing early mobility, minimizing thromboembolic complications, and improving graft survival in the setting of peripheral vascular surgery. Regional anesthesia/analgesia techniques are associated with fewer complications, reduced morbidity and mortality, a high patient satisfaction rate, and the ability to discharge the patient with prolonged analgesia (Rodgers et al., 2000). Postoperative pain control can be obtained using oral, IM, and IV analgesia. Postoperative pain control may also be supplemented by physical and psychological interventions. The ideal pain control method should have minimal side effects, maintain mental clarity, and allow early ambulation and movement in the postoperative period.

Considerations:
Lower extremity surgery is associated with a high degree of morbidity related to venous thromboembolic complications. Because of this, intermittent leg and foot compression devices are commonly used in conjunction with various anticoagulant regimens. The potential for complications associated with the

combination of anticoagulants and regional anesthesia/analgesia must be taken into consideration in developing a perioperative pain control plan.

Operations requiring a cast or other form of external fixation for stabilization require frequent post-operative evaluation of circulation and neurologic functions. If a regional anesthetic/analgesic is to be used for postoperative pain control, this must be planned in conjunction with the surgeon so that it does not compromise required postoperative evaluation and monitoring. The presence of a regional anesthetic may prevent the patient from reporting a painful area of pressure or moving spontaneously in response to prolonged pressure on an area of the body, resulting in injury if appropriate monitoring and padding are not utilized.

Indwelling catheters may be inserted with many types of regional anesthetic/analgesic techniques. This facilitates delivery of continuous or intermittent local anesthetic +/- opioid or clonidine or agonist/antagonist through the catheter to provide postoperative pain relief. This can be done both as an inpatient and as an outpatient.

In many settings, the use of regional anesthesia/analgesia provides superior postoperative analgesia compared to oral, intramuscular, or intravenous opioid analgesics.

Minor Surgery:
Minor operations, such as carpal tunnel release, ganglion cystectomies, and other minor peripheral procedures are frequently performed on an outpatient basis, using local or regional anesthesia. Pain resulting from these procedures can be readily controlled using mild opiate analgesics supplemented by NSAIDs. Local or regional anesthesia used intraoperatively will provide analgesia in the postoperative period. In some cases, addition of other drugs (e.g., clonidine) to the local anesthetic will prolong the duration of action (Reinhart et al., 1996).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Regional anesthesia/analgesia techniques are associated with fewer complications, reduced morbidity and mortality, a high patient satisfaction rate, and the ability to discharge the patient with prolonged analgesia.	Rodgers et al., 2000	I	A
2	In some cases, addition of other drugs (e.g., clonidine) to the local anesthetic will prolong the duration of action.	Reinhart et al., 1996	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES

Total Hip Replacement

Type of Pain:
Pain from total hip replacement is primarily nociceptive in nature.

Severity/Duration:
Total hip replacement produces mild to severe pain of several days' to weeks' duration.

Interventions:
Postoperative analgesia following total hip replacement may be provided by a number of methods. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Lumbar plexus blocks
- Oral, intravenous, intramuscular, and IV PCA opioids
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioids

Considerations:
Intravenous morphine administered at the end of surgery to spontaneously breathing patients is associated with rapid postoperative pain control, decreased opiate doses, and reduced respiratory depression (Pico et al., 2000). Lumbar plexus blocks performed prior to hip surgery are associated with a moderate reduction in blood loss and a significant improvement in early analgesia (Stevens et al, 2000). Three-in-one block does not contribute in a significant fashion to postoperative pain control following total hip arthroplasty using the posterior approach (Uhrbrand et al., 1992).

There is a significant potential for developing thromboembolic complications following total hip replacement. Medical interventions intended to reduce this risk may dictate the choice of anesthetic and postoperative analgesic technique by increasing the risk associated with the performance of neuraxial anesthetic/analgesic techniques. Careful planning with the surgeon and adherence to guidelines for neuraxial anesthesia/analgesia in the presence of anticoagulants (ASRA, 1998) will help to minimize the risk.

At rest, epidural analgesia is slightly better than IV patient-controlled analgesia (Wulf et al., 1999). Intrathecal administration of morphine in small doses is capable of providing excellent analgesia (Slappendel et al., 1999). The choice of fentanyl or morphine along with bupivicaine does not appear to make a significant difference in postoperative pain relief or side effects (Berti et al., 1998). Continuous spinal anesthesia may provide more complete analgesia and less muscle spasm than epidural analgesia (Mollmann et al., 1999). Intrathecal clonidine is capable of prolonging the duration of spinal anesthesia, but is markedly inferior to intrathecal morphine in providing subsequent postoperative analgesia (Fogarty et al., 1993). Administration of ketorolac tromethamine to patients receiving intrathecal opiates for postoperative pain control will reduce the need for additional opiates, but will not change the incidence of side effects (Fogarty et al., 1995).

Patients may typically be converted to oral analgesics on the second to third postoperative day. Regularly administered oral opiates are capable of providing good postoperative pain control at that time (Bourke et al., 2000).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Intravenous morphine administered at the end of surgery to spontaneously breathing patients is associated with more rapid postoperative pain control, decreased opiate doses, and reduced respiratory depression.	Pico et al., 2000	I	A
2	Lumbar plexus blocks performed prior to hip surgery are associated with a moderate reduction in blood loss and a significant improvement in early analgesia.	Stevens et al., 2000	I	A
3	Three-in-one block does not contribute in a significant fashion to postoperative pain control following total hip arthroplasty using the posterior approach.	Uhrbrand et al., 1992	I	A
4	Adherence to guidelines for neuraxial anesthesia/analgesia in the presence of anticoagulants will help to minimize the risk of thromboembolic complications.	ASRA, 1998		
5	At rest, epidural analgesia is slightly better than IV patient-controlled analgesia.	Wulf et al., 1999	I	B
6	Intrathecal administration of morphine in small doses is capable of providing excellent analgesia.	Slappendel et al., 1999	I	A
7	The choice of fentanyl or morphine along with bupivicaine does not appear to make a significant difference in postoperative pain relief or side effects.	Berti et al., 1998	I	B
8	Continuous spinal anesthesia may provide more complete analgesia and less muscle spasm than epidural analgesia.	Mollmann et al., 1999	I	B
9	Intrathecal clonidine is capable of prolonging the duration of spinal anesthesia, but is markedly inferior to intrathecal morphine in providing subsequent postoperative analgesia.	Fogarty et al., 1993		
10	Administration of ketorolac tromethamine to patients receiving intrathecal opiates for postoperative pain control will reduce the need for additional opiates, but will not change the incidence of side effects.	Fogarty et al., 1995	I	A
11	Patients may typically be converted to oral analgesics on the second to third postoperative day. Regularly administered oral opiates are capable of providing good postoperative pain control.	Bourke et al., 2000	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES

Total Knee Replacement

Type of Pain:
The pain from total knee replacement is typically nociceptive in nature.

Severity/Duration:
Total knee replacement produces moderate to severe pain of several days' to weeks' duration.

Interventions:
Postoperative pain control following total knee replacement surgery can be provided with a variety of techniques. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Lumbar plexus blocks
- Femoral nerve blocks
- Fascia iliaca blocks
- Sciatic nerve blocks
- Oral, intravenous, intramuscular, and IV PCA opioids
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics

Considerations:
Pain is frequently exacerbated by the ongoing physical therapy that is vital to the long-term outcome of the surgery. The use of epidural analgesia or continuous femoral nerve block following total knee arthroplasty provides superior pain control as compared to opioids alone and is associated with a shorter recovery time. Improved pain control facilitates participation in physical therapy and improves outcome (Capdevila et al., 1999; Singelyn et al., 1998). For this reason, pain must be aggressively treated following total knee arthroplasty.

The potential for developing thromboembolic complications following total knee replacement is significant. Medical interventions intended to reduce this risk play a role in the choice of intraoperative anesthetic and postoperative analgesic technique. Careful planning with the surgeon and adherence to the guidelines (ASRA, 1998) for neuraxial anesthesia/analgesia in the presence of these drugs will help to minimize the risks.

Single shot, continuous epidural, and continuous regional techniques produce better overall pain control than nonregional techniques (Allen et al., 1998; Ganapathy et al., 2000; Singelyn & Gouverneur, 2000). The addition of a sciatic nerve block to a femoral nerve block does not significantly improve postoperative pain control when compared to the femoral nerve block alone (Allen et al., 1998). Intrathecal opioids may be used to improve postoperative pain control (Cole et al., 2000). Although they have been effective in other arthroscopy settings, intra-articular opioids are not effective for postoperative pain control following total knee arthroplasty (Klasen et al., 1999; Mauerhan et al., 1997). Intravenous regional delivery of opiates does not improve postoperative pain control over IM opiates following total knee arthroplasty (McSwiney et al., 1997).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Improved pain control facilitates participation in physical therapy and improves outcome.	Capdevila et al.,1999 Singelyn et al., 1998	**I** I	A A
2	Adherence to the guidelines for neuraxial anesthesia/analgesia will help to minimize the risk of thromboembolic complications.	ASRA, 1998		
3	Single shot, continuous epidural, and continuous regional techniques produce better overall pain control.	Singelyn & Gouverneur, 2000 Ganapathy et al., 2000 Allen et al., 1998	I I I	A B B
4	The addition of a sciatic nerve block to a femoral nerve block does not significantly improve postoperative pain control when compared to the femoral nerve block alone.	Allen et al., 1998	I	E
5	Intrathecal opioids may be used to improve postoperative pain control.	Cole et al., 2000	I	B
6	Intra-articular opioids are not effective for postoperative pain control following total knee arthroplasty.	Klasen et al., 1999	I	E
7	Intravenous regional delivery of opiates does not improve postoperative pain control over IM opiates following total knee arthroplasty.	McSwiney et al., 1997	I	E

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES

Knee Arthroscopy and Arthroscopic Joint Repair

Type of Pain:
Knee arthroscopy and arthroscopic joint repair procedures typically result in pain that is nociceptive in nature.

Severity/Duration:
Knee arthroscopy and arthroscopic joint repair procedures produce pain that is mild to severe lasting days to weeks.

Interventions:
Postoperative analgesia following knee arthroscopy and arthroscopic joint repair may be provided using a number of techniques. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Lumbar plexus blocks
- Femoral nerve blocks
- Fascia iliaca blocks
- Sciatic nerve blocks
- Intra-articular injections
- Wound or joint infusions of local anesthetic
- Oral, intravenous, intramuscular, and IV PCA opioids
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics
- Ice

Considerations:
As a rule, the majority of these procedures are performed on an outpatient basis. The ability to control pain and safely discharge the patient home plays a significant role in the choice of anesthetic and postoperative analgesic technique. The use of a combined sciatic and femoral nerve block provides good surgical conditions and prolonged analgesia resulting in reduced cost and hospital stays compared to general anesthesia (Sansone et al., 1999). A local anesthetic infusion either into the joint or along a nerve bundle may be safely used to provide excellent postoperative analgesia. There is also good evidence that prolonged analgesia following arthroscopic knee surgery may be obtained with the use of intra-articular morphine or clonidine that is better than local anesthetic alone (Stein et al., 1991; Dalsgaard et al., 1994; Gentili et al., 1996; Kanbak et al., 1997; Cepeda et al., 1997). Keeping a tourniquet inflated for 10 minutes after administering intra-articular morphine provides superior analgesia and decreases the need for supplemental analgesics compared to patients in whom the tourniquet is released immediately after injecting morphine into the joint (Whitford et al., 1997). Some questions remain about the efficacy of intra-articular morphine following knee surgery although the preponderance of the literature supports its use (Christensen et al., 1996). The use of ice or a "Cryo/Cuff" device following knee arthroscopy will help to control both pain and swelling (Whitelaw et al., 1995).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	The use of a combined sciatic and femoral nerve block provides good surgical conditions and prolonged analgesia.	Sansone et al., 1999	II-3	B
2	Prolonged analgesia that is better than local anesthetic alone may be obtained with the use of intra-articular morphine or clonidine.	Stein et al., 1991 Dalsgaard et al., 1994 Gentili et al., 1996 Kanbak et al., 1997 Cepeda, 1997	I I I I I	A A A A A
3	Keeping a tourniquet inflated for 10 minutes after administering intra-articular morphine provides superior analgesia and decreases the need for supplemental analgesics.	Whitford et al., 1997	I	A
4	The preponderance of the literature supports the use of intra-articular morphine following knee surgery.	Christensen et al., 1996 (Article is an example of reference for this statement.)	I	A
5	Ice or a “Cryo/Cuff" device will help to control both pain and swelling following arthroscopy.	Whitelaw et al., 1995	I	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES

Amputation

Type of Pain:
Postoperative pain following amputation of an extremity is both nociceptive and neuropathic in nature.

Severity/Duration:
Pain following amputation is generally moderate to severe in intensity and may last from days to years.

Interventions:
Postoperative pain control following amputation may be provided with a variety of techniques. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Interscalene brachial plexus blocks
- Supraclavicular brachial plexus blocks
- Infraclavicular brachial plexus blocks
- Axillary brachial plexus blocks
- Upper extremity peripheral nerve blocks
- Lumbar plexus blocks
- Femoral nerve blocks
- Fascia iliac blocks
- Ankle blocks
- Sciatic nerve blocks
- Popliteal nerve blocks
- Direct peripheral nerve local anesthetic infusions
- Oral, intravenous, intramuscular, and IV PCA opioids
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics

Considerations:
If patients have preoperative pain, aggressive preoperative intervention to reduce pain perception has been theorized to reduce the incidence of phantom limb pain postoperatively. Preoperative infusions of local anesthetic alone or local anesthetic with opiate and/or clonidine may be useful in minimizing postoperative phantom limb pain (Bach et al., 1988; Jahangiri et al., 1994). This intervention remains controversial, as available studies do not produce consistent results. Some studies using preoperative infusions have not demonstrated any benefit (Nikolajsen et al., 1997; Elizaga et al., 1994). This may reflect the lack of uniform techniques or the variety of conditions leading to a need for amputation. Patients receiving preoperative, intraoperative, and postoperative epidural bupivicaine and morphine did not have any reduction in hyperalgesia, allodynia, or wind-up-like pain at one week or six months when compared to patients receiving epidural bupivicaine and morphine postoperatively alone (Nikolajsen et al., 1997). Postoperative infusions of local anesthetic along the sciatic or posterior tibial nerve are a safe and effective method for the relief of postoperative pain but do not prevent residual or phantom limb pain in patients undergoing amputation because of ischemic changes secondary to peripheral vascular disease (Pinzur et al., 1996). Postoperative infusion of local anesthetic into nerve sheaths provides excellent postoperative analgesia following upper extremity amputation, but does not affect long term phantom limb pain (Enneking et al., 1997; Iacono et al., 1987).

In patients with a significant component of phantom limb pain, tricyclic antidepressants or antiseizure medications may need to be initiated in the postoperative period (Baron et al., 1998).

If an epidural was utilized preoperatively or intraoperatively, it may be continued for postoperative pain control. TENS treatment of below-knee amputation (BKA) is not supported (Finsen et al., 1988).

Patients are typically capable of conversion to oral analgesics within two to three days following their operation.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Preoperative infusions of local anesthetic alone or local anesthetic with opiate and/or clonidine may be useful in minimizing post-operative phantom limb pain.	Jahangiri et al., 1994 Bach et al., 1988	I I	B B
2	Some studies using preoperative infusions have not demonstrated any benefit.	Nikolajsen et al., 1997 Elizaga et al., 1994	I I	D D
3	Patients receiving preoperative, intraoperative, and postoperative epidural bupivicaine and morphine had outcomes similar to patients receiving epidural bupivicaine and morphine postoperatively alone.	Nikolajsen et al., 1997	I	D
4	Postoperative infusions of local anesthetic along the sciatic or posterior tibial nerve are a safe and effective method for the relief of postoperative pain but do not prevent residual or phantom limb pain.	Pinzur et al., 1996 Pinzer letter	I III	A C
5	Postoperative infusions of local anesthetic into nerve sheaths provide excellent postoperative analgesia following upper extremity amputation, but do not affect long term phantom limb pain.	Enneking et al., 1997 Iacono et al., 1987	II-3C Review paper; not rated	
6	In those patients with a significant component of phantom limb pain, tricyclic antidepressants or anti-epileptic medications may need to be initiated in the postoperative period.	Baron et al., 1998		
7	TENS treatment of BKA is not supported.	Finsen et al., 1988	I	D

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES

Shoulder – Open Rotator Cuff Repair or Arthroscopic Sub-acromial Decompression

Type of Pain:
Extensive shoulder surgery causes pain that is nociceptive in nature.

Severity/Duration:
Extensive shoulder surgery causes pain that is moderate to severe and lasts for weeks.

Interventions:
Pain control following shoulder surgery may be achieved using a variety of techniques. These include the following:

- Epidural analgesia
- Interscalene brachial plexus blocks
- Supraclavicular brachial plexus blocks
- Intra-articular injections
- Wound or joint infusions of local anesthetics
- Oral, intravenous, intramuscular, and IV PCA opioids
- NSAIDs
- Acetaminophen
- Agonist-antagonist analgesics
- Ice

Considerations:
Most of shoulder surgery operations are currently performed on an outpatient basis. Reasons for unanticipated hospital admission include poorly controlled pain, nausea, vomiting, or sedation. Using techniques that minimize the need for centrally acting drugs will help to minimize undesirable side-effects and the need for unplanned hospital admission (D'Alessio et al., 1995). Using NSAIDs as a part of the postoperative pain management plan following subacromial decompression significantly reduces the need for additional analgesics (Hoe-Hansen & Norlin, 1999).

Many centers routinely do these operations with regional anesthetics, with postoperative analgesic effects lasting up to 24 hours. Regional anesthesia can be utilized as a sole anesthetic or in combination with a general anesthetic to provide postoperative pain control (Al-Kaisy et al., 1998). Regional analgesic techniques may be either single shot, continuous infusion, or patient-controlled. Regional anesthetic blocks may be performed either preoperatively or postoperatively and provide improved pain control as compared to opioid analgesics alone (Borgeat, 2000; Borgeat et al., 1998; Lehtipalo et al., 1999). Suprascapular nerve blocks may provide a significant degree of postoperative analgesia (Ritchie et al., 1997). The addition of opioid analgesics to local anesthetics for interscalene block does not improve the quality or duration of analgesia as compared to local anesthetics alone (Flory et al., 1995). The addition of clonidine or the mixed agonist-antagonist opioid compounds to local anesthetic has been shown to prolong analgesia for brachial plexus blocks.

Patients may be sent home with pain pumps that deliver local anesthetic into the wound or along nerve bundles, in addition to oral medications and instructions to use ice to minimize pain and swelling (Savoie et al., 2000).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Techniques that minimize the need for centrally acting drugs will help to minimize undesirable side-effects and unplanned hospital admission.	D'Alessio et al., 1995	III	B
2	NSAIDs following subacromial decompression significantly reduce the need for additional analgesics.	Hoe-Hansen & Norlin, 1999	I	A
3	Regional anesthesia can be utilized as a sole anesthetic or in combination with a general anesthetic to provide postoperative pain control.	Al-Kaisy et al., 1998	I	A
4	Regional anesthetic blocks may be performed either preoperatively or postoperatively and provide improved pain control as compared to opioid analgesics alone.	Borgeat, 2000 Lehtipalo et al., 1999 Borgeat et al., 1998	I I I	A B A
5	Suprascapular nerve blocks may provide a significant degree of postoperative analgesia.	Ritchie et al., 1997	I	A
6	The addition of opioid analgesics to local anesthetics for interscalene block does not improve the quality or duration of analgesia as compared to local anesthetic alone.	Flory et al., 1995	I	E
7	Patients may be sent home with pain pumps that deliver local anesthetic into the wound or along nerve bundles in addition to oral medications and instructions to use ice to minimize pain and swelling.	Savoie et al., 2000	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

SURGERY OF EXTREMITIES/VASCULAR SURGERY

Vascular Surgery

The vast majority of vascular surgical procedures involve the neck, abdomen, or lower extremities. Vascular bypass procedures to the upper extremities are relatively uncommon.

Type of Pain:
Vascular bypass procedures of the extremities produce pain that is nociceptive in nature.

Severity/Duration:
Vascular surgery pain is mild to moderate in intensity and lasts days to weeks. Patients may continue to have ischemic pain in nonperfused areas.

Interventions:
Postoperative pain control for vascular surgery can be obtained by using a variety of techniques. Post-operative pain control for the neck and abdomen are covered in other areas of this document.

There are a wide variety of techniques for pain control for the lower extremities following vascular surgery. These include the following:

- Epidural analgesia
- Intrathecal analgesia
- Lumbar plexus blocks
- Femoral nerve blocks
- Fascia iliaca blocks
- Saphenous nerve blocks
- Sciatic nerve blocks
- Popliteal nerve blocks
- Oral, intravenous, intramuscular, and IV PCA opioids
- TENS
- NSAIDs
- Acetaminophen
- Mixed agonist-antagonist opioid analgesics

Considerations:
These patients are frequently anticoagulated in the perioperative period. Therefore, close cooperation with the surgeon is required to utilize a regional anesthetic/analgesic. This is especially pertinent when removing a catheter used to provide intrathecal or epidural analgesia for postoperative pain control. Guidelines have been published (ASRA, 1998) to help minimize the risks associated with neuraxial anesthetic and analgesic techniques in the presence of perioperative anticoagulation.

Supplementing conventional opioids with an epidural infusion of local anesthetic may benefit vascular surgery patients by decreasing the incidence of thromboembolism and graft occlusion after vascular bypass surgery. In addition, the use of regional anesthesia intraoperatively and postoperatively has been associated with decreased morbidity and mortality following vascular surgical procedures (Tuman et al., 1991; Christopherson et al., 1993; Rodgers et al., 2000). Peripheral nerve blocks may be used to provide superior analgesia following femoropopliteal bypass as compared to IV PCA alone (Griffith et al., 1996).

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	The use of regional anesthesia intraoperatively and postoperatively has been associated with decreased morbidity and mortality following vascular surgical procedures.	Tuman et al., 1991 Christopherson et al., 1993 Rodgers et al., 2000	I I I	A C A
2	Peripheral nerve blocks may be used to provide superior analgesia following femoropopliteal bypass as compared to IV PCA alone.	Griffith et al., 1996	I	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

OPTIONS FOR POSTOPERATIVE PAIN MANAGEMENT: NON-PHARMALOGIC MANAGEMENT

Version 1.2

NON-PHARMACOLOGIC MANAGEMENT

COGNITIVE MODALITIES

INTRODUCTION

Cognitive modalities, such as distraction, relaxation and hypnosis, have been successfully utilized as adjuncts to other analgesic interventions in the perioperative period.

These non-pharmacologic interventions have the ability to improve analgesia without producing side effects or limiting the application of other techniques. This gives them the potential for application in a wide variety of settings. In addition, addressing other issues, such as anxiety that may or may not be adequately treated with traditional pharmacologic methods of pain control, may improve overall patient satisfaction.

Although the data available to define the appropriate settings for the use of cognitive modalities is limited, the potential benefit and minimal downside risks for these techniques means that they should be considered without hesitation.

DISTRACTION, RELAXATION

Distraction and relaxation training are useful as an adjunct to analgesic interventions. Many relaxation techniques are available (McCaffery & Beebe, 1989; Williams, 1996). Biofeedback—assisted relaxation—uses an external device to help the patient learn to relax specific muscle groups. Distraction can include music and imagery (Good et al., 1999; Bruehl et al., 1993). Relaxation/distraction techniques have been widely evaluated (Good, 1996; Seers & Carroll, 1998) and do not have to be complex to be effective.

Since evidence does not favor one strategy over others in postoperative pain management, patients should be provided information about different relaxation or distraction techniques and assisted in choosing the strategy that they are most motivated to learn and practice.

Advantages:

- No prior patient training is required, but for optimal results, distraction and relaxation techniques training should be initiated preoperatively to allow the patient to practice.
- Relaxation techniques may benefit the patient by reducing muscular arousal and distracting from painful sensations. They also reduce anxiety and increase the patient's sense of control.
- Distraction skills and relaxation techniques can be practiced at home and used in any clinical setting.
- Strategies, such as breathing techniques, can be taught in only 10 to 15 minutes, but do require periodic social reinforcement through encouragement and coaching.
- These strategies are appropriate for most patients but may be of special use in situations with a patient who expresses interest in learning them; has anxiety; expresses a wish to reduce or limit analgesic medications; or who should learn skills in anticipation of prolonged pain.

Disadvantages:

- Biofeedback training requires special equipment and more extensive clinician training.
- Better benefit is achieved when patients are taught strategies prior to the operative procedure (Morgan et al., 1985).

Complications:

- If planned in conjunction with patient preferences, there should be no complications associated with the cognitive modalities (Turk & Okifuji, 2000).

Contraindications:

- Cognitive modalities require that patients understand the information and instructions involved in the use of various treatments. These modalities will be inappropriate for use with patients who are significantly cognitively impaired and unable to comprehend the information included with the cognitive modalities (e.g., comatose patients, certain stroke patients, patients who have difficulty with the language of the person available to offer the treatments).
- Cognitive therapies require cooperation and practice. These interventions would be contraindicated for use with patients who are uncooperative, unable, or unwilling to practice the necessary behaviors required for successful use of cognitive modalities (Melzack et al., 1980; Turk et al., 2000).

EVIDENCE TABLE

	Intervention	Source of Evidence	QE	R
1	Distraction and relaxation techniques are useful as adjuncts to analgesic interventions.	Good, 1996 Seers & Carroll, 1998 Bruehl et al., 1993 Good et al., 1999	III III I I	A A A A
2	Distraction techniques have shown benefit in relief of postoperative pain in : • Abdominal operation • Hysterectomy • Coronary artery bypass graft • Chest tube removal	Good et al., 1999 Broscious, 1999 Madden et al., 1978 Miro & Raich, 1999 Zimmerman et al., 1996	I I I I I	A A A A A
3	Better benefit is achieved when patients are taught strategies prior to the operative procedure.	Morgan et al., 1985	III	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HYPNOSIS

Hypnosis is a state of focused attention with a reduction of external awareness and a suspension of critical judgment. Contrary to popular belief, hypnosis does not imply suggestibility but rather the ability to focus attention to the exclusion of other stimuli. There are several mechanisms on which hypnosis is thought to have its beneficial effect.

Advantages:

- May decrease perioperative pain
- May reduce analgesic and sedative requirements
- May decrease postoperative anxiety
- Improved patient satisfaction
- Takes seconds to minutes to achieve entrance to a hypnotic state

Disadvantages:

- Requires a professional trained in hypnosis
- May not work for all patients
- Social stigma associated with its use

DISCUSSION

Most data on hypnosis for perioperative pain are from case reports. The few randomized controlled trials have conflicting results on efficacy, though risks associated with its use appear to be minimal. In at least one well-designed randomized, placebo-controlled trial, hypnosis was associated with improvements in pain and anxiety, reduction in analgesic requirements, and greater patient satisfaction (Faymonville et al., 1997). Further study is needed to clarify its exact role in the management of postoperative pain.

EVIDENCE TABLE

	Intervention	Source of Evidence	QE	R
1	Hypnosis was associated with improvements in pain and anxiety, reduction in analgesic requirements, and greater patient satisfaction	Faymonville et al., 1997	I	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

NON-PHARMACOLOGIC MANAGEMENT

PHYSICAL MODALITIES

INTRODUCTION

Physical modalities, such as TENS, heat, cold, exercise, positioning, immobilization/rest, massage and acupuncture, have all been applied to provide patient comfort during the perioperative period. Each of these techniques has a limited set of indications and often some definite contraindications.

Physical modalities may be beneficial in the treatment of primary postoperative pain or in relieving discomfort associated with positioning during surgery and immobilization/rest. In general, these techniques do not provide the primary means of providing postoperative analgesia, but often serve as useful adjuncts that augment the effects of other analgesic techniques or decrease the amount of medications required to provide analgesia.

There are many postoperative pain settings in which the use of physical modalities has not been examined. However, their ability to contribute to the patient's general well being, facilitate exercise in the perioperative period and their lack of systemic side effects means that they should be considered whenever they are available. Expanded use and future research will help to better define their application for perioperative pain control in the future.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

TENS is a method of producing electro-analgesia through the spinal cord gating mechanism. An electrical impulse is conducted through electrodes applied to the skin. TENS has been used as an effective adjunct for providing postoperative pain control. TENS facilitates movement and exercise by decreasing pain perception and improving physical functioning (Wall & Melzack, 1989; Bonica, 2001).

Advantages:

- Relatively rapid onset (30-60 minutes)
- Patient-controlled features
- Absence of appreciable side effects

Disadvantages:

- Requires special equipment
- Requires skilled personnel for patient instruction
- May cause burns if used inappropriately
- May cause skin irritation

Considerations:

- Requires the active involvement, understanding and cooperation of the patient

Contraindications:

- Cognitive impairment
- Should not be used near demand-type cardiac pacemakers, over a pregnant uterus, carotid sinus, laryngeal or pharyngeal muscles, or around the eye

EVIDENCE TABLE

	Intervention	Source of Evidence	QE	R
1	TENS is effective for pain management in postoperative conditions.	Gersh, 1992 Carroll et al., 1996 Mannheimer & Lampe, 1984	III III III III	A C A A
2	TENS is effective over incision sites.	Tyler et al., 1982	III	B
3	TENS is effective for hand operations.	Bourke et al., 1984	III	A
4	TENS is effective for thorocotomy.	Warfield et al., 1985	III	A
5	TENS is effective for oral facial pain.	Hansson et al., 1986	III	A
6	TENS is effective for abdominal pain.	Hamza et al., 1999 Chen et al., 1998 Hymes et al., 1974 Cooperman et al., 1977 Ali et al., 1981	I I I I III	A A B B A
7	TENS is effective for post-cesarean section.	Smith et al., 1986	III	A

	Intervention	Source of Evidence	QE	R
8	TENS is effective for pain for total hip replacements.	Pike, 1978	III	A
9	TENS is effective for knee replacements.	Sabile & Mallory, 1978	I	B
10	TENS is effective for shoulder pain.	Bruzga & Speer, 1999	III	B
11	TENS is effective for pain from cholecystectomy.	Rosenberg et al., 1978	I	A
12	TENS is effective for pain from lumbar spine.	Solomon et al., 1980	III	A
13	TENS is effective for pain from foot surgery.	Cornell et al., 1984	I	B
14	TENS is effective for use in combination with exercise for pain.	Harvie, 1979	II-2	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

COLD

Cold, or cryotherapy, is the application of cold for therapeutic effects. Cooling agents may include cold packs, cold baths, vapocoolant sprays, cold compression, continuous-flow cold therapy, and ice massage. Cold alters the pain threshold, reduces local swelling, decreases tissue metabolism and/or bleeding, and decreases muscle spasm and spasticity (Wall & Melzack, 1989; Bonica, 2001).

Advantages:

- Easy to apply

Disadvantages:

- Prolonged exposure may cause injury
- Patient discomfort
- Can be complicated to apply

Considerations:

- Use with caution in patient with sensory deficit (e.g., neuropathy, spinal cord injury)

Contraindications:

- Decreased level of consciousness
- Patient's inability to provide feedback about his/her tissue temperature
- Hypersensitivity to cold (i.e., Raynaud's phenomenon)
- Marked hypertension
- Arteriosclerosis
- Diminished circulation

EVIDENCE TABLE

	Intervention	Source of Evidence	QE	R
1	Can increase pain threshold, reduce local swelling, decrease tissue metabolism and/or bleeding, and decrease muscle spasm and spasticity.	Wall & Melzack, 1989 Bonica, 2001	III III	A A
2	Effective for knee pain.	Barber et al., 1998 Brandsson et al., 1996 Webb et al., 1998 Lessard et al., 1997 Brown, 1996 Cohn et al., 1989 Levy & Marmer, 1992 Healy et al., 1994	I I I I III I I I	A A B B B B A A
3	Effective for shoulder pain.	Speer et al., 1996 Bruzga & Speer, 1999	III III	A B
4	Effective for perineal pain.	Steen et al., 2000	I	A
5	Effective for incisional pain.	Hargreaves & Lander, 1989	I	A

	Intervention	Source of Evidence	QE	R
6	Effective for dental pain.	Bastian et al., 1998 Melzack, 1980	I I	A A
7	Effective for thoracotomy.	Seino et al., 1985	III	A
8	Use is recommended as an adjunct to other treatments, especially compression.	Moore & Cardea, 1977 Basur et al., 1976	III III	A A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

HEAT

Heat can usually be initiated 48 hours following the operation, and is commonly used in combination with other treatments (AHCPR,1992). Thermal agents are used to apply heat superficially or as deep heating applications. Superficial methods include hot packs, warm whirlpools and paraffin. Deep heat, such as ultrasound, can increase the temperature of the tissues three to five centimeters in depth (Wall & Melzack, 1989; Bonica, 2001).

Advantages:

- Induces relaxation
- Decreases joint stiffness, muscle spasm, and guarding
- Assists in increasing range of motion
- Increases superficial circulation

Disadvantages:

- Increased swelling or bleeding at surgical site when applied
- Prolonged exposure may cause injury or burns.

Considerations:

- Monitor patient's physical response.
- Use with caution in patient with sensory deficit (e.g., neuropathy, spinal cord injury).
- Use of deep heat, such as ultrasound, can increase the temperature of tissues three to five centimeters in depth.

Contraindications:

- Decreased level of consciousness
- Inability to provide feedback about tissue temperature
- Acute injuries less than two days
- Inflammation
- Superficial or skin infection
- Hemorrhage
- Over site of malignancy

EVIDENCE

	Intervention	Source of Evidence	QE	R
1	Technique should be initiated 48 hours following the operation and used in combination with other treatments.	AHCPR, 1992	III	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

EXERCISE

Exercise may include active or passive range of motion, continuous passive motion machine (CPM), active exercise, bed mobility, or ambulation, e.g., getting out of bed and walking to the bathroom. Exercise can increase or maintain range of motion, increase blood flow, and prevent muscle guarding, spasms, and contractures (Wall & Melzack, 1989; Bonica, 2001).

Advantages:

- Assists with edema management
- Reduces risk of venous thrombosis after surgery (Mc Nally et al., 1997; Sochart et al., 1999)

Disadvantages:

- May require patient education and instruction by skilled staff
- May require the use of assistive devices, e.g., walkers, crutches, etc.

Considerations:

- Effectiveness could be limited by weight bearing status.
- Exercise may cause exacerbation of existing postoperative pain.
- Patient with motor blockade from other therapies may need assistance.

Contraindications:

- Immobilization
- Extremity with known deep venous thrombosis should not be exercised.

EVIDENCE TABLE

	Intervention	Source of Evidence	QE	R
1	Exercise reduces the risk of venous thrombosis after surgery.	Mc Nally et al., 1997 Sochart & Hardinge, 1999	I I	A B
2	Effective for management of knee pain.	Campbell, 1990 Brown, 1996 Morris, 1995 McCarthy et al., 1993 Smidt et al., 1990 Walsh, 1980 Paulos et al., 1980 Andrews, 1980 Coutts et al., 1989	III III III I III III III III III	B B C A C A A A B
3	Effective for shoulder pain.	Bruzga & Speer, 1999	III	B
4	Effective for discectomy pain.	Danielson et al., 2000 Deyo, 1983	I III	A B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

POSITIONING

Positioning is used to support or assist the patient. It may be accomplished with pillows, wedges, supports, specialty beds, and weight shifting. Repositioning increases blood flow and prevents muscle guarding and spasms, which reduces acute pain or prevents additional pain (Lerner et al., 1998).

Advantages:

- Prevents formation of decubitus ulcers
- Prevents pressure injuries and contractures

Disadvantages:

- May require specialized equipment

Considerations:

- Repositioning should be done every two hours (AHCPR, 1992), with assistance if necessary.

Contraindications:

- Necessity for immobilization

EVIDENCE

	Intervention	Source of Evidence	QE	R
1	Technique should be done every two hours, with assistance if necessary.	AHCPR, 1992	III	A

QE-= Quality of Evidence; R = Recommendation (See Appendix A)

IMMOBILIZATION/REST

Patients may be immobilized, as in casting, traction, or prescribed bed rest. Immobilization facilitates the healing process after the operation, but is not recommended as a sole intervention for pain control. An example of immobilization would be for a fracture, rest, or back surgery. Immobilization may reduce edema.

Advantages:

- May assist in the healing process and prevent further trauma to an area

Disadvantages:

- Increased risk for deep venous thrombosis
- Extended use of rest, without mobilization, may lead to stiffness, contracture, atrophy, weakness, pneumonia, thrombophlebitis, or increased pain.
- Potential for pressure ulcers

Considerations:

- Bed rest may be indicated for a limited time period, less than two days (Quebec Task Force, 1981; Deyo, 1983).

EVIDENCE

	Intervention	Source of Evidence	QE	R
1	Bed rest	Quebec Task Force, 1981	II-2	E
2	Limited period of time, less than two days.	Deyo, 1983	III	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

MASSAGE

Massage is the repetitive movements of the therapist's hands or the use of devices such as effleurage, petrissage, tapotement, and friction. A medium may be used on the skin such as lotions, oil, powder or ice. Massage may be used to stretch muscle length and is usually used in combination with other treatments (Wall & Melzack, 1998; Bonica, 2001).

Advantages:

- Effective in general pain management (Quebec, 1981; Jurf et al., 1993; Heffline, 1990)
- Mechanically assists in venous and lymphatic flow
- Improves skin integrity and mobility
- Desensitizes tissue
- Provides comfort and psychological support

Disadvantages:

- Personnel and time intensive

Contraindications: (Relative)

- Skin graft
- Hematoma
- Infection
- Malignancy
- Pleural effusion
- Liver or kidney disease
- Congestive heart failure
- Carotid disease
- Deep venous thrombosis

EVIDENCE

	Intervention	Source of Evidence	QE	R
1	Massage is beneficial as adjunct treatment for general pain management.	Quebec Task Force, 1981 Jurf & Nirschl, 1993 Heffline, 1990	II-2 III III	E C C

QE = Quality of Evidence; R = Recommendation (See Appendix A)

ACUPUNCTURE

Acupuncture might be considered an option in control of postoperative pain in general (National Institutes of Health, 1997).

- Pre-emptive use of acupuncture during standard anesthesia had no effect on postoperative pain following knee arthroscopy (Gupta et al., 1999). Complementary therapy using acupuncture in combination with conventional pharmacological interventions may lower the need for medication and reduce the risk for side effects from these drugs (NCCAM, 1999).

Adverse reactions to acupuncture are rare. However, serious side effects have been reported, and treatment should be administered by a medically trained and licensed acupuncture practitioner (Rosted, 1997).

Advantages:

- Relief of postoperative nausea and vomiting
- Relief of postoperative dental pain

Disadvantages:

- Complications associated with improper needle use and management, e.g., self-manipulation of needle, broken needle
- Few RCTs to clarify the definitive role of acupuncture in the management of acute postoperative pain

Considerations:

- Use of proper infection-control measures
- Administration by a medically trained and licensed acupuncture practitioner

Contraindications:
Absolute:

- Patient refusal
- Anticoagulation
- Decreased level of consciousness
- Infection at site
- Pacemaker (for electro-acupuncture [Rosted, 1997])

Relative

- Cognitive impairment
- Bleeding disorder
- Patient fear of needles

DISCUSSION

There are few RCTs on the role of needle acupuncture in the management of postoperative pain. Even with respect to control of dental pain following surgery, the data are conflicting (Mayer, 2000). The consensus statement, based on clinical experience and limited research data, indicated that acupuncture could be considered a treatment option in postoperative pain (National Institutes of Health, 1997). This has been shown in pain relief following ablation and auxiliary lymphadenectomy in patients with breast cancer. In this study, patients also had increased range of arm motion without pain when compared with controls (He et al., 1999).

Acupuncture is considered a safe therapeutic modality with rare serious side effects and complications. In a review of complications published between 1965-97 (Rosted, 1997), many of the complications were avoidable. For example, complications are associated with:

- Self-insertion of needles
- Migration of broken needles
- Infection due to length of time the needle is in place
- Self-manipulation of needles
- Use of improper infection control measures
- Electroacupuncture in the setting of a pacemaker
- Improper technique in the use of excessively long needles
- Inaccurate needle placement
- Lack of medical training of the acupuncturist including knowledge of anatomy

In the United States, the FDA has addressed the issue of safety in the approval of acupuncture needles for use by licensed, registered or certified practitioners and manufacturing standards to include sterility of the product and approval for single use only. A listing of medical acupuncturists for each state can be obtained through the American Academy of Medical Acupuncture at http://www.medicalacupuncture.org/

EVIDENCE

	Intervention	**Source of Evidence**	**QE**	**R**
1	May reduce nausea and vomiting if used in early postoperative period.	NIH, 1997 Mayer, 2000	III III	B B
2	Acupuncture, in combination with pharmacological interventions, may lower the need for medication and reduce the risk for side effects from these drugs.	NCCAM, 2001	III	C

QE = Quality of Evidence; R = Recommendation (See Appendix A)

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

OPTIONS FOR POSTOPERATIVE PAIN MANAGEMENT: PHARMACOLOGIC MANAGEMENT

Version 1.2

Pharmacologic Management

How to use this section:

This section of the guideline includes information and recommendations about medications used in acute pain management. The pharmacologic options for pain control include four major classes of medications. Preceding the classes of medication is an overview of routes of administration commonly used in postoperative pain management.

This section is organized in the following sequence to facilitate efficient reference by the clinician:

A. Overview of the routes of administration commonly used in applying medication for pain control
B. Opioids
C. Acetaminophen and NSAIDs
D. Local anesthetics
E. Glucocorticoids

The information about each of the medication classes includes the following:

- Overview of the medication class
- Summary table for site-specific indications for pain management for the medication class
- Mechanisms of action, contraindications and considerations
- Specific agents, detailing dosing and pharmacokinetic information
- Drug interactions
- List of references

ROUTES OF ADMINISTRATION

ORAL

Oral (PO) medication is the most common method of pain control. The advantages of safety, simplicity, ease of administration, and economy can be overwhelmed by the needs of the postoperative patient requiring application of more advanced techniques.

Advantages:

- Ease of delivery; patient can self-medicate
- Can continue at home—longer term
- Tablet or liquid application
- Simple and easy to understand

Disadvantages:

- More likely for clinician to under-dose
- Patient must be able to absorb the medication
- Slower onset
- Harder to titrate

Considerations:

- Because this route requires absorption through the gastrointestinal (GI) tract, it may not be appropriate for patients with difficulty swallowing or with airway obstruction.

Contraindications:

- Allergy to the medication being used
- Medication incompatibility

INTRAMUSCULAR (IM)

The most common use of IM pain control is for patients who are hospitalized for major surgical procedures, or for outpatients prior to discharge. This technique is successfully used to control moderate to severe pain in all regions of the body. Commonly used IM medications include NSAIDS, opioids, mixed opioid agonist-antagonists and opioid-antihistamine combinations.

IM has been the most common route of administration for postoperative pain. Due to the variable absorption and the time and staff necessary to administer, other routes are preferred. Ideally, patients with moderate to severe postoperative pain should receive pain medication through the IV route.

Advantages:

- More rapid onset
- Works for people who can't self-medicate or take oral medication

Disadvantages:

- Variable absorption
- Labor-intensive
- Pain on injection

Considerations:

- Patients receiving IM are also at risk of peripheral nerve injury.
- Possible infection or sterile abscess

Contraindications:

- Patients with known bleeding disorders (relative) or those who are being actively anticoagulated (absolute)
- Allergy to the medication being used

INTRAVENOUS (IV)

IV drug administration has distinct advantages over other routes of administration, providing better efficacy at lower doses.

Advantages:

- Wide variety of medications available
- Reliable delivery with 100 percent rapid absorption
- More rapid onset and increased potency, allowing for decreased total drug dose

Disadvantages:

- Requires the presence of an IV catheter
- Requires a qualified individual to deliver the drug
- Needs appropriate monitoring and is highly labor-intensive
- Relies on a qualified caregiver to administer the dose. This can result in use of relatively larger doses that produce side effects, including excessive sedation alternating with periods of inadequate analgesia.
- Associated with anxiety on the part of the patient who wonders when the provider will return to deliver more medication

Considerations:

- Inappropriate dose
- Medication toxicity/side effects

Contraindications:

- Allergy to the medication being used

INTRAVENOUS PATIENT CONTROLLED ANALGESIA (IV PCA)

The development of IV PCA has advanced the delivery of IV medications. Patients are capable of self-administering drugs in adequate doses that produce better pain control.

Advantages:

- Higher patient satisfaction
- Decreased drug use
- Decreased side effects
- Decreased labor-intensity
- Allows the provision of low dose basal infusion to minimize the return of pain while patients are sleeping

Disadvantages:

- Requires the presence of a functioning IV
- Requires knowledgeable staff to program it
- Requires an IV PCA device

Considerations:

- Overdose
- Delivery of the wrong drug, replacing a medication cartridge with the wrong concentration or mis-programming the device
- Patient misuse
- Use by someone other than the patient that may result in excessive dosage beyond the patient's requirement
- Basal infusion for IV PCA is optional. Some evidence exists that a basal infusion offers no advantages and may increase adverse effects; routine use of basal infusions are not recommended for acute pain management by some authors.

Contraindications:

- Patients with mental or physical inability to activate the device (absolute)
- Patients with reluctance to assume responsibility over analgesic administration (relative)
- Allergy to the medication being used

REGIONAL

Regional analgesia is a preferred method of providing postoperative pain control to a specific area of the body. This technique can also be used as the anesthetic for the operation either solely or in combination with other anesthetic techniques. Regional analgesia ranges from local wound or joint infiltration to specific peripheral nerve blocking techniques affecting specific regions of the body. Examples include: interscalene block, lumbar plexus block, Bier's block, intercostal block, paravertebral block, ankle block, sciatic nerve block, popliteal block, and incisional infiltration.

Patient outcomes are improved with better pain control using these techniques compared to other methods of pain control. The role of regional anesthesia/analgesia in the production of preemptive analgesia remains controversial. Several clinical studies have demonstrated benefit in the perioperative period following regional anesthesia/analgesia initiated prior to surgical incision. These benefits include decreased pain immediately after the operation and well into the recovery period. Some of the beneficial effects may last beyond the duration of the anesthetic/analgesic technique.

Advantages:

- Allows for decrease in, or elimination of, systemic analgesics by limiting the analgesia to a region of the body
- Allows for earlier discharge of ambulatory surgery patients due to the minimized use of systemic analgesics (opioids) improved pain control, and decreased incidence of associated side-effects. These techniques can be done as a single injection or continuously.

Disadvantages:

- Requires knowledgeable providers capable of performing a wide variety of techniques in a reliable and timely manner
- Limited duration of action if a single administration is used—patients may require a combination of other modalities
- Requires specialized equipment
- Produces a short period of irreversibility, limiting physical examination

Considerations:

- Block failure to provide analgesia
- Local anesthetic toxicity
- Injection of medication intravascularly, epidurally, or intrathecally leading to respiratory compromise or cardiovascular collapse
- Bleeding
- Hematoma
- Neurologic injury
- Pneumothorax
- Organ injury
- Infection

Contraindications:

- Patient refusal to undergo procedure (absolute)
- Failure to obtain consent (absolute)
- Patients who are anticoagulated (absolute)
- Infection at the site of proposed needle insertion (absolute)
- Allergy to medication being used in technique (absolute)
- Altered anatomy (relative)
- Bleeding disorders (relative)
- Inability to communicate (relative)
- Patients with peripheral neurologic diseases (relative)

EPIDURAL

Epidural is one of the techniques used to provide regional anesthesia/analgesia. It is widely used and accepted, but requires skilled providers and institutional commitment for optimal benefit. Epidural technique can improve analgesia using decreased doses of opioids to provide equal analgesia as compared with IM, PO, and IV, because medication is delivered to opioid receptors in the dorsal horn of the spinal cord.

Advantages:

- Places medication near site of action
- Decreases side effects
- Can be used as the anesthetic for the operation
- Provides improved active pain control with movement as compared to other techniques. This is especially true when local anesthesia is used and the catheters are placed at the appropriate level of the incision (e.g., thoracic epidural for thoracotomy).
- Increases blood flow below the level of analgesia; may improve graft survival
- Is usually a continuous technique
- Improves return of bowel function
- Can be used for extended periods of time postoperatively

Disadvantages:

- Requires knowledgeable and competent providers to perform procedure in a reliable and timely manner
- Requires specialized equipment
- Requires high-level supervision and monitoring
- If local anesthesia is used with epidural infusion, it may produce weakness from unwanted motor blockade, hypotension, or urinary retention that may require bladder catheterization.
- If opioids are used in epidural infusion, they may produce sedation or respiratory depression, nausea, vomiting and pruritis.
- Interference with neurologic monitoring

Considerations:

- Post-dural puncture headache
- Infection, including meningitis
- Epidural hematoma with risk of paralysis
- Arachnoiditis
- Respiratory compromise and cardiovascular collapse with overdose
- Inadvertent administration of inappropriate medication (drugs that should not be in the spinal canal)

Contraindications:

- Allergy or medication toxicity (absolute)
- Failure to obtain consent (absolute)
- Patient refusal (absolute)
- Anticoagulated patient (absolute)
- Infection at site (absolute)
- Hemodynamic instability (relative)
- Prior spinal surgery at site of insertion (relative)
- Spinal column abnormality (relative)
- Bleeding disorders (relative)
- Compromised cardiac function (relative)
- Inability to communicate (relative)
- Patients with peripheral neurologic diseases (relative)
- Systemic infection (relative)

SPINAL

Spinal administration is one of the techniques used to provide regional anesthesia/analgesia. It is widely used and accepted; however, it is not recommended as a continuous technique for postoperative pain management due to inherent risks involved.

Advantages:

- Improved analgesia with decreased dose of opioids to provide equal analgesia as compared with IM, PO and IV
- Places medication near site of action
- Decreases side effects
- Can be used as the anesthetic for the operation
- May be used as a single administration or continuous technique

Disadvantages:

- Requires knowledgeable providers
- Needle and/or catheter insertion is limited to the lumbar region due to the risk of potential spinal cord injury during insertion.
- Needs to be done in both a reliable and timely manner
- Requires specialized equipment
- Requires high-level supervision and monitoring
- If local anesthesia is used with spinal infusion it may produce weakness from unwanted motor blockade, hypotension, urinary retention that may require bladder catheterization.
- If opioids are used in spinal infusion they may produce sedation or respiratory depression, nausea, vomiting and pruritis. The duration of catheter insertion is limited due to the risk of developing meningitis.

Considerations:

- Post-dural puncture headache
- Infection including meningitis
- Subarachnoid hematoma with risk of paralysis
- Arachnoiditis
- Respiratory compromise and cardiovascular collapse with overdose
- Inadvertent administration of inappropriate medication
- Drug toxicity producing permanent neurologic deficit, incorrect drug administration in the presence of continuous spinal catheters
- Spinal cord or nerve injury

Contraindications:

- Allergy or medication toxicity (absolute)
- Patient refusal (absolute)
- Failure to obtain consent (absolute)
- Anticoagulated patient (absolute)
- Infection at site (absolute)
- Hemodynamic instability (relative)
- Bleeding disorders (relative)
- Prior spinal surgery at site of insertion (relative)
- Patients with peripheral neurologic diseases (relative)
- Spinal column abnormality (relative)
- Compromised cardiac function (relative)
- Inability to communicate (relative)
- Systemic infection (relative)

OPIOIDS

Opioid agents are the mainstay of postoperative analgesia. They offer safe and effective pain control and are typically used in the treatment of moderate to severe pain. Pain management with these agents should be individually tailored to patient response. There is no ceiling dose for pure agonist opioids.

Opioids should be administered by the safest and most effective route available. These agents can be used safely in conjunction with other analgesic agents and by various administration techniques. In comparison with conventional methods of administration (e.g., intermittent IM or SC injections), contemporary delivery systems (e.g., PCA) and techniques (e.g., neuraxial) help to improve postoperative pain control and patient satisfaction. The route of administration may vary throughout the peri-operative period. When selecting an appropriate route, consideration must be given to the patient's overall condition and the availability of specialized equipment and trained staff. The availability of these resources may vary between institutions.

Opioids have significant adverse effects that can be managed by modification of dose, route, or adjunctive agents. Respiratory depression should not be a concern if the appropriate dose, route, and dosing frequency are used with adequate patient monitoring.

The Working Group does not recommend the use of meperidine for postoperative pain management. Longer-acting and safer alternatives to meperidine exist. Meperidine has a relatively short duration of action and the potential for underdosing; the risk of inadequate pain management is greater with its use. Regular dosing or high doses in patients with normal or impaired renal function may result in accumulation of normeperidine, a neurotoxic metabolite, which may cause seizures. It is difficult to identify patients at risk for meperidine-induced seizures. If meperidine is indicated (e.g., for the rare patient with hypersensitivity to opioids from another class), its use should be restricted to the recovery room or limited to less than 24 hours in doses less than 600 mg / 24 hours.

Key points

- Opioids produce their analgesic effects by mimicking the actions of endogenous opioid peptides at specific opiate receptor sites in the central nervous system.
- Physiologic effects of opioids include the following:
  - Respiratory effects
  - Gastrointestinal effects
  - Cardiovascular effects
  - Genitourinary effects
  - Physiologic dependence
  - Tolerance
- Evidence indicates that there is no significant risk of addiction with short term use of opioids for postoperative pain management. Addiction is often a concern of patients and should be addressed preoperatively.
- Routes of opioid administration for postoperative pain include the following:
  - Conventional (IV / IM / SQ / PO / PR)
  - Patient controlled analgesia (PCA)
  - Neuraxial (spinal/epidural)
  - Novel (e.g., transmucosal)
- Commonly used opioids in postoperative pain include agents in the following classes:
  - Pure agonists
  - Morphine, hydromorphone
  - Meperidine, fentanyl
  - Codeine, oxycodone, and hydrocodone (e.g., in combination with acetaminophen)
  - Mixed agonists-antagonist opioid analgesics

DISCUSSION

Mechanism of opioid action and receptor types

Opioids produce their analgesic activity by mimicking the actions of endogenous opioid peptides at specific opiate receptors in the central nervous system (CNS). Endogenous opioids all contain the amino acid sequence tyr-gly-gly-phenyl. They include metenkephalin, beta-endorphin, and dynorphin. The three main types of opiate receptors, each with its own subtypes, are mu (μ, μ_1 and μ_2), delta (δ, δ_1 and δ_2), and kappa (κ, $\kappa_{1\text{-}4}$).

Most commonly used opioids, for example morphine and codeine, bind to the μ receptor. Activation at the μ_1 receptor is responsible for supraspinal analgesia, whereas μ_2-receptor activation leads to the undesired effects of respiratory depression, cardiovascular depression, and decreased gastrointestinal motility.

- The enkephalins are the primary endogenous ligands of the δ receptor and are primarily responsible for spinal analgesia. Enkephalins are found in areas not only known to be involved with nociception but also in the gastrointestinal (GI) tract, sympathetic nervous system, and adrenal medulla.
- Dynorphin is the prototypic ligand for the κ receptor. Activation of the κ receptor results in segmental spinal analgesia and sedation. Most of the mixed agonist-antagonist opioids (e.g., butorphanol) bind to the κ receptor.

Physiologic effects of opioids

Respiratory effects

All opioids depress minute ventilation by depressing the response of the brain to carbon dioxide. Opioids primarily reduce respiratory rate, although in high doses they can also depress tidal volumes. Respiratory depression, apnea and even death may occur. However, when prescribed and administered for pain in a properly monitored patient, opioids rarely cause respiratory depression. Fear of inducing respiratory depression should never be used as a reason to avoid treating pain. Opioids are also potent antitussives.

Gastrointestinal effects

Opioids universally decrease GI motility by reducing peristalsis in the small intestine and large intestine, and by increasing tone in the pyloric sphincter, ileocecal valve, and anal sphincter. Thus, opioid use is associated with constipation. These agents were first used for the treatment of diarrhea (dysentery). When these agents are prescribed for longer than 1 or 2 days, stimulant laxatives and stool softeners are necessary. Unlike other opioid-induced adverse effects, tolerance to constipation does not develop over time.

All μ-agonist opioids, including meperidine, can cause spasms of the sphincter of Oddi. This effect can be problematic in patients with pancreatitis, cholelithiasis, or sickle cell disease.

Opioids are also associated with nausea and vomiting, which are caused by the binding of opioids to receptors in the chemoreceptor trigger zone of the brainstem and by slowed GI motility. Drug treatment of nausea and vomiting differs according to the cause. If caused by stimulation of the chemoreceptor trigger zone, ondansetron, prochlorperazine, thiethylperazine or haloperidol may be helpful. If caused by slowed GI motility, metoclopramide may be helpful. Nalbuphine (a mixed opioid agonist-antagonist) or a low-dose infusion of naloxone (an opioid antagonist) are also useful in the treatment of nausea and vomiting. For nausea associated with motion (often accompanied by vertigo), dimenhydrinate may be helpful. Scopolamine patches are sometimes used for nausea associated with motion but may cause confusion.

Cardiovascular effects

Opioids have few hemodynamic adverse effects. They do not affect the contractile state of the heart or alter cardiac output. All opioids can cause dose-dependent, asymptomatic bradycardia, with the exception of meperidine, which produces tachycardia. Morphine is a vasodilator and venodilator. It affects preload and afterload by relaxing vascular smooth muscle and by releasing histamine from mast cells. These actions may produce hypotension, especially in hypovolemic (e.g., trauma) patients. Histamine release occurs to a lesser extent with codeine and meperidine, and not at all with hydromorphone, fentanyl, sufentanil or remifentanil. The hypotensive effects of the opioids can be minimized by slow infusion, keeping patients supine, and maintaining an adequate intravascular volume.

Genitourinary effects

Opioids increase the tone of the detrussor muscle of the bladder and may cause urinary retention, which may require bladder catheterization. This adverse effect may occur regardless of the route of opioid administration but is more common after neuraxial administration.

Physiologic dependence

Sudden cessation of opioid medication after continued therapy may lead to the development of abstinence syndrome or withdrawal. Symptoms include tachycardia, lacrimation, yawning, sneezing, coryza, nausea, vomiting, hypertension, restlessness, and insomnia. Physiologic dependence can develop after only 5 days of therapy. Symptoms typically occur within 24 hours and peak about 72 hours after discontinuation of opioid therapy. Tolerance and withdrawal seem to be linked. Note the difference between physiologic dependence and addiction, which is a behavioral effect of opioids (see below).

Tolerance

Continued exposure to opioids often results in the need for higher doses to achieve the same clinical effect. This phenomenon is known as *tolerance* and usually begins within 21 days after beginning opioid therapy. Shorter-acting, more lipophilic agents, such as fentanyl, may lead to tolerance faster than longer-acting, hydrophilic agents, such as morphine. On the other hand, results from animal studies suggest that tolerance develops less frequently with opioids that have high receptor affinity, such as sufentanil.

Some degree of cross-tolerance occurs between opioids, although it is incomplete. Patients who are becoming tolerant to morphine may benefit from a change to a drug with increased binding affinity, such as hydromorphone. Tolerance develops more quickly when continuous infusions, rather than intermittent boluses, are used.

Behavioral effect of opioids (addiction)

Addiction is defined by the World Health Organization as "A state, psychologic and sometimes also physical, resulting from the interactions between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present." Addiction is a psychiatric disorder associated with excessive self-medication against medical advice and compulsive, often criminal, acquisition of drug. It should not be a concern for the acute postoperative patient receiving opioids for a short, determinable period.

Commonly used opioids in postoperative pain

The opioids commonly used in the treatment of postoperative pain can be classified as pure agonists or mixed agonist-antagonists. A pure agonist has maximal physiologic effect at the binding site (e.g., morphine). An antagonist occupies the site but has no physiologic action (e.g., naloxone). A partial agonist occupies the site but has submaximal physiologic activity even at high doses (e.g., buprenorphone). A mixed opioid agonist-antagonist has agonist effects at some receptors and antagonist effects at others

(e.g., nalbuphine). Tramadol is a centrally acting synthetic analgesic chemically unrelated to opiates; however, it is also considered to be an opioid because of its agonist activity at μ receptors.

Pure agonists

1. Morphine

Morphine is the gold standard against which all other opioids are compared. It is the most widely used opioid for the management of acute pain in adults. Morphine is hydrophilic and does not cross the blood-brain barrier well. It also has poor oral bioavailability (20% to 30%), which necessitates a larger oral (PO) dose when converting from parenteral to enteral routes of drug administration. In addition to PO, intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes, morphine can be administered by epidural and intrathecal routes using preservative-free formulations. Morphine is metabolized in the liver by microsomal mixed-function oxygenases that require the P-450 system. Two metabolites are morphine-6-glucuronide (which is active and more potent than morphine) and morphine-3-glucuronide (which is inactive but competes competitively with morphine at binding sites). These metabolites are excreted renally, so morphine (and opioids that are metabolized to morphine, e.g., codeine) must be used with caution in patients with renal failure because the active metabolite accumulates in the blood. Morphine induces histamine release and must be used carefully in patients with asthma or atopy. Histamine release also causes vasodilatation and may produce hypotension in hypovolemic patients.

2. Meperidine

Meperidine has one-tenth the analgesic potency of morphine and may have a shorter duration of analgesia (2 to 4 h vs. 2 to 7 h for morphine IM). At equipotent doses, it has an adverse effect profile similar to that of morphine. It offers no advantages over morphine in terms of sphincter of Oddi spasms, bowel motility, or respiratory depression. Meperidine produces a "rush" or euphoric feeling that some patients enjoy and thus label meperidine as the "most" effective opioid for them.

The primary metabolite of meperidine, by hepatic *N*-demethylation, is normeperidine. This compound has half the analgesic activity of meperidine, is renally eliminated, and can cause hallucinations, agitation, and seizures. Regular dosing or high doses in patients with normal or impaired renal function may result in accumulation of normeperidine. Seizures can be seen at doses of 10 mg/kg/d IV, IM, or SC. It is difficult to identify patients at risk for meperidine-induced seizures.

Patients who concomitantly take meperidine and monoamine oxidase inhibitor (MAOI) antidepressants may develop a potentially fatal drug interaction. Because of the long half-life of MAOIs, patients who have discontinued these agents within the previous two weeks are also at risk. The drug interaction may cause a serotonin-like syndrome—a life-threatening condition manifested by hyperpyrexia, acidosis, shock, and death.

Because of the toxic metabolite and potentially fatal drug-drug interaction with MAOIs, one should rarely prescribe meperidine for acute (or chronic) pain. The Working Group does not recommend the use of meperidine in the treatment of postoperative pain; longer-acting and safer opioids are available. If meperidine is indicated (e.g., for the rare patients with hypersensitivity to opioids from another class), its use should be restricted to the recovery room or limited to less than 24 hours in doses less than 600 mg / 24 h.

3. Fentanyl

Fentanyl is highly lipid soluble, equilibrates rapidly at the effector site, and has no active metabolites. Fentanyl can be administered by the IV, IM, SC, transmucosal, and transdermal route. It is most commonly used for short, painful procedures; however, it also can be used for postsurgical and burn pain relief. In general, a dose of fentanyl, 0.5 to 2.0 μg/kg/h, is appropriate whether given intermittently or by continuous infusion. Transdermal fentanyl is contraindicated for acute pain management.

4. Hydromorphone

Hydromorphone is sevenfold to tenfold more potent than morphine, and twofold to sevenfold more lipid soluble. It is metabolized to hydromorphone-3-glucuronide, which lacks analgesic effect but has been associated with neurotoxicity. The elimination half-life is 2 to 3 hours. It is typically associated with fewer adverse effects (e.g., nausea, vomiting, and pruritus) than morphine. Like morphine, it is versatile and can be administered by the IV, SC, PO, epidural, or intrathecal routes.

5. Codeine, oxycodone, and hydrocodone

Codeine, oxycodone, and hydrocodone are opioids that are commonly used to treat pain in children and adults, especially for less severe pain or when treatment is being converted from parenteral opioids to enteral ones. Codeine, oxycodone, and hydrocodone are most commonly administered by the PO route, usually in combination with acetaminophen or aspirin. About 10% of administered codeine is metabolized to morphine, which is responsible for most if not all of codeine's analgesic and antitussive effects. With all combination preparations, physicians should beware of inadvertently administering hepatotoxic doses of acetaminophen when increasing doses for uncontrolled pain; all sources of acetaminophen should be considered. Acetaminophen toxicity may result from a single toxic dose (e.g., 5.85 g), from repeated ingestion of large doses of acetaminophen (e.g., in adults, 7.5 to 10.0 g/d for 1-2 d; in children, 60 to 420 mg/kg/d for 1 to 42 d) or from chronic ingestion. The recommended maximal daily dose for acetaminophen is 4 g/d in adults with normal hepatic function and 2 g/d in chronic alcoholics.

Mixed opioid agonist-antagonists

Mixed opioid agonist-antagonists produce analgesia primarily at the κ receptor. They have a ceiling effect and produce limited respiratory depression. In patients who are physiologically dependent on opioids, these drugs can induce withdrawal symptoms. One of the most useful indications for opioid agonist-antagonists is treatment of opioid-induced adverse effects, including nausea and vomiting, sedation, and pruritus. Opioid agonist-antagonists typically reverse these effects without reversing analgesia.

Routes of opioid administration for postoperative pain

1. Conventional (IV / IM / SQ / PO / PR)

Probably the most common route of administering opioids is by intermittent IM or SC injections. Since IM and SC injections of opioids have variable absorption and are painful and time-consuming, one should use other routes if possible. Patients with severe postoperative pain should be administered opioids via IV PCA (see below) or epidural or intrathecal injections. The PO route, if tolerated, would also be an option but the likelihood of under-dosing opioids orally must be considered.

2. Patient controlled analgesia (PCA)

The rationale for PCA is the following: as-needed (prn) opioid dosing leads to episodes or cycles of pain that in turn lead to as-needed dosing of an analgesic. The episodes of pain that occur between analgesic doses lead to increased anxiety. The relatively large doses of opioids used to "rescue" patients typically are followed by periods of excessive sedation. PCA uses frequent administration of "mini" doses of analgesics initiated by patients, thereby eliminating the peaks and valleys of analgesia and pain. Overall, improved patient satisfaction results from the control over analgesic medication. Typically, the total quantity of analgesic required is smaller with PCA than conventional as-needed dosing, so less severe and fewer adverse effects occur with PCA. Nursing time may also be saved.

Relative contraindications to PCA include the inability to use the PCA button effectively because of physical or cognitive reasons, patient desire not to assume responsibility over analgesic administration, or a history of substance abuse. Family members and nurses typically are not permitted to activate the PCA device.

Institutions that have IV PCA capability have staff members who are knowledgeable in the use of the various devices available. They are also able to diagnose and are prepared to manage potential, rare complications, including respiratory distress, apnea, and other adverse effects typically seen with opioids. The three programmable parameters on most PCA devices are dose, frequency and an optional continuous, basal infusion rate. PCA is not limited to the IV route; epidural PCA, PO PCA and SC PCA have all been used with success.

3. Neuraxial (epidural/intrathecal)

Neuraxial opioids may be administered in the epidural or intrathecal (subarachnoid) space. Delivered at these sites, they bypass the blood-brain barrier and require significantly lower doses, typically 1/10 to 1/100 of the effective IV dose. Epidural and intrathecal opioids are extremely effective for the management of severe pain whether it is postoperative, chronic, or malignant in origin.

Opioids administered in the epidural space must enter the cerebrospinal fluid (CSF) by the dura and pia mater, diffuse through the water phase of the CSF, then cross the lipid membranes of the neuraxis to reach opioid receptors in the substantia gelatinosa. Hydrophilic agents, such as morphine, demonstrate increased latency and duration of action because their water solubility retards diffusion out of the CSF and into the substance of the spinal cord. Because of the depot of agent that remains dissolved in CSF, rostral spread of the drug is increased. Rostral spread of drug is associated with a small risk of delayed respiratory depression, typically 6 to 8 hours after administration.

Because hydrophilic agents remain in the CSF, uptake into the epidural blood vessels is slow, and the administration of epidural hydrophilic opioids is associated with low or undetectable systemic blood levels. Thus, water-soluble opioids administered spinally exert their analgesic effect spinally. Lipid-soluble agonists, such as fentanyl, have a rapid onset of action and provide segmental analgesia with less rostral spread of drug. Lipid-soluble opioids also have a rapid rate of diffusion into the venous plexus of the epidural space, resulting in rapid drug removal from the neuraxis and achievement of therapeutic IV blood levels. Controversy exists regarding whether epidurally administered lipid-soluble agents, such as fentanyl and sufentanil, exert their analgesic effect primarily at the neuraxis or by systemic absorption and hematogenous drug delivery to the CNS.

Neuraxial opioids can be administered by a single bolus injection into the epidural space or CSF or by a continuous infusion via an indwelling catheter. No change occurs in autonomic function, and light touch sensation and proprioception are preserved. The frequency of urinary retention is increased, mandating bladder catheterization in approximately one-third of patients. Other possible adverse effects include nausea and vomiting, pruritus, and acute or delayed respiratory depression.

4. Novel

Because fentanyl is extremely lipophilic, it can be readily absorbed across any biologic membrane, including the skin. Thus, it can be given painlessly by new, non-intravenous routes of drug administration, including the transmucosal (nose and mouth) and transdermal routes. Transmucosal fentanyl is extremely effective for acute pain relief. For oral-buccal administration using this novel delivery technique, fentanyl is manufactured in a candy matrix (Fentanyl Oralet) attached to a plastic applicator (similar to a lollipop). As the patient sucks on the candy, fentanyl is absorbed across the buccal mucosa and is rapidly absorbed (in 10 to 20 minutes) into the systemic circulation. The major adverse effect is nausea and vomiting, which occurs in approximately 20% to 33% of patients who receive it. This product is available only in hospital (and surgicenter) pharmacies and, like all sedative-analgesics, requires vigilant patient monitoring.

When drugs are administered transdermally, a patch with a selective semipermeable membrane and reservoir of drug is applied to the skin. The patch allows for the slow, steady absorption of drug across the skin. The only opioid currently approved by the Food and Drug Administration (FDA) for transdermal application is fentanyl. Transdermal fentanyl is contraindicated for acute pain management and is used only for patients with chronic pain (e.g., cancer) or in opioid tolerant patients. The onset of action is 16 hours after application of the patch, and fentanyl continues to be absorbed from the subcutaneous fat for

almost 24 hours after the patch is removed. These characteristics make it hazardous to use in an acute pain setting.

Summary Table: Site-specific Pain Management Interventions – OPIOIDS

	Pharmacologic Therapy (Route)							Non-Pharmacologic		
Type of surgery by body region	**PO**	**IM**	**IV**	**Epidural**	**Intrathecal**	**IV PCA**	**Regional**	**Physical**	**Cognitive**	**Comments**
1. Head and neck										
Ophthalmic	***OP***	OP	OP	--	--	RARELY		C	X	
Craniotomy	OP	***OP***	***OP***	--	--	OP				
Radical neck	OP	OP	OP	--	--	***OP***			X	
Oral-maxillofacial	***OP***	OP	OP	--	--	OP		**C**, **I**	X	
2. Thorax-noncardiac										
Thoracotomy	OP	OP	OP	**OP**	OP	OP		C, **T**	X	
Mastectomy	OP	OP	***OP***	OP	OP	***OP***		C, T	X	
Thoracoscopy	OP	OP	***OP***	OP	OP	OP		C, T	X	
3. Thorax-Cardiac										
CABG	OP	OP	**OP**	RARELY	OP	OP	RARELY			
MID-CAB	OP	OP	***OP***	RARELY	OP	OP			X	
Laparotomy	OP	OP	OP	**OP**	OP	***OP***		***E***, **T**	X	Opioids may impair bowel function
Laparoscopic cholecystectomy	***OP***	***OP***	***OP***	RARELY	RARELY	OP		***E***, ***T***	X	Opioids may cause biliary spasm
Nephrectomy	OP	OP	OP	**OP**	OP	OP		***E***, T	X	
5. Lower abdomen/pelvis										
Hysterectomy	OP	OP	OP	OP	OP	***OP***		***E***,	X	Opioids may impair bowel function
Radical prostatectomy	OP	OP	OP	**OP**	OP	OP	--	**E**	X	Opioids may impair bowel function
Hernia	***OP***	OP	OP	RARELY	OP	RARELY		C,	X	
7. Back/Spinal										
Laminectomy	OP	OP	***OP***	RARELY	RARELY	OP	--	C, **E**	X	
Spinal fusion	OP	OP	***OP***	RARELY	RARELY	***OP***	--	**E** **I**	X	
6. Extremities										
Vascular	OP	OP	OP	**OP**	OP	OP		***C***, **E**	X	
Total hip replacement	OP	OP	***OP***	**OP**	OP	OP		**C**, **E**, **T**	X	
Total knee replacement	OP	OP	OP	***OP***	OP	OP		**C**, **E**, **T**	X	
Knee arthroscopy / Arthroscopic joint repair	OP	OP	OP	RARELY	OP	OP		**C**, **E**, **T**	X	
Amputation	OP	OP	OP	***OP***	***OP***	OP		C, **E**, T	X	
Shoulder	OP	OP	OP	--	--	OP		**C**, **E**, **I**, **T**	X	

OP = Opioids; **C** = Cold; **E** = Exercise; **I** = Immobilization; **T** = TENS; **X** = Use of cognitive therapy is patient-dependent rather than procedure-dependent

Indications for Use: **Bold/Red/Shaded**: Preferred based on evidence (QE=1; R=A); ***Italicized/Blue:*** Common usage based on consensus (QE=III); Plain Text: Possible Use

Table OP1. Opioids: Mechanisms of Action, Contraindications, Other Considerations

DRUG CLASS	MECHANISM OF ACTION	CONTRAINDICATIONS	OTHER CONSIDERATIONS
Opioid agonists	Agonist activity at opiate receptors	Hypersensitivity to specific agent or component of the formulation — does not preclude use of agent from another subclass Acute bronchial asthma Upper airway obstruction Concurrent or recent use (within previous 2 weeks or more) of MAOIs with **meperidine** — combination may result in potentially fatal drug interaction (serotonin-like syndrome).	Opioids may interfere with neurologic evaluation after head trauma or neurosurgery. All of these agents may increase intracranial pressure; use with caution in patients with head injury or increased intracranial pressure. Muscle rigidity, typically starting in the upper body and chest, often occurs during induction of anesthesia with larger doses or rapid administration of opioids. **Alfentanil** and **fentanyl** may cause temporal lobe activation or seizures in patients with complex partial epilepsy (Manninen et al., 1999; Ragazzo et al., 2000; Tempelhoff et al., 1992). **Alfentanil, fentanyl, remifentanil**, and **sufentanil** do not cause histamine release (Cambareri et al., 1993; Flacke et al., 1987; Hermens et al., 1985; Rosow et al., 1982; Sebel et al., 1995; Warner et al., 1991). **Meperidine** has equivocal effects on biliary spasm and has no clear advantage over other opioids.[†] Fatalities have been associated with the use of **propoxyphene** in patients who are actively or previously suicidal, prone to drug addiction, taking neuroleptics or antidepressant drugs, using alcohol in excess, or inclined to excessive self-medication.
Mixed opioid agonist-antagonists	Agonist effects at some opiate receptors; antagonist effects at other opiate receptors; ceiling to analgesic effects	Hypersensitivity to any of these agents or component of the formulation. Physiologic opioid dependence (these agents may precipitate withdrawal symptoms).	Lower abuse potential than pure agonists. All of these agents may increase intracranial pressure; use with caution in patients with head injury or increased intracranial pressure. **Butorphanol** may increase blood pressure and cardiac workload; use only if benefits outweigh the risks in patients with cardiovascular disease. **Buprenorphine, nalbuphine**, and **butorphanol** may cause less biliary spasm (McCammon et al., 1984; Staritz et al., 1986). **Pentazocine** tends to cause hallucinations, confusion, or dysphoria.
Other (Tramadol)	Tramadol and its M1 metabolite are weak agonists at μ-opiate reeptors and inhibitors of norepinephrine and serotonin reuptake; these mechanisms are synergistic.	Hypersensitivity to tramadol or component of the formulation. Acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs. Concurrent use of MAOIs or SSRIs — drug interaction may cause serotonin-like syndrome. Recent use (within the previous 2 wk or more) of MAOIs may also cause a reaction.	Less respiratory depressant effects than morphine. Lacks adverse effects on heart rate, left ventricular function, and cardiac index. Does not cause histamine release. Risk of seizures may be increased in the following patients: those taking MAOIs, SSRIs, tricyclic antidepressants, neuroleptics, or other drugs that reduce seizure threshold; patients with epilepsy; patients with risk factors for seizure; or patients who take overdoses of tramadol (≥ 500 mg PO) (Gardner et al., 2000; Gasse et al., 2000; Jick et al., 1998; Spiller et al., 1997).

Table OP1. Opioids: Mechanisms of Action, Contraindications, Other Considerations

MAOI = Monoamine oxidase inhibitor; SSRI = Selective serotonin reuptake inhibitor

† There is no convincing evidence that meperidine is associated with less biliary spasm than other opioids. Some studies have found a detrimental effect (Joehl et al., 1984; Radnay et al., 1984) and others, a lack of effect on bile duct pressure, biliary clearance, or biliary contractions (Elta et al., 1994; Thune et al., 1990). Agents shown to have a lower likelihood of inducing biliary spasm are tramadol and the agonist-antagonist opioids, including buprenorphine, nalbuphine, and butorphanol (McCammon et al., 1984; Staritz et al., 1986)

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
PURE AGONISTS					
Phenanthrenes					
Codeine	PO	30 mg [15 to 60 mg] q 4 to 6 h (Max. 360 mg/d; for combinations with acetaminophen, max. 4 g/d acetaminophen)	15 to 30 30 to 60 4 to 6	Hepatic / Renal Metabolized to morphine via CYP-2D6 isoenzyme. 2 to 4	•Elderly – Use with caution. •Hepatic dysfunction – conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease. •Renal dysfunction – use lower dosage or an alternative analgesic. •May be ineffective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs) because it is not converted to morphine.
	IM	same as PO	—		
	IV	15 to 30 mg q 2 h	—		
	SC	same as PO	15 to 30 — 4 to 6		
Hydrocodone	PO	5 to 10 mg q 4 to 6 h (Max. daily dose is 60 mg when given in fixed combination with acetaminophen, and 37.5 mg when given in fixed combination with ibuprofen)	15 to 30 30 to 60 4 to 8	Hepatic / Renal Metabolized to hydromorphone via CYP-2D6 isoenzyme. 3.3 to 4.5	•Elderly (≥ 65 y) – Use with caution, starting at low end of dosing range. •Hepatic / Renal dysfunction – Use with caution. •May be ineffective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs).

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Hydromorphone	PO	2 mg [2 to 4 mg or 0.04 to 0.08 mg/kg] q 4 to 6 h	15 to 30 30 to 60 4 to 6	Hepatic / Renal Metabolized to hydromorphone-3-glucuronide (H3G) 2 to 3	•Elderly (≥ 65 y) – Use with caution, starting at low end of dosing range. •Hepatic / Renal dysfunction – Use with caution.
	IM	1 to 2 mg [2 to 4 mg or 0.04 to 0.08 mg/kg] q 4 to 6 h	< 15 30 to 60 4 to 6		
	IV	0.5 mg [0.5 to 2 mg or 0.01 to 0.04 mg/kg] q 4 h (slowly over 2 to 3 min.)	< 0.5 5 to 20 2 to 4		
	SC	1 to 2 mg [2 to 4 mg or 0.04 to 0.08 mg/kg] q 4 to 6 h	< 15 30 to 60 4 to 6		
	PR	3 mg q 6 to 8 h	— — 6 to 8		
	ED[§]	*Single dose* 0.5 to 1.5 mg (0.01 to 0.03 mg/kg) *Infusion* 0.1 to 0.2 mg/h *PCEA* Load 0.5 to 1.5 mg; basal infusion 0.08 to 0.12 mg/h; demand dose 0.02 to 0.03 mg; lockout 6 to 8 min. Bupivacaine 0.031% often added. [‡‡]	5 to 15 30 10 to 16[§]		
	IT[§]	—			
	IV PCA	Load 0.1 to 0.5 mg (0.002 to 0.01 mg/kg); bolus/demand dose 0.1 to 0.5 mg; lockout 6 to 8 min; basal infusion[‖] 0.1 to 0.3 mg/h			

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Levorphanol	PO	2 mg [2 to 4 mg] q 6 to 8 h (Max. initial dose: 6 to 12 mg/d)	30-60 60 to 120 4 to 8	Hepatic / Renal 11 to 16	•Elderly – consider reducing dose by ≥ 50% or more. •Hepatic / Renal dysfunction – No pharmacokinetic data; use with caution. •Respiratory disease / respiratory depressants – Reduce initial dose by ≥ 50%. •Duration of analgesic effect is longer than that of morphine or meperidine. When making dosage adjustments, allow sufficient time (72 h) to permit a new steady-state before making subsequent dosage changes to avoid excessive drug accumulation.
	IM	1 mg [1 to 2 mg] q 6 to 8 h (Max. initial dose: 3 to 8 mg/d)	15 to 30 — —		
	IV	≤ 1 mg (0.02 mg/kg) q 3 to 6 h (slowly) (Max. initial dose: 4 to 8 mg/d)	10 to 15 <20 6 to 8		
	SC	1 mg [1 to 2 mg] q 6 to 8 h (Max. initial dose: 3 to 8 mg/d)	60 to 90 6 to 8		
Morphine	PO	IR: 10 to 30 mg [10 to 60 mg] q 4 h CR/SR: 15 mg q 12 h [15 to 200 mg q 8 to 12 h for morphine CR and q 12 to 24 h for morphine SR/Kadian]	15 to 60 60 to 90 2 to 6 60 to 90 60 to 240 6 to 12 [(up to 24 for morphine SR/Kadian)]	Hepatic/Renal Metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G); M6G has analgesic activity. *PO* 1.5 to 4.5; *ED* 0.6 to 4.2 (mean, 1.5) *IT* 0.7 to 2.3 (mean, 1.5)	•Elderly or debilitated – give with extreme caution; use lower dose. •Hepatic dysfunction – use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 h) and, with oral morphine, bioavailability is increased. •Renal dysfunction – reduce dose or, if severe renal impairment exists, avoid use. •M3G may accumulate in renal impairment and may be associated with neurotoxicity. •Parenteral and IR oral opioids are generally preferred over CR/SR oral opioids for management of post-operative pain.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Morphine (cont.)	IM	10 mg q 3 to 4 h [2.5 to 20 mg q 4 h]	1 to 5 30 to 60 2 to 7		
	IV	3 to 5 mg [2 to 15 mg] q 2 to 3 h; (dilute in 4 to 5 ml of sterile water for injection and inject slowly over 4 to 5 min); Larger doses (0.5 to 3 mg/kg) have been given for open-heart surgery.	<1 5 to 25 2 to 7		
	SC	10 mg q 3 to 4 h [2.5 to 20 mg q 4 h]	— 50 to 90 2 to 7		
	PR	10 to 20 mg q 4 h [10 to 40 mg q 3 to 4 h]	— 20 to 60 —		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
	ED[§]	*Single dose* 2 to 5 mg (0.04 to 0.10 mg/kg) [2 to 7.5 mg]; if pain relief is inadequate after 1 h, incremental doses of 1 to 2 mg may be given at intervals long enough to assess effectiveness; max. 10 mg/24 h *Infusion* 0.08 to 0.17 mg/h (2 to 4 mg/24 h) [0.1 to 1 mg/h]; additional 1 to 2 mg may be given if pain relief is not obtained initially. *PCEA* Load 2 to 4 mg; basal infusion[‖] 0.3 to 0.6 mg/h; demand dose 0.1 to 0.2 mg; lockout interval 10 to 15 min. [‡‡] (Usual initial dose, 4 to 10 mg/d; often titrated up to 20 to 30 mg/d).	15 to 60 30 6 to 24[§]		
Morphine (cont.)	IT[§]	0.2 to 1 mg/d [0.2 to 1 mg/d]; (0.004 to 0.02 mg/kg/d); repeated doses **not** recommended.	15 to 60 30 6 to 24[§]		
	IV PCA	Load 0.5 to 3 mg (0.01 to 0.06 mg/kg); bolus/demand dose 0.5 to 3 mg; lockout 6 to 8 min; basal infusion[‖] 0.5 to 2 mg/h	—		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Oxycodone	PO	IR: 5 mg q 6 h [5 to 15 mg q 4 to 6 h] CR: 10 mg [10 to 80 mg] q 12 h	10 to 15 30 to 60 3 to 6 30 to 60 90 to 180 8 to 12	Hepatic / Renal Metabolized to oxymorphone via CYP-2D6 isoenzyme. 3.2 — — 4.5	•Elderly and debilitated patients – reduce dosage. •Hepatic / Renal – Use with caution. •Patients on other CNS depressants: reduce dosage. •Metabolized to oxymorphone. May be ineffective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs). •Parenteral and IR oral opioids are generally preferred over CR/SR oral opioids for management of post-operataive pain.
Oxymorphone	IM	0.5 to 1.5 mg q 4 to 6 h	10 to 15 30 to 60 3 to 6	Hepatic / Renal 1.3 ± 0.7 (mean ± SD)	•Elderly and debilitated – reduce dosage.
	IV	0.5 mg q 4 to 6 h [0.5 to 1 mg q 2 to 6 h]	5 to 10 30 to 60 3 to 6		•Hepatic dysfunction – reduce dosage. •Renal dysfunction – use with caution.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Oxymorphone (cont.)	SC	0.5 to 1.5 mg q 4 to 6 h	10 to 15 — 3 to 6		
	PR	5 mg q 4 to 6 h [5 to 10 mg q 3 to 6 h]	15 to 30 — 3 to 6		
Phenylpiperidines					
Alfentanil	ED[§]	*Single dose* 500 to 1000 µg (10 to 20 µg/kg) *Infusion* 100 to 250 µg/h (2 to 5 µg/kg/hr) *PCEA* No recommendation for basal infusion[‖]; demand dose 200 to 250 µg; lockout interval 10 min.[‡‡]	15 — 1 to 3[§]	Hepatic / Renal Metabolized by CYP-3A3/4 1 to 2[††]	•Elderly – 50% reduction in dose typically. •Hepatic dysfunction – in patients with moderate hepatic insufficiency, protein binding is decreased (free, active drug is increased), clearance is decreased about 50%, and half-life is increased; use with caution as effects may be increased and prolonged. In patients with severe hepatic insufficiency, reduce dose. •Renal dysfunction – no dosage modification. •Obesity (> 20% above IBW) – base dose on IBW.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Fentanyl	IM	[25 to 100 µg (0.7 to 2 µg/kg)] prn	< 7 to 15 <15 1 to 2	Hepatic, intestinal mucosa / Renal Metabolites are inactive and nontoxic. *IV* 3.6 to 7.1	•Elderly – 50% reduction in dose typically required. •Hepatic disease – no dosage modification if given as a single bolus; recovery may be prolonged with continuous infusions. •Renal dysfunction – no dosage modification if given as a single bolus to patients with ESRD; in critically ill patients with acute renal failure, use continuous fentanyl infusions with caution or consider an alternative agent. •Vulnerable patients, pulmonary disease – use lower dose. •Respiratory depressant effects may persist longer than analgesic effects.
	IV	*Bolus* 2 to 20 µg/kg initially, then 25 to 100 µg (0.7 to 2 µg/kg) prn *Infusion* 1.5 to 2.5 µg/kg/h	< 0.5 < 5 0.5 to 1		
	ED[§]	*Single dose* 50 to 100 µg (1 to 2 µg/kg) *Infusion* 25 to 100 µg/h *PCEA* Load 75 to 100 µg; basal infusion[‖] 30 to 75 µg/h; demand dose 10 to 15 µg; lockout 6 min.[‡‡] In combination with bupivacaine (0.625% bupivacaine + fentanyl 2 µg/ml)—Load with 0.5% bupivacaine; basal infusion 6 ml; demand dose 3 ml; lockout 6 min.	4 to 10 ~ < 30 1.5 to 8[§]		
	IT[§]	*Bolus* 5 to 20 µg (0.1 to 0.4 µg/kg) *Infusion* 0.8 µg/kg/h	4 to 10 ~ < 30 4 to 8[§]		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Fentanyl (cont.)	IV PCA	Load 15 to 75 µg (0.5 to 1 µg/kg); bolus/demand dose 10 to 75 µg; lockout 4 to 6 min; basal infusion‖ 15 to 60 µg/h	—		
Meperidine	PO	100 to 150 mg q 3 h [50 to 150 mg (1 to 3 mg/kg) q 2 to 4 h]	10 to 45 < 60 2 to 4	Hepatic / Renal Metabolized to neurotoxic metabolite, normeperidine, which is renally eliminated. *PO* 3 to 4, meperidine; *IM* 8 to 21, normeperidine	•Suggested max. dose 600 mg / 24 h, and max. duration 24 h. •Has local anesthetic properties. •May be useful for prevention and treatment of postoperative shivering. •Elderly – consider age-dependent renal impairment; reduce dosage or avoid use. •Hepatic dysfunction – decrease dose, frequency of administration, and avoid regular use; bioavailability is increased and half-life (7 to 11 h) prolonged in patients with cirrhosis or active viral hepatitis. Normeperidine may accumulate, although less is formed. •Renal dysfunction – not recommended because of accumulation of neurotoxic metabolite; elimination half-life of normeperidine in renal failure is increased (35 h). •Concomitant therapy with other CNS depressants (e.g., phenothiazines, other tranquilizers) – reduce dose of meperidine 25% to 50%. •Seizures may occur with regular or high doses and with renal failure. Alkaline urine reduces elimination of meperidine and normeperidine. •SC meperidine causes local irritation and is not recommended when repeated injections are required.
	IM	75 to 100 mg q 3 h [50 to 150 mg q 2 to 4 h]	1 to 5 30 to 50 2 to 4		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Meperidine (cont.)	IV	*Intermittent dosing* 25 to 50 mg q 2 h (slowly at ≤ 25 mg/min) [25 to 100 mg (0.5 to 2 mg/kg) q 2 to 4 h] *Slow, continuous infusion* [15 to 35 mg/h]	< 1 5 to 20 2 to 4		
	SC	same as PO	— — 2 to 4		
	ED[§]	*Single dose* 20 to 100 mg (0.5 to 2 mg/kg) *Infusion* [2 to 20 mg/h] *PCEA* Load 30 mg; no basal infusion; demand dose 30 mg; lockout 30 min.[‡‡]	2 to 12 — 4 to 8[§]		
	IV PCA	Load 25 to 50 mg (0.5 to 1 mg/kg); bolus/demand dose 5 to 25 mg; lockout 6 to 8 min; basal infusion[‖] 5 to 20 mg/h.	—		
Remifentanil	IV	*Continuation of analgesia into immediate postoperative period*: continuous infusion 0.1 µg/kg/min (range: 0.025 to 0.2 µg/kg/min); supplemental bolus not recommended.	1 1 5 to 10 min	Nonspecific plasma and tissue esterases *IV* ~3 to 10 min[††]	•Note: Before stopping the infusion of remifentanil, consider the short offset of the drug (5 to 10 min); give alternate analgesic before stopping remifentanil. •Should be used only under immediate direction and supervision of anesthesia care provider. •Elderly (> 65 y) – Decrease starting doses by 50%; cautiously titrate to effect. •Hepatic / Renal dysfunction – No dosage modification required. •Obesity (> 30% over IBW) – Base initial dose on IBW.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Sufentanil	IV	*For minor general surgery (duration ≤ 2 h)*: total dose 1 to 2 µg/kg; maintenance: 10 to 25 µg in increments as needed for surgical stress or lightening of anesthesia. Adjust maintenance infusion rates based on the induction dose so that the total dose is < 1 µg/kg/h of expected surgical time. *For major surgery (duration 2 to 8 hr)*: total dose 2 to 8 µg/kg; maintenance: 10 to 50 µg. Adjust maintenance infusion rates based on the induction dose so that the total dose is < 1 µg/kg/h of expected surgical time.	— 2.5 1 to 2 after 1 to 2 µg/kg IV 2 to 8 h after 2 to 8 µg/kg IV	Hepatic / Renal, fecal *IV* 2.5[††]	•Elderly and debilitated – reduce dosage. •Hepatic / renal dysfunction – No change in pharmacokinetics; use with caution in patients with chronic renal failure due to possible prolonged respiratory depression. •Obesity (> 20% above IBW) – base dose on IBW. •For IV injection, individualize supplemental dosages. •Sufentanil and bupivacaine may be mixed together before ED administration.
	ED[§]	*Single dose*: 4 to 75 µg, or 10 to 15 µg with 10 ml bupivacaine 0.125% (12.5 mg, with or without epinephrine); may repeat twice at ≥ 1 h intervals (total, 3 doses) *Infusion* 4 to 8 µg/h. *PCEA* Load 30 to 50 µg; basal infusion[‖] 5 to 10 µg/h; demand dose 4 to 6 µg; lockout interval 6 min. [‡‡]	5 — 2 to 4[§]		.
	IV PCA	Load 2 to 10 µg (0.03 to 0.1 µg/kg); bolus/demand dose 2 to 10 µg; lockout 4 to 6 min; basal infusion[‖] 2 to 8 µg/h	—		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Diphenylheptanes					
Methadone	PO	5 to 10 mg q 4 to 6 h for first 2 to 3 d; with repeated dosing, extend interval to q 6 to 12 h [2.5 to 10 mg q 4 to 6 h for first 2 to 3 d, then 5 to 20 mg q 6 to 12 h (0.05 to 0.1 mg/kg)]	30 to 60 — 4 to 12; increases with continued use and cumulative effects	Hepatic / Renal, fecal Primarily metabolized by CYP-3A4 13 to 47 (mean, 25, with repeated PO doses)	•Elderly, poor-risk, or debilitated patients – reduce dosage. •Hepatic dysfunction – In severe hepatic dysfunction, half-life is increased and accumulation may occur. In mild to moderate hepatic dysfunction, no dosage modification required. •Renal dysfunction – reduce dose by up to 50% in end-stage renal failure or dialysis patients. •Patients on other CNS depressants – reduce dosage. •Undergoes renal reabsorption, which decreases as urinary pH decreases. Urinary excretion is dose-dependent and is the major route of elimination at doses > 55 mg/d. •SC injection may cause local irritation. •Oral route usually not used for postoperative pain.
	IM	2.5 to 5 mg q 4 h; with repeated dosing, extend interval to q 6 h [2.5 to 10 mg q 3 to 4 h then 5 to 20 mg q 6 to 8 h (0.05 to 0.1 mg/kg)]	1 to 5 30 to 60 4 to 6 (single dose)		
	IV	Not FDA-approved. 2.5 mg q 2 h; with repeated dosing, extend interval to q 3 h	<1 5 to 20 4 to 6		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT[†]	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Methadone (cont.)	SC	same as IM	1 to 5 — 4 to 6 (single dose)		
	ED[§]	*Single dose* 1 to 5 mg (0.02 to 0.1 mg/kg) *Infusion* 0.3 to 0.5 mg/h	5 to 10 — 6 to 10[§]		
Propoxyphene	PO	HCl 65 mg q 6 to 8 h [65 to 130 mg q 8 h]; max. 390 mg/d Napsylate 100 mg q 6 to 8 h [100 to 200 mg q 8 h]; max. 600 mg/d Equianalgesic doses for propoxyphene salts: 65 mg HCl ≡ 100 mg napsylate.	15 to 60 120 to 180 4 to 6	Hepatic / Renal 6 to 12 (30 to 36, norpropoxyphene) Metabolized to norpropoxyphene (associated with cardiotoxicity).	• Elderly – Use is not recommended (Beers 1997); half-life of propoxyphene and norpropoxyphene may be markedly prolonged (36 and 53 h, respectively) (Crome et al. 1984). • Hepatic disease – Increased bioavailability of propoxyphene; reports of hepatotoxicity; avoid use in patients with liver disease. • Renal dysfunction – Propoxyphene and norpropoxyphene accumulate in renal insufficiency; may result in respiratory or CNS depression, neurotoxicity, or cardiotoxicity; avoid use. • Seizures and cardiac arrhythmias may occur with the use of high doses or with renal failure.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
MIXED AGONIST-ANTAGONIST OPIOIDS					
Buprenorphine	IM	0.3 to 0.6 mg q 6 to 8 h (0.006 to 0.012 mg/kg); repeat once (up to 0.3 mg) in 30 to 60 min prn	15 60 6	Hepatic / Fecal 2 to 3	•Elderly, debilitated – reduce dose by 50%. •Hepatic dysfunction – insufficient data. •Renal dysfunction – no dosage modification required. •Respiratory disease; presence of other CNS depressants – reduce dose by 50%. •Relative antagonist activity: equipotent to that of naloxone. •Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.
	IV	same as IM (give slowly)	< 15 < 60 6		
Butorphanol	IM	2 mg [1 to 4 mg (0.02 to 0.08 mg/kg)] q 3 to 4 h *Preoperative / Preanesthetic use*: 2 mg 60 to 90 min before surgery.	10 to 15 30 to 60 3 to 4	Hepatic / Renal, Fecal *IV* 2.1 to 8.8	• Elderly (≥ 65 y) – IM/IV: reduce dose by ½ and double the dosing interval. • Hepatic / Renal dysfunction (CrCl < 30 ml/min) – extend dosing frequency to q 6 to 8 h. • Relative antagonist acitvity: ~30x pentazocine or 1/40 naloxone. • Ceiling effect on respiratory depression occurs at ~30 to 60 µg/kg. •Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.
	IV	1 mg [0.5 to 2 mg (0.01 to 0.04 mg/kg)] q 3 to 4	< 3 < 30 3 to 4		

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Dezocine	IM	10 mg [5 to 20 mg]; repeat q 3 to 6 h prn Max. ~120 mg/d	< 30 30 to 150 3 to 4 (after 10 to 15 mg IM)	Hepatic / Renal *IV* 0.6 to 7.4	•Elderly – reduce initial dose and individualize subsequent doses. •Hepatic / Renal dysfunction – reduce dose. Half-life is increased by 30% to 50% in patients with cirrhosis compared with healthy volunteers after 10 mg IV. •Exhibits nonlinear (dose-dependent) pharmacokinetics at doses > 10 mg with serum concentration-time curve ~25% greater, and total body clearance ~20% lower compared with doses ≤ 10 mg. •Relative antagonist acitvity less than that of nalorphine and greater than that of pentazocine. •Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.
	IV	5 mg [2.5 to 10 mg] q 2 to 4 h	< 15 — 2 (after 5 mg IV)		
	SC	Not recommended because of injection site reactions (4% in clinical trials)	—		
Nalbuphine	IM	10 mg [10 to 20 mg (0.1 to 0.3 mg/kg)] q 3 to 6 h prn Max. 160 mg/d	< 15 60 3 to 6	Hepatic / Renal 5	•Elderly – insufficient data; use with caution •Hepatic / Renal dysfunction – reduce dose •Relative antagonist activity: 10x that of pentazocine •Ceiling to respiratory depressant effects seen at doses ~30 mg •Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Nalbupine (cont.)	IV	same as IM	2 to 3 30 —		
	SC	same as IM	< 15 ND —		.
Pentazocine	PO	25 to 50 mg [25 to 100 mg] every 4 to 8 h Max. 600 mg/d	< 15 to 30 < 60 to 180 3	Hepatic / Renal 2.2 to 3.6	•Elderly (60 to 90 y) – Clearance is decreased and half-life increased (Ritschel, 1986) consider dosage modification. •Hepatic dysfunction – Oral bioavailability is increased 2- to 3-fold, clearance decreased about 50%, and half-life doubled in patients with cirrhosis. Use lower dosage and extend dosing interval, or use alternative analgesic. •Renal dysfunction – insufficient data. •Weak antagonist activity. •Wide interindividual variability in rate of metabolism may explain variable and unpredictable analgesic response after oral administration. •SC injections may result in severe tissue damage and should be used only when necessary. •Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.

Table OP2. Opioids: Dosing and Pharmacokinetics

OPIOID AGENT†	ROUTE	INITIAL DOSAGE REGIMEN [TYPICAL DOSAGE RANGE] FOR 70-KG ADULT (18 TO 65 Y)	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	METABOLISM / ELIMINATION HALF-LIFE (H)	DOSING IN SPECIAL POPULATIONS AND OTHER CONSIDERATIONS
Pentazocine (cont.)	IM	20 to 30 mg [20 to 60 mg (0.5 to 1 mg/kg)]; may repeat q 2 to 4 h (max. 60 mg/dose, 360 mg/d)	< 15 to 20 < 15 to 60 3		
	IV	30 mg (0.3 to 0.5 mg/kg); may repeat q 2 to 4 h (max. 30 mg/dose, 360 mg/d)	< 12 to 30 ND 3		
	SC	20 to 30 mg [20 to 60 mg]; may repeat q 2 to 4 h (max. 60 mg/dose, 360 mg/d)	ND ND 3		
OTHER					
Tramadol	PO	50 to 100 mg q 4 to 6 h (max. 400 mg/d)	< 60 ~120 to 240 3 to 6	Hepatic / Renal Hepatically metabolized to active M1 metabolite. (In animal studies, M1 had 6 times the analgesic potency and 200 times the μ-opiate binding potency of tramadol.) 6 to 7 (for tramadol and M1 metabolite)	• Elderly– 65 to 75 y: no dosage adjustment except with renal or hepatic impairment; >75 y: give < 300 mg/d in divided doses. • Hepatic dysfunction – decrease dosage to 50 mg q 12 h in patients with cirrhosis. • Renal dysfunction (CrCl < 30 ml/min) – increase dosing interval to 12 h and decrease maximum daily dose to 200 mg. Dialysis patients can receive their regular dose on the day of dialysis (< 7% of a dose is removed by hemodialysis). • Do not use in patients who have physiologic opioid dependence as it may precipitate withdrawal.

Sources (AHFS, 2000; Anonymous, 2001a; Anonymous, 2001b; Austrup & Korean, 1999; Davies et al., 1996; Donnelly & Shafer, 1995; DuPen et al., 2000; Koo, 1995; Kruger & McRae, 1999; MCCaffery & Pasero 1999; Miyoshi & Leckband, 2000; Omoigui, 1995; Picard et al., 1997; Rawal, 1999; Ready, 2000; Scholz et al. , 1996; Stevens & Edwards, 1999; Tegeder et al.,1999).

CNS = Central nervous system; CR=Controlled release; CrCl = Creatinine clearance; ED = Epidural; GI = Gastrointestinal; IBW = Ideal body weight; IM = Intramuscular; IT = Intrathecal; IV = Intravenous; ND = No data; PCEA = Patient-controlled epidural analgesia; PCIA = Patient-controlled intravenous analgesia;; PO = Per os (oral); PR = Per rectum; prn = pro re nata (as needed); SC = Subcutaneous; SD = Standard deviation; SR = Sustained release,.

Table OP2. Opioids: Dosing and Pharmacokinetics

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

‖ Basal infusion for IV PCA is optional. Some evidence exists that a basal infusion offers no advantages and may increase adverse effects; routine use of basal infusions are not recommended for acute pain management by some authors (Parker RK, Holtzman B, et al., 1992; Parker RK, Sawaki Y, et al., 1992).

§ Central neuraxial (epidural or intrathecal) drugs should be preservative-free and diluted with sterile normal saline. Doses refer to injections of the lumbar region; low doses may be effective when injected in the cervical or thoracic region. The epidural space can safely tolerate up to about 20 ml/h of fluid. ED and IT doses and duration of analgesia vary widely between individuals; doses shown are only guidelines. Epidural doses are usually about 1/10 of intravenous doses, and intrathecal doses are about 1/10 to 1/5 of epidural doses. Elderly patients may require very small doses of ED morphine. The dose of ED morphine required after abdominal hysterectomy has been found to be inversely related to patient age according to the equation:

Effective 24-h epidural morphine dose (mg) = 18 – age (0.15) (Ready et al., 1987).

†† Because the pharmacokinetics of alfentanil, fentanyl, sufentanil, and remifentanil are multi-compartmental, the context-sensitive half-*time* (CSHT) is a more useful parameter than elimination half-life to describe the time for blood drug concentrations to decrease by 50% after variable-length infusions (Hughes et al., 1992; Shafer & Varvel, 1991). For alfentanil, fentanyl, and sufentanil, the CSHT may increase the longer the infusion. For example, based on computer simulations, the CSHT for 100- and 200-min infusions are, respectively, about 45 and 55 min for alfentanil, 50 and > 100 min for fentanyl, and 20 and 25 min for sufentanil. The CSHT for remifentanil is unique in that it is consistently short (< 5 min) and analgesic effects dissipate rapidly independent of the infusion duration (Egan et al., 1993: Kapila et al., 1995).

‡‡ PCEA doses are for use with lumbar epidural catheters. Consider reducing dosage for use with thoracic catheters.

Table OP2.5. Opioids: Dosage Formulations

OPIOID†	ROUTE	FORMULATIONS
PURE AGONISTS		
Phenanthrenes		
Codeine	PO	**Tablets/Capsules (doses in mg):** Codeine alone 15, 30, 60 Codeine/APAP 15/300, 30/300, 60/300 Codeine/ASA 30/325, 60/325 Liquids: Codeine alone 15 mg/5 ml Codeine/APAP 12/120 mg/5 ml
	IM IV SC	Injection: 30 and 60 mg/ml
Hydrocodone	PO	Tablets/Capsules (doses in mg): Hydrocodone/APAP 2.5/500, 5/500, 7.5/650, 7.5/750, 10/325, 10/500, 10/650 Hydrocodone/ASA 5/500 Hydrocodone/Ibuprofen 7.5/200 Liquid: Hydrocodone/APAP 2.5/167 mg/5 ml (7.5/500 mg/15 ml)
Hydromorphone	PO	Tablets: 1, 2, 3, 4 and 8 mg Liquids: 5 mg/5 ml
	IM IV SC IV PCA	Injection: 1, 2, 4, and 10 mg/ml
	PR	Suppositories: 3 mg
	ED IT	Check label for preservative-free formulation for injection.

OPIOID†	ROUTE	FORMULATIONS

Table OP2.5. Opioids: Dosage Formulations

OPIOID†	ROUTE	FORMULATIONS
Levorphanol	PO	Tablets: 2 mg
	IM IV SC	Injection: 2 mg/ml
Morphine	PO	IR tablets: 15, 30 mg CR/SR tablets: 15, 30, 60, 100, 200 mg Liquids: 10 mg/5 ml, 20 mg/5 ml, 20 mg/1 ml
	IM IV SC IV PCA	Injection: 0.5, 1, 2, 4, 5, 8, 10, 15, 25, 50 mg/ml PCA syringes: 1 and 5 mg/ml, 30 ml
	PR	Rectal suppositories: 5, 10, 20, 30 mg
	ED IT	Preservative-free injection: 0.5, 1, 10, 15, 25, and 50 mg/ml
Oxycodone	PO	IR tablets/capsules (doses in mg): Oxycodone alone 5, 15, 30 Oxycodone/APAP: 2.5/325, 5/325, 5/500, 7.5/500, 10/650 Oxycodone/ASA: 2.25/325, 4.5/325 CR tablets: 10, 20, 40 and 80 mg Liquids: Oxycodone alone 5 mg/5 ml, 20 mg/1 ml Oxycodone/APAP 5/325 mg per 5 ml
Oxymorphone	IM IV SC	Injection: 1 and 1.5 mg/ml
	PR	Suppositories: 5 mg
Phenylpiperidines		
Alfentanil	ED	Preservative-free Injection: 500 mcg/ml

Table OP2.5. Opioids: Dosage Formulations

OPIOID†	ROUTE	FORMULATIONS
Fentanyl	IM IV IV PCA	Injection: 50 mcg/ml
	ED IT	Check label for preservative-free formulation for injection.
Meperidine	PO	Tablets: 50, 100 mg Liquid: 50 mg/5 ml
	IM IV SC IV PCA	Injection: 10, 25, 50, 75 & 100 mg/ml
	ED	Check label for preservative-free formulation for injection.
Remifentanil	IV	Preservative-free injection: 1 mg/ml
Sufentanil	IV IV PCA	Injection: 50 mcg/ml
	ED	Preservative-free injection: 50 mcg/ml
Diphenylheptanes		
Methadone	PO	Tablets: 5 & 10mg Liquids: 5 mg/5ml, 10 mg/5ml, 10 mg/1ml
	IM IV SC	Injection: 10 mg/ml
	ED	Check label for preservative-free formulation for injection.
Propoxyphene	PO	Tablets/capsules (doses in mg): Propoxyphene 65, 100 Propoxyphene HCl/APAP 65/650 Propoxyphene Napsylate/APAP 50/325, 100/650 Propoxyphene HCl/ASA/Caffeine 65/389/32.4

Table OP2.5. Opioids: Dosage Formulations

OPIOID†	ROUTE	FORMULATIONS
MIXED AGONIST-ANTAGONISTS OPIOIDS		
Buprenorphine	IM IV	Injection: 0.324 mg (equivalent to 0.3 mg buprenorphine) / ml
Butorphanol	IM IV	Injection: 1 and 2 mg/ml
Dezocine	IM IV SC	Injection: 5, 10, and 15 mg/ml
Nalbuphine	IM IV SC	Injection: 10 and 20 mg/ml

Table OP2.5. Opioids: Dosage Formulations

OPIOID†	ROUTE	FORMULATIONS
Pentazocine	PO	Tablets (doses in mg): Pentazocine/APAP 25/650 Pentazocine/ASA 12.5/325 Pentazocine/Naloxone 50/0.5
	IM IV SC	Injection: 30 mg/ml
OTHER		
Tramadol	PO	Tablets: 50 mg

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

Table OP3. Opioids: Drug Interactions

PRECIPITANT DRUG	OBJECT DRUG	EFFECT OF OBJECT DRUG	DESCRIPTION
Agonist-antagonist opioids	Pure agonist opioids	↓	Opioid-dependent patients may develop withdrawal symptoms.
Barbiturate anesthetics, other CNS depressants	Pure agonist and mixed agonist-antagonist opioids	↑	Additive pharmacologic effects may increase the respiratory and CNS depression of the opioid.
Chlorpromazine Thioridazine	Pure agonist opioids	↑	Potentiate analgesic effects, but also toxic effects. Avoid combination with meperidine.
MAOIs: • Phenelzine • Tranylcypromine • Isocarboxazid • Selegiline	Pure agonist opioids Tramadol	↑	Unpredictable, potentially fatal serotonin-like syndrome due to combination of meperidine and nonselective MAOIs; interaction is possible with the selective MAOI, selegiline. Reaction may occur 2 to 3 weeks, possibly > 3 weeks, after discontinuation of MAOIs. Morphine use with MAOIs doesn't seem to result in such severe reactions; however, MAOIs markedly potentiate the effects of morphine.
Cimetidine	Alfentanil Fentanyl Meperidine Methadone	↑	Possible increased central nervous system or respiratory depression due to decreased metabolism (CYP-3A4) and clearance. Alternatives to cimetidine with less potential to interact: famotidine, nizatidine, ranitidine. Cimetidine may also inhibit opioid-induced histamine release.
Carbamazepine Phenobarbital Phenytoin Primidone	Meperidine Methadone	↓ / ↑	Possible decreased pharmacologic effects of meperidine or methadone, or opioid withdrawal due to increase in hepatic metabolism of the opioids. Increase in normeperidine formation occurs with phenobarbital and phenytoin, and is also possible with carbamazepine and primidone. Combination of antiepileptic and analgesic agents has additive CNS depressant effects.
Protease inhibitors: • Indinavir • Nelfinavir • Ritonavir • Saquinavir	Alfentanil Fentanyl Hydrocodone Meperidine Methadone Oxycodone Propoxyphene	↑	Marked increase in bioavailability, especially with fentanyl, meperidine, and propoxyphene. Avoid combination with meperidine and propoxyphene. Monitor for increased central nervous system and respiratory depression with the other opioids.
Rifampin	Hydrocodone Oxycodone Methadone Morphine Alfentanil Fentanyl	↓	Rifampin-induced increase in hepatic metabolism may decrease opioid blood concentrations, resulting in withdrawal symptoms or loss of analgesic effect.
Propoxyphene	Warfarin	↑	Propoxyphene in combination with acetaminophen has been reported to enhance hypoprothrombinemic effects of warfarin. Effect of propoxyphene alone on oral anticoagulant effects has not been documented.

Table OP3. Opioids: Drug Interactions

PRECIPITANT DRUG	OBJECT DRUG	EFFECT OF OBJECT DRUG	DESCRIPTION
Propoxyphene	Carbamazepine	↑	May increase carbamazepine concentrations and result in clinical signs of toxicity.
Quinidine, SSRIs (paroxetine, fluoxetine, sertraline), and other CYP-2D6 inhibitors	Codeine Dihydrocodeine Hydrocodone Oxycodone Tramadol	↓	Avoid combination; decreased or loss of analgesic effects due to inhibition of metabolism of codeine to morphine (may decrease morphine concentration by 95%); interaction expected to affect extensive metabolizers. Similar interaction may decrease conversion of hydrocodone to hydromorphone, and oxycodone to oxymorphone. Tramadol metabolism is partially dependent on CYP-2D6 and is expected to be less affected than codeine.
Erythromycin Clarithromycin Troleandomycin	Alfentanil	↑	Marked increase in bioavailability of alfentanil; possible prolonged anesthesia or increased respiratory depression. Clarithromycin and troleandomycin are also likely to interact. Alternatives to erythromycin with less potential to interact: azithromycin and dirithromycin.
SSRIs: • Citalopram • Sertraline • Fluoxetine • Fluvoxamine • Paroxetine	Tramadol Meperidine	↑	Serotonin-like syndrome reported with combination of tramadol and sertraline or paroxetine. Interaction is possible with other SSRIs and with meperidine. Consider non-serotonergic analgesics. Use combination with caution; monitor for signs and symptoms of excessive serotonergic effects.
Diltiazem Verapamil	Alfentanil Fentanyl Sufentanil	↑	Diltiazem appears to inhibit CYP-3A4 metabolism of alfentanil. Interaction has resulted in prolonged half-life of alfentanil and delayed extubation. Fentanyl and sufentanil are likely to be affected. Verapamil may also inhibit metabolism of alfentanil.
Alcohol	Propoxyphene	↑	Acute alcohol ingestion may increase propoxyphene bioavailability. Ingestion of large quantities of alcohol with propoxyphene has been associated with fatalities. Mechanism is unclear, but appears to be due to additive or synergistic CNS and respiratory depressant effects.

Sources / Adapted from: (Anonymous, 2001; Fromm et al., 1997; Hansten et al., 2000; Michalets, 1998).

CNS = Central nervous system; MAOI = Monoamine oxidase inhibitor; SSRI = Selective serotonin reuptake inhibitor

↑ = Effect of object drug increased ↓ = Effect of object drug decreased

Table OP4. Opioids: Equianalgesic Dosing

OPIOID AGENT†	EQUIANALGESIC DOSE (mg) BY ROUTE‡					
	PO	**IM**	**IV**	**SC**	**PR**	**TM**
PURE AGONISTS						
Phenanthrenes						
Codeine	180 to 200‡‡	120 to 130	120	120		
Hydrocodone	30					
Hydromorphone	7.5	1 to 2	1.3 to 1.5	1 to 1.5	6	
Levorphanol	4	2	2	2		
Morphine	30 to 60	10	10	10	22.5	
Oxycodone	20 to 30‡‡					
Oxymorphone		1 to 1.5	1	1 to 1.5	5 to 10	
Phenylpiperidines						
Fentanyl		0.1 to 0.2	ND			0.4 to 0.8
Meperidine	300‡‡	75 to 100	ND	75 to 100		
Diphenylheptanes						
Methadone	10 to 20††	10††	10††	8 to 10††		
Propoxyphene	100 to 130					
MIXED AGONIST-ANTAGONIST OPIOIDS						
Buprenorphine		0.3	0.3			
Butorphanol		2 to 3	2			
Dezocine		10	10			
Nalbuphine		10	10	10		
Pentazocine	150	30	30	30		
OTHER						
Tramadol	~100 to 150					

Sources: Drug Facts and Comparisons, 2001; AHFS Drug Information, 2000; PDR, 2001; Du Pen et al., 2000; Koo, 1995, American Pain Society 1999.

A blank cell means the drug is not available in the U.S. by the respective route of administration and therefore an equianalgesic dose is not applicable.

ED = Epidural; IM = Intramuscular; IT = Intrathecal; IV = Intravenous; ND = No data; PO = Per os (oral); PR = Per rectum; SC = Subcutaneous; TM = Transmucosal

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

‡ Equivalent doses based on morphine 10 mg IM or SC. The initial dose of the new drug applies to patients who are not tolerant to opioids and should be given at 50% to 67% of the calculated dose (except use 10% to 25% for methadone; see footnote below) to allow for incomplete cross-tolerance (the new drug may have more relative analgesic efficacy and more adverse effects). **Doses of mixed agonist-antagonist opioids and tramadol should NOT be considered equianalgesic to the doses of pure agonists.**

Table OP4. Opioids: Equianalgesic Dosing

†† The initial dose of methadone should be given at 10% to 25% of the calculated dose; dosing of methadone is controversial.

‡‡ Starting doses lower (codeine, 30 mg; oxycodone, 5 mg; meperidine, 50 mg). Codeine exhibits a ceiling effect at doses > 60 mg.(Walker and Zacny, 1998).

Opioids

References

AHFS. AHFS Drug Information. Bethesda: American Society of Health-System Pharmacists, Inc.; 2000.

Anonymous. Drug Facts and Comparisons. St. Louis: A Wolters Kluwer Company; 2001.

Anonymous. Physicians' Desk Reference. Montvale, New Jersey: Medical Economics Company; 2001.

Austrup ML, Korean G. Analgesic agents for the postoperative period. Opioids. Surg Clin North Am 1999; 79(2):253-73.

Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157(14):1531-6.

Cambareri JJ, Afifi MS, Glass PS, Esposito BF, Camporesi EM. A-3665, a new short-acting opioid: a comparison with alfentanil. Anesth Analg 1993; 76(4):812-6.

Crome P, Gain R, Ghurye R, Flanagan RJ. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in elderly hospital patients after single and multiple doses of distalgesic. Preliminary analysis of results. Hum Toxicol 1984; 3 Suppl:41S-8S.

Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 1996; 31(6):410-22.

Donnelly A, Shafer A. Perioperative Care in Applied Therapeutics: The Clinical Use of Drugs. LY Young & MA Koda-Kimble, eds. Vancouver: Applied Therapeutics Inc.; 1995.

Du Pen S, DeRidder M, Du Pen A, Stanley K, Kim D. Cynergy Group Opioid Conversion Calculator;Cynergy Group Web site. Available at: http://www.cynergygroup.com/cgi-bin/calc/Convert.asp; December 2000, version 1.0M. Accessed 15 Dec. 2000

Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 1993; 79(5):881-92.

Elta GH, Barnett JL. Meperidine need not be proscribed during sphincter of Oddi manometry. Gastrointest Endosc 1994; 40(1):7-9.

Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg 1987; 66(8):723-30.

Fromm MF, Eckhardt K, Li S, Schanzle G, Hofmann U, Mikus G, Eichelbaum M. Loss of analgesic effect of morphine due to coadministration of rifampin. Pain 1997; 72(1-2):261-7.

Gardner JS, Blough D, Drinkard CR, Shatin D, Anderson G, Graham D, Alderfer R. Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy 2000; 20(12):1423-31.

Gasse C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 2000; 20(6):629-34.

Hansten P, Horn J. Drug Interactions: Analysis and Management. St.Louis, MO: Facts and Comparisons; 2000.

Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. Anesthesiology 1985; 62(2):124-9.

Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76(3):334-41.

Jick H, Derby LE, Vasilakis C, Fife D. The risk of seizures associated with tramadol. Pharmacotherapy 1998; 18(3):607-11.

Joehl RJ, Koch KL, Nahrwold DL. Opioid drugs cause bile duct obstruction during hepatobiliary scans. Am J Surg 1984; 147(1):134-8.

Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, Howell S, Smith RL. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 1995; 83(5):968-75.

Koo P. Pain. Applied Therapeutics; The Clinical Use of Drugs. In: LY Young & MA Koda-Kimble, eds. Vancouver: Applied Therapeutics Inc.; 1995:7-1 to 7-28.

Kruger M, McRae K. Pain management in cardiothoracic practice. Surg Clin North Am 1999; 79(2):387-400.

Manninen PH, Burke SJ, Wennberg R, Lozano AM, El Beheiry H. Intraoperative localization of an epileptogenic focus with alfentanil and fentanyl. Anesth Analg 1999; 88(5):1101-6.

McCaffery M, Pasero C. Pain: Clinical Manual, 2nd ed. St. Louis: Mosby Inc., 1999.

McCammon RL, Stoelting RK, Madura JA. Effects of butorphanol, nalbuphine, and fentanyl on intrabiliary tract dynamics. Anesth Analg 1984; 63(2):139-42.

Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 1998; 18(1):84-112.

Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: JD Loeser, ed. Bonica's Management of Pain. New York: Lippincott Williams & Wilkins; 2000:1682-1709.

Omoigui, S. The Pain Drugs Handbook. St. Louis: Mosby-Year Book, Inc.; 1995.

Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. Anesthesiology 1992; 76(3):362-7.

Parker RK, Sawaki Y, White PF. Epidural patient-controlled analgesia: influence of bupivacaine and hydromorphone basal infusion on pain control after cesarean delivery. Anesth Analg 1992; 75(5):740-6.

Picard PR, Tramer MR, McQuay HJ, Moore RA. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. Pain 1997; 72(3):309-18.

Radnay PA, Duncalf D, Novakovic M, Lesser ML. Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol, and naloxone. Anesth Analg 1984; 63(4):441-4.

Ragazzo PC, Galanopoulou AS. Alfentanil-induced activation: a promising tool in the presurgical evaluation of temporal lobe epilepsy patients. Brain Res Brain Res Rev 2000; 32(1):316-27.

Rawal N. Epidural and spinal agents for postoperative analgesia. Surg Clin North Am 1999; 79(2):313-44.

Ready LB. Acute Perioperative Pain. In: Anesthesia 5th ed. RD Miller, editor. Philadelphia: Churchill Livingstone; 2000.

Ready LB, Chadwick HS, Ross B. Age predicts effective epidural morphine dose after abdominal hysterectomy. Anesth Analg 1987; 66(12):1215-8.

Ritschel WA, Hoffmann KA, Willig JL, Frederick KA, Wetzelsberger N. The effect of age on the pharmacokinetics of pentazocine. Methods Find Exp Clin Pharmacol 1986; 8(8):497-503.

Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982; 56(2):93-6.

Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet 1996; 31(4):275-92.

Sebel PS, Hoke JF, Westmoreland C, Hug Jr CC, Muir KT, Szlam F. Histamine concentrations and hemodynamic responses after remifentanil. Anesth Analg 1995; 80(5):990-3.

Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991; 74(1):53-63.

Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage MM, Anderson DL. Prospective multicenter evaluation of tramadol exposure. J Toxicol Clin Toxicol 1997; 35(4):361-4.

Staritz M, Poralla T, Manns M, Meyer Zum Buschenfelde KH. Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. Gut 1986; 27(5):567-9.

Stevens DS, Edwards WT. Management of pain in intensive care settings. Surg Clin North Am 1999; 79(2):371-86.

Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 1999; 37(1):17-40.

Tempelhoff R, Modica PA, Bernardo KL, Edwards I. Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. J Neurosurg 1992; 77(2):201-8.

Thune A, Baker RA, Saccone GT, Owen H, Toouli J. Differing effects of pethidine and morphine on human sphincter of Oddi motility. Br J Surg 1990; 77(9):992-5.

Walker DJ, Zacny JP. Subjective, psychomotor, and analgesic effects of oral codeine and morphine in healthy volunteers. Psychopharmacology (Berl) 1998; 140(2):191-201.

Warner MA, Hosking MP, Gray JR, Squillace DL, Yunginger JW, Orszulak TA. Narcotic-induced histamine release: a comparison of morphine, oxymorphone, and fentanyl infusions. J Cardiothorac Vasc Anesth 1991; 5(5):481-4.

ACETAMINOPHEN AND NSAIDs

Acetaminophen and the NSAIDs are among the most commonly used analgesic medications. Their efficacy has been established in certain types of postoperative pain (cf. Cochrane reviews, acetaminophen with and without codeine, ibuprofen and diclofenac). They are most effective in the treatment of mild to moderate pain and are also effective as adjunctive or opioid-sparing agents in the treatment of moderate to severe pain (NHMRC, 1999). Although these medications are widely used and have documented efficacy for postoperative pain, they are associated with adverse effects that should be considered when selecting analgesic therapy.

Key points

- Acetaminophen and the NSAIDs (including COX-2–selective inhibitors) act by mediating pyretic and pain pathways. NSAIDs (including COX-2–selective inhibitors) also have anti-inflammatory properties.
- These agents are generally safe and well tolerated. However, excessive doses of acetaminophen have been associated with hepatotoxicity. NSAIDS (including COX-2–selective inhibitors) can cause significant alteration in renal, bronchial, and gastric mucosa function.
- NSAIDs (including COX-2–selective inhibitors) should be avoided in patients who have
  - hypersensitivity to NSAIDs, particularly in patients who have developed NSAID- or aspirin-induced asthma, rhinitis, nasal polyps, or other symptoms of allergic or anaphylactoid reactions;
  - hypersensitivity to sulfonamides (avoid celecoxib);
  - peptic ulcer disease; or
  - significant renal impairment.
- NSAIDS (including COX-2–selective inhibitors) should be used with caution in patients who
  - are elderly (age > 65 years);
  - have hypertension;
  - have renal impairment; or
  - have congestive heart failure.
- Adverse reactions occurring with NSAIDs (including COX-2–selective inhibitors) include the following:
  - anaphylaxis
  - GI bleeding
  - intraoperative bleeding
  - acute renal failure
  - bronchospasm
  - thrombocytopenia
  - Stevens-Johnson syndrome
  - nephritis
  - hepatotoxicity
  - agranulocytosis

- Common reactions experienced by patients taking NSAIDs (including COX-2–selective inhibitors) include the following:
  - stomach upset
  - nausea
  - abdominal pain
  - constipation
  - diarrhea
  - headache
  - dizziness
  - rash
  - urticaria
  - drowsiness
  - fluid retention
  - tinnitus
- Decisions regarding the use of acetaminophen or an NSAID for postoperative analgesia should be guided by the patient's characteristics and the desired balance between analgesic efficacy and adverse effect.

Summary Table. Site-specific Indications—Acetaminophen & NSAIDs

	Pharmacologic Therapy (Route)							Non-Pharmacologic		
Type of surgery by body region	**PO**	**IM**	**IV**	**Epidural**	**Intrathecal**	**IV PCA**	**Regional**	**Physical**	**Cognitive**	**Comments**
1. Head and neck										
Ophthalmic	***NS***	NS	NS	--	--	RARELY		C	X	If there is risk of or actual bleeding, avoid NS*
Craniotomy	NS	***NS***	***NS***	--	--					If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Radical neck	NS	NS	NS	--	--				X	
Oral-maxillofacial	***NS***	NS	NS	--	--			**C**, **I**	X	
2. Thorax-noncardiac										
Thoracotomy	NS	NS	NS					C, **T**	X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Mastectomy	NS	NS	***NS***					C, T	X	
Thoracoscopy	NS	NS	***NS***					C, T	X	
3. Thorax-Cardiac										
CABG	NS	NS	**NS**	RARELY			RARELY			If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
MID-CAB	NS	NS	***NS***	RARELY					X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
4. Upper abdomen										
Laparotomy	NS	NS	NS					***E*,** **T**	X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Laparoscopic cholecystectomy	***NS***	***NS***	***NS***	RARELY	RARELY			***E*,** ***T***	X	
Nephrectomy	NS	NS	NS					***E*,** T	X	
5. Lower abdomen/pelvis										
Hysterectomy	NS	NS	NS					***E*,**	X	
Radical prostatectomy	NS	NS	NS				--	**E**	X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Hernia	***NS***	NS	NS	RARELY		RARELY		C,	X	
7. Back/Spinal										
Laminectomy	NS	NS	***NS***	RARELY	RARELY		--	C, **E**	X	
Spinal fusion				RARELY	RARELY		--	**E** **I**	X	Use of NS may be associated with nonunion
6. Extremities										
Vascular	NS	NS	NS					***C*,** **E**	X	If there is risk of or actual bleeding, avoid NS* If there is renal hypoperfusion, avoid all NS
Total hip replacement	NS	NS	***NS***					**C**, **E,** **T**	X	Use of NS is controversial
Total knee replacement	NS	NS	NS					**C**, **E,** **T**	X	Use of NS is controversial
Knee arthroscopy / Arthroscopic joint repair	NS	NS	NS	RARELY				**C**, **E,** **T**	X	
Amputation	NS	NS	NS					C, **E,** T	X	
Shoulder	NS	NS	NS	--	--			**C**, **E,** **I**, **T**	X	

NS = NSAIDs; **C** = Cold; **E** = Exercise; **I** = Immobilization; **T** = TENS; **X** = Use of cognitive therapy is patient-dependent rather than procedure-dependent

Indications for Use: **Bold/Red/Shaded**: Preferred based on evidence (QE=1; R=A); ***Italicized/Blue:*** Common usage based on consensus (QE=III); Plain Text: Possible Use; * = bleeding is not contraindication for selective COX-2 inhibitors.

Table NS1. Acetaminophen and NSAIDs: Mechanisms of Action, Contraindications, Other Considerations

AGENTS	MECHANISMS OF ACTION	CONTRAINDICATIONS	OTHER CONSIDERATIONS
Acetaminophen	Analgesic and antipyretic properties due to inhibition of central prostaglandin synthesis; does not inhibit peripheral prostaglandin synthesis Lacks anti-inflammatory effects	Hypersensitivity to drug class	The oral route may not be available after oral-maxillofacial surgery. There is no good evidence that NSAIDs are more effective than high-dose acetaminophen for acute musculoskeletal syndromes or postoperatively (Gotzche, 2000; Romsing et al., 2000). There is good evidence that other NSAIDS are more effective than standard acetaminophen/codeine combinations postoperatively (Ahmad et al., 1997). Acetaminophen produces less postoperative bleeding complications compared with NSAIDs that inhibit cyclooxygenase. Acetaminophen does not prolong bleeding time.
All NSAIDs	Analgesic, antipyretic, and anti-inflammatory	Hypersensitivity to drug class ASA/NSAID – induced asthma Renal impairment Bleeding disorder or coagulopathy PUD/GERD IBD Prior or concomitant glucocorticoid use Use with caution if patient: – Has nasal polyps – Is elderly – Has congestive heart failure – Is hypertensive – Is volume depleted Agents with anti-platelet effects may be contraindicated in some craniotomies due to concerns related to intracranial bleeding.	The peri-operative administration of NSAIDs reduces pain scores, morphine consumption and rehabilitation times. Diclofenac and ibuprofen at standard doses give analgesia equivalent to 10mg IM morphine (McQuay et al., 1998). NSAIDs have a ceiling effect with regards to analgesia (Eisenberg et al., 1994; Gotzche, 1993; Gotzche, 2000) and are usually ineffective as the sole analgesic for postoperative pain in more extensive operations. (Joris, 1996). There is no ceiling effect for adverse effects (Chalmers, 1988; Eisenberg et al., 1994; Henry et al., 1996). Administering NSAIDs by injection or per rectum does not appear to be any more effective than by mouth and may cause more harm than good (McQuay & Moore, 1998). Oral agents may not be indicated in radical neck surgery due to frequent limitations in oral intake.

Table NS1. Acetaminophen and NSAIDs: Mechanisms of Action, Contraindications, Other Considerations

AGENTS	MECHANISMS OF ACTION	CONTRAINDICATIONS	OTHER CONSIDERATIONS
All NSAIDs (cont.)			Aspirin use alone or in combination with other NSAIDs can lead to increased incidence of postoperative bleeding complications (Scher, 1996). For noncardiac thoracic surgery, ketorolac may be useful for reducing pain and inflammation associated with chest tubes (Carretta et al., 1996; Puntillo, 1996). There is minimal risk of renal complications when NSAIDs are given to patients without pre-existing renal disease, congestive heart failure, cirrhosis or hemodynamic instability (Lee et al., 2000). There is little risk of gastrointestinal bleeding with short-term perioperative use in healthy patients without pre-existing gastrointestinal ulceration, steroid use or prior heavy NSAID use. Caution should be used in all other patients. Use is generally not recommended in pregnant women because of potential cardiac effects on the fetus and tocolytic effects on labor. In aspirin-sensitive patients, all NSAIDs (including acetaminophen) should be avoided or used with caution (Stevenson, 1998). . NSAIDs have been shown to raise mean blood pressure (Johnson et al., 1994).
Salicylates			
Aspirin	Analgesic, antipyretic, anti-platelet and anti-inflammatory	See contraindications under all NSAIDs	Aspirin use results in a doubling of bleeding time for 4 to 7 days after ingestion. All patients should have their aspirin therapy discontinued at least 7 days prior to surgery. It is not recommended for use as a postoperative analgesic because of its anti-platelet effects (Kallis et al., 1994; Sethi et al., 1990; Wierod et al., 1998). Aspirin should be avoided in children with acute febrile illness due to the potential development of Reyes Syndrome. There is a high incidence of potentially fatal aspirin intolerance (up to 40%) in patients with nasal polyps, asthma and chronic urticaria (Stevenson, 1998).
Non-acetylated salicylates (e.g., salsalate)	Analgesic, antipyretic, and anti-inflammatory	See contraindications under all NSAIDs	See other considerations under all NSAIDs. Non-acetylated salicylates do not affect platelet aggregation. Bleeding times are prolonged by non-salicylate NSAIDs and ASA, but bleeding times are not prolonged by non-acetylated salicylates.

Table NS1. Acetaminophen and NSAIDs: Mechanisms of Action, Contraindications, Other Considerations

AGENTS	MECHANISMS OF ACTION	CONTRAINDICATIONS	OTHER CONSIDERATIONS
Nonspecific Cyclooxygenase (COX) inhibitors			
Diclofenac & other acetic acids Mefenamic acid & other fenamates Nabumetone, Piroxicam and other oxicams Ibuprofen and other propionic acids, etodolac, ketorolac	Analgesic, antipyretic, and anti-inflammatory effects due to inhibition of COX-1 and –2, and leukotriene synthesis; also anti-bradykinin and lysosomal membrane stabilizing activity.	See contraindications under All NSAIDs	Ketorolac offers advantage of parenteral routes (IV/IM) of administration. For noncardiac thoracic surgery, ketorolac may be useful for reducing pain and inflammation associated with chest tubes (Carretta et al., 1996; Puntillo, 1996).
Cyclooxygenase-2 (COX-2)–selective inhibitors			
Celecoxib Rofecoxib	Analgesic, antipyretic, and anti-inflammatory effects due to inhibition of COX-2.	See contraindications under All NSAIDs Sulfonamide allergy (celecoxib)	Bleeding times are not prolonged. Limited evidence suggests that COX-2 inhibitors lack a cardioprotective effect. Rofecoxib has been associated with an increased risk of MI in comparison with naproxen (Bombardier et al., 2000). In patients with acute postoperative pain or chronic pain due to RA or OA and who were NOT taking low doses (</= 325 mg) of ASA, these agents have been associated with a lower frequency of GI toxicity in comparison with ibuprofen, naproxen, or diclofenac SR (Package Insert; Silverstein et al., 2000; Bombardier et al., 2000). Even low doses of ASA reduce or eliminate the gastroprotective benefit of selective COX-2 inhibitors (Silverstein et al., 2000). No analgesic benefit over nonselective NSAIDs (naproxen or ibuprofen) for postoperative dental or orthopedic pain (Malmstrom et al., 1999; Package Insert). Opioid-sparing effects demonstrated in spinal surgery (Reuben et al., 2000). Have no renal benefits over nonselective NSAIDs. May interfere with bone remodeling (Package Insert).

Table NS2. Acetaminophen and NSAIDs: Dosing and Pharmacokinetics

Agent[†‡]	Dosage Regimen (Dose, route, frequency)	Max Daily Dose (mg)	Onset (min)	Peak (min)	Duration (h)	Half-life (h)	Other Considerations
ACETAMINOPHEN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) (See previous bullet section for general considerations for acetaminophen and NSAIDs.)							
Para-aminophenols							
Acetaminophen	650mg PO q4-6h	4000	15 to 30	10 to 60	4 to 6	2	Overdose may lead to fatal hepatotoxicity. Lacks anti-inflammatory effect. Can be used safely in pregnancy.
Salicylates							
Acetylsalicylic Acid	650 mg PO q4-6h	4000	15 to 30	15 to 120	2 to 4	0.25 to 0.3 (ASA) 2 to 12 (salicylic acid)	Consider enteric coated formulation. Avoid 7 to 10 days before surgery. Avoid in children with febrile illness.
Diflunisal	500-1000 mg loading dose, then 250-500 mg PO q8-12h	1500	15 to 30	120 to 180	8 to 12	8 to 12	
Salsalate	1000 mg PO TID or 1500 mg PO BID	3000	15 to 30	120 to 180	8 to 12	≥ 16	Low gastric toxicity; lacks antiplatelet effect. Relatively selective COX-2 inhibitor.
Acetic Acids							
Diclofenac Potassium (immediate-release)	50 mg PO TID (may give initial dose of 100 mg)	200 on first day; 150 thereafter	30 to 60	20 to 120	4 to 8	1 to 2	
Diclofenac Sodium (delayed-release)	50 mg PO TID	225	15 to 30	60 to 180	4 to 8	1 to 2	Also available in combination with misoprostil; this formulation (Arthrotec) reduces gastrointestinal ulcers and erosions but can lead to diarrhea.
Indomethacin	25-50 mg PO q8h	200	15 to 30	60 to 120	4 to 6	4.5 to 6	May aggravate depression or other psychiatric disturbances, epilepsy or Parkinson's.
Sulindac	150-200 mg PO BID	400	< 180	120 to 240	6 to 12	7.8	A pro-drug safer for long-term use with fewer gastrointestinal complications. It is safer for those with renal impairment.
Tolmetin	200 to 400 mg PO TID	2000	15 to 30	30 to 60	4 to 8	1 to 1.5	
Fenamates							
Meclofenamate	50 mg PO q4-6h	400	15 to 30	30 to 60	2 to 4	3.3	Higher incidence of GI side effects of dyspepsia and diarrhea. Serious side effect of hemolytic anemia has occurred.
Mefenamic Acid	500 mg then 250 mg PO q4-6h	1000	15 to 30	120 to 240	2 to 4	2 to 4	Higher incidence of GI side effects of dyspepsia and diarrhea. Serious side effect of hemolytic anemia has occurred.
Naphthylalkanones							
Nabumetone	500 mg PO BID	2000	60 to 90	150 to 240	8 to 12	22.5 to 30	Pro-drug with low risk of gastrointestinal complications; relatively selective COX-2 inhibitor.
Oxicams							
Meloxicam	7.5 to 15 mg PO QD	15	≥ 30	240 to 300	12 to 24	15 to 20	

Table NS2. Acetaminophen and NSAIDs: Dosing and Pharmacokinetics

Agent†‡	Dosage Regimen (Dose, route, frequency)	Max Daily Dose (mg)	Onset (min)	Peak (min)	Duration (h)	Half-life (h)	Other Considerations
Piroxicam	20 mg PO QD	20	60 to 300	180 to 300	≥ 24	30 to 86	May take at least 2 weeks to achieve stable analgesia.
Propionic Acids							
Fenoprofen	200 mg PO q4-6h	3200	15 to 30	60 to 120	2 to 4	2 to 3	
Flurbiprofen	100 mg PO BID-TID	300	60 to 90	90	6 to 8	5.7	
Ibuprofen	400 mg PO q4-6h	3200	15 to 30	60 to 120	4 to 6	1.8 to 2.5	
Ketoprofen	50 to 75 mg PO TID-QID	300	15 to 30	30 to 120	6 to 8	2 to 4	
Naproxen	250 to 500 mg PO q12h	1500	60 to 90	120 to 240	7	12 to 15	Best tolerated of the propionic acids.
Naproxen Sodium	275 to 550 mg PO q12h	1650	15 to 30	60 to 120	7	12 to 13	
Oxaprozin	600 to 1200 mg PO QD	1800	60 to 90	180 to 300	12 to 24	42 to 56	
Pyranocarboxylic acid							
Etodolac	200-400 PO q6-8h	1200	15 to 30	60 to 120	4 to 12	7.3	Have less gastrointestinal side effects than other non-selective COX-2 inhibitors.
Pyrrolizine carboxylic acid							
Ketorolac	20 mg PO initial dose, then 10 mg PO q4-6h	40	30 to 60	60 to 90	4 to 6	2 to 9	Use for up to 5 days maximum.
	30mg IM/IV q 6h	120	30	60 to 120	4 to 6	2 to 9	Use for up to 5 days maximum. Only currently available parenteral NSAID routinely used for postoperative use. Available in topical form for ophthalmic pain.
COX-2–selective Inhibitors							
Celecoxib	400 mg initially, followed by an additional 200-mg dose if needed on the first day, then 200 mg BID	400	60 to 120	180	12 to 24	11	Avoid in those with sulfa allergies. Even low doses of aspirin reduce or eliminate gastroprotective effect. Does not affect platelet aggregation or bleeding times. Limited evidence suggests that COX-2 inhibitors lack a cardioprotective effect.
Rofecoxib	50 mg PO QD	50	60 to 90	120 to 180	24	17	Use for longer than 5 days has not been studied in treatment of acute pain. Even low doses of aspirin reduce or eliminate gastroprotective effect. Does not affect platelet aggregation or bleeding times. Limited evidence suggests that COX-2 inhibitors lack a cardioprotective effect.

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

‡ Not all agents are FDA-approved for treatment of acute pain. Generally, agents that have a delayed onset and longer duration of action may not be suitable for treating acute post-operative pain.

Table NS3. Acetaminophen and NSAIDs: Drug Interactions

PRECIPITANT DRUG	OBJECT DRUG	EFFECT OF OBJECT DRUG	DESCRIPTION
Acetaminophen (APAP) Drug Interactions			
Alcohol, ethyl	APAP	↑	Hepatotoxicity has occurred in chronic alcoholics following various (moderate to excessive) dose levels of acetaminophen.
Anticholinergics	APAP	↓	The onset of acetaminophen effect may be delayed or decreased slightly, but the ultimate pharmacologic effect is not significantly affected by anticholinergics.
APAP	Lamotrigine	↓	Serum lamotrigine concentrations may be reduced, producing a decrease in therapeutic effects.
APAP	Loop diuretics	↓	The effects of the loop diuretic may be decreased because APAP may decrease renal prostaglandin excretion and decrease plasma renin activity.
APAP	Zidovudine	↓	The pharmacologic effects of zidovudine may be decreased because of enhanced nonhepatic or renal clearance of zidovudine.
APAP	Anticoagulants, Oral	↑	Acetamionphen may increase the anticoagulant effect of warfarin particularly when used in doses > 2 grams/day for 1 week or more.
Beta blockers, propranolol	APAP	↑	Propranolol appears to inhibit the enzyme systems responsible for the glucuronidation and oxidation of acetaminophen. Therefore, the pharmcologic effects of acetaminophen may be increased.
Charcoal, activated	APAP	↓	Reduces acetaminophen absorption when administered as soon as possible after overdose.
Contraceptives, oral	APAP	↓	Increase in glucuronidation results in increased plasma clearance and a slightly decreased half-life of acetaminophen.
Probenecid	APAP	↑	Probenecid may slightly increase the therapeutic effectiveness of acetaminophen.
Salicylate Drug Interactions			
Alcohol	Salicylates	↑	The risk of GI ulceration increases when salicylates are given concomitantly. Ingestion of alcohol during salicylate therapy may prolong bleeding time.
Ammonium chloride Ascorbic acid Methionine	Salicylates	↑	Urinary acidifiers decrease salicylate excretion.
Antacids Urinary alkalinizers	Salicylates	↓	Antacids and urinary alkalinizers may decrease the pharmacologic effects of salicylates. Urinary alkalinization increases the renal excretion of salicylic acid due to decreased tubular reabsorption of the non-ionized drug. The magnitude of the antacid interaction depends on agent, dose and pretreatment urine pH.
Carbonic anhydrase inhibitors Salicylates	Salicylates Carbonic anhydrase inhibitors	↑	Salicylate intoxication has occurred after coadministration of these agents. However, salicylic acid renal elimination may be increased if urine is kept alkaline. Conversely, salicylates may displace acetazolamide from protein binding sites resulting in toxicity. Further study is needed.
Charcoal, activated	Aspirin	↓	Coadministration decreases aspirin absorption, depending on charcoal dose and interval between ingestion. May be useful.
Corticosteroids	Salicylates	↓	Corticosteriods increase salicylate clearance and decrease serum levels.

Table NS3. Acetaminophen and NSAIDs: Drug Interactions

PRECIPITANT DRUG	OBJECT DRUG	EFFECT OF OBJECT DRUG	DESCRIPTION
Nizatidine	Salicylates	↑	Increased serum salicylate levels have occurred in patients receiving high-dose aspirin (3.9 g/day) and concurrent nizatidine.
Aspirin	Anticoagulants, Oral	↑	Therapeutic aspirin has an additive hypoprothrombinemic effect. Impaired platelet function may prolong bleeding time. Use with caution.
Aspirin	Heparin	↑	Aspirin can increase bleeding risk in heparin- anticoagulated patients.
Aspirin	Nitroglycerin	↑	Nitroglycerin, when taken with aspirin, may result in unexpected hypotension. Data are limited. If hypotension occurs, reduce the nitroglycerin dose.
Aspirin	NSAIDs	↓	Aspirin may decrease NSAID serum concentrations. Concomitant use offers no advantage and may significantly increase incidence of GI effects.
Aspirin	Valproic acid	↑	Aspirin displaces the drug from its protein-binding sites and may decrease its total body clearance, thus increasing the pharmacologic effects.
Salicylates	Angiotensin-converting enzyme inhibitors	↓	Antihypertensive effects of these agents may be decreased by concurrent salicylate administration, possibly due to prostaglandin inhibition. Consider discontinuing salicylates if problems occur.
Salicylates	Beta-adrenergic blockers	↓	Antitypertensive effects of beta-adrenergic blockers may be blunted by concurrent salicylate administration, possibly due to prostaglandin inhibition. Consider discontinuing salicylates if problems occur.
Salicylates	Loop diuretics	↓	Loop diuretics may be less effective when given with salicylates in patients with compromised renal function or with cirrhosis with ascites; however, data conflict.
Salicylates	Methotrexate	↑	Salicylates increase drug levels and may cause toxicity by interfering with protein binding and renal elimination of the antimetabolite.
Salicylates	Probenecid Sulfinpyrazone	↓	Salicylates antagonize the uricosuric effect of probenecid and sulfinpyrazone. While salicylates in large doses (>3g/day) have a uricosuric effect, smaller amounts may reduce the uricosuric effect of these agents.
Salicylates	Spironolactone	↓	Salicylates may inhibit the diuretic effects; antihypertensive action does not appear altered. Effects depend on the dose of spironolactone.
Salicylates	Sulfonylureas Insulin	↑	Salicylates in doses >2 g/day have a hypoglycemic action, perhaps by altering pancreatic beta cell function. They may potentiate the glucose-lowering effect of these drugs.
NSAID Drug Interactions			
NSAIDs	Anticoagulants	↑	Coadministration may prolong prothrombin time (PT). Also consider the effects NSAIDs have on platelet function and gastric mucosa. Monitor PT and patients closely, and instruct patients to watch for signs and symptoms of bleeding.
NSAIDs	ACE inhibitors	↓	Antihypertensive effects of captopril may be blunted or completely abolished by indomethacin.
NSAIDs	Beta blockers	↓	The antihypertensive effect of the beta blockers may be impaired. Sulindac and naproxen did not affect atenolol.
NSAIDs	Cyclosporine	↑	Nephrotoxicity of both agents may be increased.
NSAIDs	Digoxin	↑	Ibuprofen and indomethacin may increase digoxin serum levels.
NSAIDs	Dipyridamole	↑	Indomethacin and dipyridamole coadministration may augment water retention.

Table NS3. Acetaminophen and NSAIDs: Drug Interactions

PRECIPITANT DRUG	OBJECT DRUG	EFFECT OF OBJECT DRUG	DESCRIPTION
NSAIDs	Hydantoins	↑	Serum phenytoin levels may be increased, resulting in an increase in pharmacologic and toxic effects of phenytoin.
NSAIDs	Lithium	↑	Serum lithium levels may be increased; however, sulindac has no effect or may decrease lithium levels.
NSAIDs	Loop diuretics	↓	Effects of the loop diuretics may be decreased.
NSAIDs	Methotrexate	↑	The risk of methotrexate toxicity (eg, stomatitis, bone marrow suppression, nephrotoxicity) may be increased.
NSAIDs	Penicillamine	↑	Indomethacin may increase the bioavailability of penicillamine.
NSAIDs	Sympathomimetics	↑	Indomethacin and phenylpropanolamine coadministration may result in increased blood pressure.
NSAIDs	Thiazide diuretics	↓	Decreased anthypertensive and diuretic action of thiazides may occur with concurrent indomethacin. Naproxen has also been implicated. Sulindac may enhance the effects of thiazides.
Cimetidine	NSAIDs	↔	NSAID plasma concentrations may be increased or decreased by cimetidine; some studies report no effect. Also, indomethacin and sulindac have increased ranitidine and cimetidine bioavailability.
Probenecid	NSAIDs	↑	Probenecid may increase the concentrations and, possibly, the toxicity of the NSAIDs.
Salicylates	NSAIDs	↓	Plasma concentrations of NSAIDs may be decreased by salicylates. Avoid concurrent use because it offers no therapeutic advantage and may significantly increase the incidence of GI effects. Use of salicylates resulted in decreased binding of ketorolac (2-fold increase of free drug).
DMSO	Sulindac	↓	DMSO may decrease the formation of the active metabolite of sulindac, possibly resulting in decreased therapeutic effect. Also, topical DMSO with sulindac has resulted in severe peripheral neuropathy.
Diflunisal Drug Interactions			
Diflunisal	Acetaminophen	↑	Administration of difunisal resulted in 50% increase in acetaminophen plasma levels. Acetaminophen had no effect on difunisal plasma levels.
Diflunisal	Anticoagulants, oral	↑	Coadministration of diflunisal may increase hypoprothrombinemic effects of anticoagulants. Diflunisal competitively displaces coumarins from protein-binding sites. Monitor prothrombin time during and for several days after coadministration. Adjust dosage of oral anticoagulants as required.
Diflunisal	Hydrochlorthiazide	↑	Coadministration of diflunisal resulted in significantly increased plasma levels of hydrochlorothiazide. Diflunisal decreased the hyperuricemic effects of hydrochlorothiazide.
Diflunisal	Indomethacin	↑	Administration of diflunisal decreased renal clearance and significantly increased plasma levels of indomethacin. The combined use has also been associated with fatal GI hemorrhage.
Diflunisal	Sulindac	↓	Administration of diflunisal resulted in lowering of the plasma levels of the active sulindac sulfide metabolite by 1/3.

↑ = Effect of object drug increased ↓ = Effect of object drug decreased ↔ = Undetermined clinical effect

NSAIDs
References

Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Locker D. The efficacy of nonopioid analgesics for postoperative dental pain: a meta-analysis. Anesth Prog 1997; 44(4):119-26.

Anonymous. Celebrex Prescribing Information. Chicago, IL: G.D. Serle & Co.

Anonymous. Nonsteroidal anti-inflammatory agents. In: Burnham TH, Short RM, eds. Drug Facts and Comparisons. St Louis: Wolters Kluwer Co.; 2001: 836-848.

Anonymous. Nonsteroidal anti-inflammatory agents 28:08;04. In: McEvoy GK, Ed. AHFS Drug Information. Bethesda. American Society of Health-System Pharmacists, 2001 (electronic version).

Anonymous. Vioxx Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.

Auvinet B, Ziller R, Appelboom T, Velicitat P. Comparison of the onset and intensity of action of intramuscular meloxicam and oral meloxicam in patients with acute sciatica. Clin Ther 1995; 17(6):1078-98.

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343(21):1520-8.

Carretta A, Zannini P, Chiesa G, Altese R, Melloni G, Grossi A. Efficacy of ketorolac tromethamine and extrapleural intercostal nerve block on post-thoracotomy pain. A prospective, randomized study. Int Surg 1996; 81(3):224-8.

Chalmers TC, Berrier J, Hewitt P, et al. Meta-analysis of randomized controlled trails as a method of estimating rare complications of non-steroidal anti-inflammatory drug therapy. Aliment Pharmacol Ther 1988(2 (supplement 1)):9-26.

Gotzche P. Non-steroidal anti-inflammatory drugs. In: Clinical Evidence. 4th ed: British Medical Journal Publishing Group; 2000.

Harley EH, Dattolo RA. Ibuprofen for tonsillectomy pain in children: efficacy and complications. Otolaryngol Head Neck Surg 1998; 119(5):492-6.

Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta- analysis. BMJ 1996; 312(7046):1563-6.

Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: JG Hardman, LE Limbird, eds.-in-chief. Goodman and Gilman's The Pharmacologic Basis of Therapeutics 9th Edition. New York: McGraw-Hill; 1996:617-757.

Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta- analysis. Ann Intern Med 1994; 121(4):289-300.

Joris J. Efficacy of non-steroidal anti-inflammatory drugs in post-operative pain. Acta Anaesthesiol Belg 1996; 47(3):115-23.

Kallis P, Tooze JA, Talbot S, Cowans D, Bevan DH, Treasure T. Pre-operative aspirin decreases platelet aggregation and increases post- operative blood loss--a prospective, randomised, placebo controlled, double-blind clinical trial in 100 patients with chronic stable angina. Eur J Cardiothorac Surg 1994; 8(8):404-9.

Lacy CF, Armstrong LL, et al., eds. Drug Information Handbook, 7th edition. Hudson, OH: Lexi-Comp; 1999-2000.

Lee TH, Marcantonio ER., Mangione CM., Thomas EJ., Polanczyk CA., Cook EF., Sugarbaker DJ., Donaldson MC., Poss R., Ho KK., Ludwig LE., Pedan A., Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100(10):1043-9.

McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day- case surgery: a systematic review. Health Technol Assess 1998; 2(12):1-236.

Puntillo KA. Effects of interpleural bupivacaine on pleural chest tube removal pain: a randomized controlled trial. Am J Crit Care 1996; 5(2):102-8.

Reuben S, Connely N. Post-operative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000; November, 91(5):1221-5.

Romsing J, Ostergaard D, Drozdziewicz D, Schultz P, Ravn G. Diclofenac or acetaminophen for analgesia in paediatric tonsillectomy outpatients. Acta Anaesthesiol Scand 2000; 44(3):291-5.

Rusy LM, Houck CS, Sullivan LJ, Ohlms LA, Jones DT, McGill TJ, Berde CB. A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. Anesth Analg 1995; 80(2):226-9.

Sethi GK, Copeland JG, Goldman S, Moritz T, Zadina K, Henderson WG. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. J Am Coll Cardiol 1990; 15(1):15-20.

Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti- inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284(10):1247-55.

Stage J, Jensen JH, Bonding P. Post-tonsillectomy haemorrhage and analgesics. A comparative study of acetylsalicylic acid and paracetamol. Clin Otolaryngol 1988; 13(3):201-4.

Stevenson D. Drug Hypersensitivity: Adverse reactions to non-steroidal anti-inflammatory drugs. Imunol Aller Clin North Amer 1998; November, 18(4):773-98.

Wierod FS, Frandsen NJ, Jacobsen JD, Hartvigsen A, Olsen PR. Risk of haemorrhage from transurethral prostatectomy in acetylsalicylic acid and NSAID-treated patients. Scand J Urol Nephrol 1998; 32(2):120-2.

LOCAL ANESTHETICS

Key Points

- Local anesthetics provide analgesia by blocking transmembrane sodium channels and thus impairing propagation of the nerve action potential along the axon.
- Local anesthetics are effective for postoperative pain management when administered by local, regional, epidural, or intrathecal injection or infusion.
- The combination of local anesthetics with other agents (e.g., epinephrine, clonidine, opioids, or mixed agonist antagonist opioids) may prolong the duration of action for many local anesthetics.
- Allergic reactions occur mainly with the ester type local anesthetics. There may be crossover hypersensitivity between local anesthetics of the ester class. Amide-type local anesthetics have not shown cross-sensitivity with the esters.
- Patients with cardiac disease, hyperthyroidism, or other endocrine diseases may be more susceptible to the toxic effects of local anesthetics.

Summary Table: Site-specific Pain Management Interventions – Local Anesthetics

	Pharmacologic Therapy (Route)							Non-Pharmacologic		
Type of surgery by body region	**PO**	**IM**	**IV**	**Epidural**	**Intrathecal**	**IV PCA**	**Regional**	**Physical**	**Cognitive**	**Comments**
1. Head and neck										
Ophthalmic				--	--	RARELY	**LA**	C	X	
Craniotomy				--	--		LA			
Radical neck				--	--		LA		X	
Oral-maxillofacial				--	--		LA	**C**, **I**	X	
Thoracotomy				**LA**	LA		**LA**	C, **T**	X	
Mastectomy				LA	LA		LA	C, T	X	
Thoracoscopy				LA	LA		LA	C, T	X	
CABG				RARELY			RARELY			
MID-CAB				RARELY			LA		X	
Laparotomy				**LA**	LA		LA	***E***, **T**	X	
Laparoscopic cholecystectomy				RARELY	RARELY		LA	***E***, ***T***	X	
Nephrectomy				***LA***	LA		LA	***E***, T	X	
Hysterectomy				LA	LA		LA	***E***,	X	
Radical prostatectomy				**LA**	LA		--	**E**	X	
Hernia				RARELY		RARELY	**LA**	C,	X	
Laminectomy				RARELY	RARELY		--	C, **E**	X	
Spinal fusion				RARELY	RARELY		--	**E** **I**	X	
Vascular				**LA**	LA		LA	***C***, **E**	X	
Total hip replacement				**LA**	LA		LA	**C**, **E**, **T**	X	
Total knee replacement				***LA***	LA		**LA**	**C**, **E**, **T**	X	
Knee arthroscopy / Arthroscopic joint repair				RARELY			***LA***	**C**, **E**, **T**	X	
Amputation				***LA***	***LA***		***LA***	C, **E**, T	X	
Shoulder				--	--		***LA***	**C**, **E**, **I**, **T**	X	

LA = Local Anesthetics; **C** = Cold; **E** = Exercise; **I** = Immobilization; **T** = TENS; **X** = Use of cognitive therapy is patient-dependent rather than procedure-dependent

Indications for Use: **Bold/Red/Shaded**: Preferred based on evidence (QE=1; R=A); ***Italicized/Blue:*** Common usage based on consensus (QE=III); Plain Text: Possible Use

Table LA1. Local Anesthetics: Mechanisms of Action, Contraindications, Other Considerations

AGENTS	MECHANISMS OF ACTION	CONTRAINDICATIONS	OTHER CONSIDERATIONS
Esters • Benzocaine (Americaine, Cetacaine, Hurricaine) • Chloroprocaine (Nesacaine) • Cocaine • Procaine (Novocaine) • Tetracaine (Pontocaine) **Amides** • Bupivacaine (Marcaine, Sensorcaine) • Dibucaine (Nupercainal) • Etidocaine (Duranest) • Lidocaine (Xylocaine) • Levobupivacaine (Chirocaine) • Mepivacaine (Carbocaine, Polocaine) • Prilocaine (Citanest) • Ropivacaine (Naropin) •	• Local anesthetics block nerve conduction by binding to the transmembrane sodium channels resulting in inhibition of sodium influx. This impairs propagation of the nerve action potential along the axon. • The use of vasoconstrictors (e.g., epinephrine) with local anesthetics promotes local hemostasis, decreases systemic absorption, and prolongs the duration of action. • The use of epidural local anesthetics (bupivacaine) with opioids may allow for comparable or improved analgesia with fewer side effects when compared with using either agent alone.	• Hypersensitivity • Myasthenia gravis • Severe shock • Impaired cardiac conduction • Epidural and spinal anesthesia is contraindicated in serious diseases of the CNS or spinal cord such as meningitis, spinal fluid block, hemorrhage, tumors, polio, syphilis, tuberculosis, or metastatic lesions of the spinal cord. • Regional analgesia with local anesthetics is absolutely contraindicated in anticoagulation, bleeding disorders, infection, and allergy. • Regional analgesia with local anesthetics is relatively contraindicated in altered anatomy, inability to communicate, and peripheral neurologic disease.	• Any local anesthetic may be employed for infiltration anesthesia. Choice of a specific drug is primarily based on desired duration of action. • Peripheral nerve blocks are categorized into minor (involve single nerves) or major (involve two or more nerves or a nerve plexus) types. Most local anesthetics can be used for minor nerve blocks. • Use of local anesthetics in epidural infusions may produce weakness from unwanted motor blockade, hypotension, or urinary retention that may require bladder catheterization. • Administration of local anesthetics may interfere with neurologic monitoring. • In thoracoscopy, injection of local anesthetics through the thoracoscope at the end of the procedure may provide pain control in the immediate postoperative period. • For infiltration and regional block anesthesia, always inject slowly, with frequent aspirations, to prevent intravascular injection. • Epidural analgesia is not used in thoracic cardiac surgery because of the frequent use of anticoagulation and the potential for complications. • Patients with cardiac disease, hyperthyroidism, or other endocrine diseases may be more susceptible to the toxic effects of local anesthetics. • Use with caution in severely debilitated patients and those with liver disease.

Table LA2. Local Anesthetics: Pharmacologic, Pharmacokinetic, and Clinical Characteristics

Chemical Group	Generic (Brand) Names†	Clinical Use	Concentration (%)	Onset (min)	Duration Plain Solution (minutes)	Duration With Epinephrine (minutes)	Recommended maximum single dose (mg)	pH (pKa) of Plain Solution	Comments
Esters	**Procaine**	Infiltration	0.5-1.0	2-5	15-60	30-90	1000	5.0-6.5 (8.9-9.1)	Use has declined because of relatively low potency, slow onset, and short duration of action. Currently used mainly for local infiltration anesthesia and differential spinal blocks to evaluate chronic pain patients. Maximum single dose 15 mg/kg and no more than 1000 mg. Allergic reaction potential increases with repeated use. Metabolized by plasma pseudocholinesterases to para-aminobenzoic acid and other metabolites and excreted in the urine.
		Peripheral blocks	1.0-2.0	2-5	15-30	30-60	1000		
		Spinal	10	ND	30-60	NA	200		
	Chloroprocaine	Infiltration	0.5-2.0	6-12	15-30	30	800 1000 + epinephrine	2.7-4.0 (8.7-9)	An analog of procaine but is hydrolyzed four times faster. Rapid onset, brief duration, and low systemic toxicity. Not used for spinal anesthesia due to reports of neurotoxicity with sensory/motor deficits. Used in obstetrics because it can be metabolized by the fetal enzyme system. Maximum single dose 15 mg/kg and no more than 800 mg (1000 mg with epinephrine). Metabolized by plasma pseudocholinesterases. Metabolites excreted in the urine.
		Peripheral blocks	1.0-2.0	6-12	15-30	30-60	1000 + epinephrine		
		Epidural	1.5	5-15	ND	30-90	1000 + epinephrine		
	Tetracaine	Spinal	0.25-1	Up to 15	75-200	NA	15	4.5-6.5 (8.5-8.6)	An analog of procaine but is ten times more potent and toxic and is hydrolyzed four times slower. Main benefit is its long duration of action. Has poor diffusion qualities so is not a good agent for peripheral blockade unless combined with fast onset local anesthetics. Maximum single dose is 2.5 mg/kg. Used mainly for spinal anesthesia. Metabolized by plasma pseudocholinesterases to para-aminobenzoic acid. Metabolites are mainly excreted in the urine.
	Cocaine	Topical	4.0-10.0	Slow	30-60	NA	150	NA	Used topically primarily in ear, nose and throat procedures. Addictive, causes vasoconstriction, CNS toxicity, marked excitation. May cause cardiac arrhythmia related to sympathetic stimulation. Cocaine is the only local anesthetic that consistently causes vasoconstriction at all concentrations because it inhibits the uptake of norepinephrine by storage granules.
	Benzocaine	Topical	Up to 20.0	Slow	30-60	NA	200	NA	Useful for topical anesthesia of the skin and mucous membranes. There in no applicable pH or pKa for this topical product because pH is an aqueous phenomenon. Polyethylene glycol (PEG) is used in the topical formulation rather than water.

Table LA2. Local Anesthetics: Pharmacologic, Pharmacokinetic, and Clinical Characteristics

Chemical Group	Generic (Brand) Names†	Clinical Use	Concentration (%)	Onset (min)	Duration Plain Solution (minutes)	Duration With Epinephrine (minutes)	Recommended maximum single dose (mg)	pH (pKa) of Plain Solution	Comments
Amides	**Lidocaine**	Infiltration	0.25-1.0	< 2	30-60	120	300	5.0-7.0 (7.9)	Rapid onset and moderate duration of action. Absorption and plasma level will vary by site of administration. Maximum single dose should not exceed 4.5 mg/kg or 300 mg (7 mg/kg or 500 mg with epinephrine) for infiltration and peripheral blocks. The maximum dose for brachial plexus block is 900 mg with epinephrine. Maximum spinal dose is 100 mg. Plasma protein binding is 60-80%. Plasma elimination half-life is 1.5-2.0 hours. Metabolized by the liver with metabolites excreted by the biliary tree, reabsorbed, and then excreted in the urine. Topical solutions of 2-4% are used for procedures involving the oropharynx, tracheobronchial tree, and nose. A 2% topical jelly is used in the urethra. A 2.5-5% ointment is used on the skin, mucous membranes, and rectum. A 2% viscous formulation is used on the oropharynx.
		Peripheral blocks	0.5-1.5	< 2 to 30	60-120	120-240	500 + epinephrine 900 + epinephrine for brachial plexus block or femoral/sciatic block		
		Epidural	1.0-2.0	5-15	ND	30-90	500 + epinephrine		
		Epidural infusion	0.5-2.0	5-15	NA	NA	1.0 mg/kg/hr continuous infusion		
		Spinal	5.0 with dextrose	ND	30-90	NA	100		
		Topical	2.0-5.0	ND	30-60	NA	500 + epinephrine		
	Prilocaine	Infiltration	0.5-1.0	< 2	30-90	120	600	4.5 (7.7-7.9)	An analog of lidocaine. It has a rapid onset and moderate duration of action. Plasma protein binding is 55%. Metabolized by the liver to an aminophenol that can oxidize hemoglobin and methemoglobin, resulting in cyanosis. There is increased risk of methemoglobinemia at doses above 600 mg. Maximum single dose 8 mg/kg or 600 mg.
		Peripheral blocks	0.5-2.0	< 3 to 20	15-30	30-300	600		
		Epidural	1.0-3.0	5-15	ND	60-180	600 + epinephrine		

Table LA2. Local Anesthetics: Pharmacologic, Pharmacokinetic, and Clinical Characteristics

Chemical Group	Generic (Brand) Names†	Clinical Use	Concentration (%)	Onset (min)	Duration Plain Solution (minutes)	Duration With Epinephrine (minutes)	Recommended maximum single dose (mg)	pH (pKa) of Plain Solution	Comments
Amides (cont.)	**Lidocaine and Prilocaine**	Topical	2.5% and 2.5%	< 60	NA	NA	1000-2000 per 10 cm^2	NA	The cream is a eutectic mixture of lidocaine and prilocaine. It is used as a topical anesthetic on intact skin for local analgesia. It is useful in dermal procedures such as intravenous cannulation, venipuncture, and split-thickness skin graft harvesting. A thick layer of cream is applied to intact skin and covered with occlusive dressing and left in place for 1-2 hours. Alternatively, an EMLA™ anesthetic disc is applied and left in place for 1-2 hours. Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and to persist for 1-2 hours after removal of the cream. See the individual agents for further information.
	Mepivacaine	Infiltration	0.25-1.0	0.5-4	45-90	120	400 500 + epinephrine	4.5 (7.6-7.8)	Duration of action slightly longer than lidocaine without epinephrine. Useful for epidural when epinephrine is contraindicated. The maximum dose for brachial plexus block is 750 mg (10 mg/kg). Not used for spinal anesthesia. Plasma protein binding is 60%-85%. Metabolism is markedly decreased in the fetus and newborn so it is infrequently used in obstetrics. Metabolized by the liver. Metabolites undergo enterohepatic circulation and are excreted in the urine. Use with caution in patients with renal disease.
		Peripheral blocks	0.5-2.0	2-30	60-120	120-300	400 500 + epinephrine 750 for brachial plexus block or femoral/sciatic block		
		Epidural	1.0-2.0	5-15	ND	60-180	100		
	Bupivacaine	Infiltration	0.125-0.25	2-10	120-240	180	175	4.0-6.5 (8.1)	Maximum single dose should not exceed 225 mg for infiltration and peripheal blocks. Has inherent vasoconstrictive ativity and the addition of epinephrine does notsignificantly alter the onset or duration of action. For brachial plexus blocks doses of 1.5-2 mg/kg or 200 mg have been used. Avoid exceeding 400 mg/day since clinical experience with higher doses is lacking and drug accumulation may occur. Use in combination with opioids has resulted in good analgesia. The 0.75% solution should not be used for obstetrical analgesia because of reports of associated cardiac arrest with difficult resuscitation or death. Should not be used for regional IV anesthesia. Plasma protein binding is 82%-96%. Mean plasma elimination half-life is 3.5 hours. Metabolized in the liver; drug and metabolites eliminated in the urine.
		Peripheral blocks	0.25-0.5	230	180-360	240-720	225-250 for brachial plexus block or femoral/sciatic block		
		Epidural	0.125-0.375	4-17	ND	180-300	225 + epinephrine		
		Epidural infusion	0.0625-0.125	4-17	NA	NA	0.4 mg/kg/hr continuous infusion		
		Spinal	0.75 in dextrose	1-15	75-200	NA	20		

Table LA2. Local Anesthetics: Pharmacologic, Pharmacokinetic, and Clinical Characteristics

Chemical Group	Generic (Brand) Names†	Clinical Use	Concentration (%)	Onset (min)	Duration Plain Solution (minutes)	Duration With Epinephrine (minutes)	Recommended maximum single dose (mg)	pH (pKa) of Plain Solution	Comments
Amides (cont.)	Etidocaine	Infiltration	0.50	2-8	120-180	180	300	Plain 4.0-5.0 (7.7)	A longer acting derivative of lidocaine that is four times more potent and toxic. It has a rapid onset and prolonged duration. It can cause profound sensory and motor blockade. Not used for obstetrical or spinal analgesia or regional IV anesthesia. Profound motor block is useful in surgical analgesia but makes it less useful in postoperative analgesia. Maximum single doses of plain solution and solution with epinephrine are 6 mg/kg not to exceed 300 mg, and 8 mg/kg not to exceed 400 mg. Plasma protein binding is 95%. Mean plasma elimination half-life is 1.5 hours. Metabolized in the liver. Drug and metabolites excreted in the urine.
		Peripheral blocks	0.25-1.0	2-8	120-240	180-720	400 + epinephrine		
		Epidural	0.5-1.0	5-15	ND	180-300	300 + epinephrine		
	Dibucaine	Topical	1.0	Slow	30-60	NA	50	NA	Used topically in dosage forms applied to the skin (cream, ointment, aerosol), ear (solution), and rectum (suppositories). No longer marketed for spinal administration in the U.S.
	Ropivacaine	Infiltration	0.2-.0.5	1-5	120-360	Same	200	ND (8.1)	Structurally related to bupivacaine. Has inherent vasoconstrictive activity and the addition of epinephrine has not significantly altered the onset or duration of action. Maximum single dose is 4 mg/kg not to exceed 250 mg. Plasma protein binding is 94%. Mean plasma elimination half-life is 1.8 hours. Metabolized by liver cytochrome P-450 1A enzyme system. Metabolites eliminated in the urine. Patients receiving doses in excess of 700 mg/day should be carefully monitored as drug accumulation may occur.
		Peripheral blocks	0.5-0.75	1-5	120-360	Same	250		
		Epidural	0.2-0.5	10-30	ND	NA	200 or 0.4 mg/kg/hr continuous infusion		
	Levobupivacaine	Infiltration	0.25	2-10	ND	NA	150	4.0-6.5 (8.09)	Not approved for intrathecal administration in the U.S. Pharmacokinetic profile similar to bupivacaine. Maximum single dose is 2 mg/kg, not to exceed 150 mg. Plasma protein binding is >97%. Mean plasma elimination half-life is 1.3 hours. Metabolized by liver cytochrome P-450 enzyme system (CYP3A4 and CYP1A2). Metabolites eliminated in the urine and feces.
		Peripheral blocks	0.25-0.5	<9	900-1200	NA	225-250		
		Epidural	0.125-0.25	5-15	600-1020	NA	150 0.4 mg/kg/hr continuous infusion		
		Spinal	0.5	≤ 15	264-390	NA	15		

ND = no data NA = not applicable

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

Table LA3. Local Anesthetics: Adverse Effects

ADVERSE EFFECT	COMMENTS
Allergic or Dermatologic Reactions	Urticaria, pruritis, erythema, angioneurotic edema, sneezing, syncope, excessive sweating, elevated temperature, and anaphylactoid reactions have been reported. Allergic reactions occur mainly with the ester type local anesthetics. There may be crossover hypersensitivity between local anesthetics of the ester class. Use of ester local anesthetics is contraindicated in patients with para-aminobenzoic acid (PABA) allergy. True allergic reactions to the amide type local anesthetics are rare. The amide type local anesthetics have not shown cross-sensitivity with the esters.
Local Tissue Toxicity	Tissue toxicity is rare when proper technique and concentrations of local anesthetics are used. Neurotoxicity may result from intraneural injections, needle trauma, injections of large concentrations or volumes, chemical contamination, and neural ischemia produced by local neural compression or systemic hypotension.
Central Nervous System (CNS)Toxicity	CNS toxicity is related to blood concentration and the rate at which the concentration is presented to the nervous system. This most frequently arises from accidental intravascular injections or administration of an excessive dose. Ester type local anesthetics generally produce stimulant and euphoric effects. Amide type local anesthetics tend to produce sedation and amnesia. High plasma concentrations may initially produce CNS stimulatory effects such as anxiety, apprehension, restlessness, nervousness, disorientation, confusion, dizziness, blurred vision, tremors, twitching, shivering, and seizures. Seizures generally occur with lower blood concentrations than those required to produce cardiovascular collapse. CNS stimulation may be followed by CNS depression manifested by drowsiness, unconsciousness, and respiratory arrest. Commonly reported symptoms associated with increasing blood levels include headache, lightheadedness, numbness and tingling of the perioral area or distal extremities, tinnitus, drowsiness, a sensation of flushing or chilling, and blurred vision.
Cardiovascular Toxicity	Cardiovascular toxicity most frequently arises from accidental intravascular injections or administration of an excessive dose. The patient should be monitored for myocardial depression, hypotension, decreased cardiac output, heart block, syncope, bradycardia, and ventricular arrhythmias. Local anesthetics can decrease myocardial contractility, decrease rates of cardiac conduction, and decrease cardiac contractility in a dose dependent fashion. Local anesthetics may affect vascular smooth muscle tone resulting in either vasoconstriction or vasodilatation depending on the vascular bed affected and on the dose. Cardiovascular toxicity is increased by hypoxia, acidosis, hyperkalemia, and pregnancy.
Miscellaneous Reactions	A transient burning sensation may occur at the site of injection of local anesthetics. Rarely, prolonged burning, pain, skin discoloration, tissue irritation, swelling, and tissue necrosis and sloughing may occur. Unintentional penetration of the subarachnoid space may result in high or total spinal block, hypotension, urinary retention, urinary or fecal incontinence, loss of perineal sensation and sexual function, paresthesia, weakness or paralysis of the lower extremities, loss of sphincter control, headache, backache, meningitis, meningismus, slowing of labor and increased incidence of forceps delivery, cranial nerve palsies, arachnoiditis, and persistent neurologic deficits. Adverse effects of epinephrine-containing solutions: anxiety, palpitations, dizziness, headache, restlessness, tremors, tachycardia, anginal pain, hypertension may occur.

Local Anesthetics
References

AHCPR. AHCPR Clinical Practice Guideline, Acute Pain Management: Operative of Medical Procedures and Trauma. U. S. Department of Health and Human Services 1992.

Anonymous. Chirocaine Prescribing Information. Stanford, CT: Purdue Pharmacology LP.

Anonymous. Cocaine Hydrochloride Topical Solution Prescribing Information. Columbus, Ohio: Roxane Laboratories, Inc.

Anonymous. Duranest Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. EMLA Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Injectable Local Anesthetics. In: T Burnham, Short RM, Eds. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Co; 2000; p 1000-5.

Anonymous. Naropin Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Sensorcaine Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Xylocaine Prescribing Information. Wilmington, DE: AstraZeneca LP.

Ashburn MA, Ready LB. Postoperative pain. In: JD Loeser, ed. Bonica's Management of Pain. New York: Lippincott Williams & Wilkins; 2000:765-779.

Badner N. Epidural agents for postoperative analgesia. Anesth Clin North Am 1992; 10(2):321-37.

Berde CB, Strichartz GR. Local anesthetics. In: RD Miller, ED Miller, JG Reves, eds. Anesthesia. Philadelphia: Churchill Livingston; 2000:506-510 (electronic version).

Buckley FP. Regional anesthesia with local anesthetics. In: JD Loeser, ed. Bonica's management of pain. New York: Lippincott Williams & Wilkins; 2001:1893-1952.

Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999; 91(1):8-15.

Choyce A, Chan VW, Middleton WJ, Knight PR, Peng P, McCartney CJ. What is the relationship between paresthesia and nerve stimulation for axillary brachial plexus block? Reg Anesth Pain Med 2001; 26(2):100-4.

Cockings E, Moore P, Lewis R. Transarterial brachial plexus blockade using high doses of 1.5% mepivacaine. Reg Anesth 1987; 12:159-64.

Cox CR, Checketts MR, Mackenzie N, Scott NB, Bannister J. Comparison of S(-)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 1998; 80(5):594-8.

Foster R, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anesthetic. Drugs 2000; 59(3):551-79.

Freysz M, Beal JL, D'Athis P, Mounie J, Wilkening M, Escousse A. Pharmacokinetics of bupivacaine after axillary brachial plexus block. Int J Clin Pharmacol Ther Toxicol 1987; 25(7):392-5.

Hansen T, Ilett K, Lim S. Pharmacokinetics and clinical efficacy of long-term epidural ropivacaine infusion in children. Br J Anaesth 2000; 85(3):347-53.

Injectable local anesthetics. In: TH Burnham, RM Short, eds. Drug Facts and Comparisons. St. Louis, MO: Wolters Kluwer Co.: 2000:1000-1005.

Kart T, Walther-Larsen S, Svejborg S. Comparison of continuous epidural infusion of fentanyl and bupivacaine with intermittent epidural administration of morphine for postoperative pain management in children. Acta Anaesthesiol Scand 1997; 41(4):461-5.

Local anesthetics 72:00. In: GK McEvoy, ed. AHFS Drug Information. Bethesda: American Society of Health-System Pharmacists, 2000 (electronic version).

Lovstad R, Halvorsen P, Raeder J. A post-operative epidural analgesia with low dose fentanyl, adrenaline and bupivacaine in children after major orthopaedic surgery. A prospective evaluation of efficacy and side effects. Eur J Anaesthesiol 1997; 14(6):583-9.

McBride WJ, Dicker R, Abajian JC, Vane DW. Continuous thoracic epidural infusions for postoperative analgesia after pectus deformity repair. J Pediatr Surg 1996; 31(1):105-7; discussion 7-8.

McGlade DP, Kalpokas MV, Mooney PH, Chamley D, Mark AH, Torda TA. A comparison of 0.5% ropivacaine and 0.5% bupivacaine for axillary brachial plexus anaesthesia. Anaesth Intensive Care 1998; 26(5):515-20.

Palve H, Kirvela O, Olin H, Syvalahti E, Kanto J. Maximum recommended doses of lignocaine are not toxic. Br J Anaesth 1995; 74(6):704-5.

Rawal N. Epidural and spinal agents for postoperative analgesia. Surg Clin North Am 1999; 79:313-344.

Rygnestad T, Zahlsen K, Bergslien O, Dale O. Focus on mobilisation after lower abdominal surgery. A double-blind randomised comparison of epidural bupivacaine with morphine vs. lidocaine with morphine for postoperative analgesia. Acta Anaesthesiol Scand 1999; 43(4):380-7.

Scherhag A, Kleemann PP, Vrana S, Stanek A, Dick W. Plasma concentrations of bupivacaine for continuous peridural anesthesia in children. Anaesthesist 1998; 47(3):202-8.

Silvasti M, Pitkanen M. Continuous epidural analgesia with bupivacaine-fentanyl versus patient- controlled analgesia with I.V. morphine for postoperative pain relief after knee ligament surgery. Acta Anaesthesiol Scand 2000; 44(1):37-42.

Urban MK, Urquhart B. Evaluation of brachial plexus anesthesia for upper extremity surgery. Reg Anesth 1994; 19(3):175-82.

William MJ. Local anesthetics. In: PP Raj, ed. Pain medicine-a comprehensive review. St Louis: Mosby Year Book, Inc.; 1996:162-175.

GLUCOCORTICOIDS

Summary

- Glucocorticoids are potent anti-inflammatory agents that are used as adjunctive agents for the short-term prevention of postoperative pain following certain types of surgery. In a limited number of small studies, these agents have been shown to reduce postoperative pain following arthroscopic, lumbar disc, or other orthopedic surgery and oral surgery. Their role in management of postoperative pain needs further study.
- There is limited evidence that glucocorticoids can significantly reduce requirements for other oral or injectable analgesics, allow earlier mobilization, reduce convalescence time, shorten the length of hospitalization, or reduce patient suffering, anxiety, or irritability postoperatively.
- In addition to anti-inflammatory and analgesic activity, dexamethasone has antiemetic effects that may be beneficial in managing postoperative nausea or vomiting (PONV), or nausea or vomiting related to epidural morphine.
- Increased risk of infection and delayed wound healing are major concerns with the postoperative use of glucocorticoids. There has been little published evidence of these complications, however, after short-term perioperative use of these agents.

Mechanism of Action

The mechanism of analgesic action of glucocorticoids is unclear. Several explanations for their anti-inflammatory effects have been proposed (De Bosscher et al., 2000), including repression of deoxyribonucleic acid transcription (Liden et al., 2000). By inhibiting the production of chemical mediators of inflammation, such as prostaglandins (Muramoto et al., 1997) and bradykinin (Hargreaves & Costello, 1990), glucocorticoids are believed to prevent the lowering of nociceptor thresholds that occurs in response to surgical tissue damage. In addition, the anti-inflammatory effects of glucocorticoids are thought to reduce swelling and thereby prevent the compression of nerves by edematous tissue (Curda, 1983).

The action of glucocorticoids may involve changes in protein (mediator) synthesis, which may take time. It has been suggested that greater reduction in swelling after oral surgery can be obtained when glucocorticoids are given preoperatively as compared to postoperatively (Holland, 1987). Administration of dexamethasone before induction of anesthesia is more effective in preventing PONV than administration after anesthesia (Wang et al., 2000). There is no evidence from randomized controlled trials, however, that earlier rather than later administration of these agents is more effective in preventing postoperative pain.

Therapeutic Uses Evaluated in Randomized Controlled Trials

Pain following orthopedic surgery. Systemic or intra-articular administration of glucocorticoids before or immediately after arthroscopic surgery (Rasmussen et al., 1998; Wang et al., 1998), lumbar disc surgery (King, 1984; Watters et al., 1989), bunion surgery (Curda, 1983), or hallux valgus correction (Asaboe et al., 1998) is effective in reducing pain or reducing the use of narcotic analgesics postoperatively. Treatment with a combination of high-dose, systemic methylprednisolone and bupivacaine followed by application of methylprednisolone to the affected nerve root has been shown to reduce pain following lumbar discectomy (Glasser et al., 1993). Intraoperative irrigation with dexamethasone has also been reported to be a useful adjunctive therapy for lumbar microdiscectomy (Foulkes & Robinson, 1990).

A single RCT has shown that narcotic analgesic requirements following surgery for spinal stenosis can be significantly reduced by postoperative administration of epidural (ED) methylprednisolone acetate. (McNeill et al., 1995). The reduction in analgesic requirements with ED methylprednisolone was similar to that seen with ED administration of morphine or morphine in combination with methylprednisolone acetate. The use of epidural methylprednisolone acetate, however, is controversial. Given the lack of studies documenting its perioperative analgesic efficacy, its use cannot be routinely recommended (Nelson, 1993). (See Adverse Effects.)

Although intrathecal (IT) application of betamethasone before wound closure has short-term efficacy in reducing pain after surgery for herniated disc, the risks associated with disruption of the dural barrier probably outweigh the analgesic benefits of this treatment (Nelson, 1993; Langmayr et al., 1995).

Pain following oral surgery. Systemic administration of glucocorticoids either alone (Beirne & Hollander, 1986) or in combination with local anesthetics or NSAIDs before third molar extraction (Beirne & Hollander, 1986; Hooley & Francis, 1969; Skjelbred & Lokken 1982a; Holland, 1987; Neupert et al, 1992; Schultze-Mosgau et al., 1995) or endodontic procedures (Kaufman et al., 1994) is effective for prevention of postoperative dental pain.

Pain associated with other types of surgery. Glucocorticoids used before or after neurosurgery for cerebral tumors, spinal metastases, head injuries, or acute spinal cord injury may indirectly relieve pain by reducing cerebrospinal fluid formation or tissue edema. The analgesic efficacy of glucocorticoids in these situations, however, has been poorly documented in the literature.

Topical application of a combination of pramoxine and hydrocortisone was found to be ineffective in relieving post-episiotomy pain (Hanretty et al., 1984).

Other clinical outcomes. A combination of preoperative methylprednisolone, intraoperative neural blockade, and postoperative analgesics has been found to produce other beneficial effects postoperatively, such as attenuate reductions in pulmonary function and mobility, and reduce plasma cascade activation following bowel surgery (Schulze et al., 1997). By reducing inflammation and postoperative pain, glucocorticoids can significantly reduce requirements for other oral or injectable analgesics (King, 1984; Vargas & Ross 1989; Watters et al., 1989; Foulkes & Robinson 1990; Glasser et al., 1993; McNeill et al., 1995; Rasmussen et al., 1998), allow earlier mobilization (Vargas & Ross, 1989; Rasmussen et al., 1998), reduce convalescence time (Rasmussen et al., 1998), shorten the duration of hospitalization (Vargas & Ross, 1989; Watters et al., 1989; Foulkes & Robinson, 1990; Glasser et al., 1993), or reduce patient suffering, anxiety, or irritability postoperatively (Watters et al., 1989).

Related Uses

PONV. A recent systematic review found IV dexamethasone to be an effective antiemetic for prevention of early and late PONV in adults (usual dose, 8 or 10 mg) and children (usual dose, 1 or 1.5 mg/kg) (Henzi et al., 2000). Dexamethasone has antiemetic effects that may be beneficial in the prevention of PONV following major gynecologic surgery (Lopez-Olaondo et al., 1996; Liu et al., 1999; Wang et al., 2000), ambulatory laparoscopic tubal ligation (Wang et al. 2000), or other types of surgical procedures (Schulze et al., 1997; Asaboe et al., 1998; Wang et al., 1999;). For major gynecologic surgery, a minimum dose of 2.5 mg is required for antiemetic efficacy (Liu et al., 1999).

Nausea or vomiting related to epidural morphine. Prophylactic administration of dexamethasone (8 mg IV) can reduce nausea or vomiting associated with epidural injection of morphine (3 mg) (Wang et al., 1999).

Contraindications

- History of allergy to glucocorticoids
- Overt or latent tuberculosis
- Peptic ulcer disease
- Systemic viral or fungal infections
- Diabetes mellitus
- Glaucoma
- Congestive heart failure

Adverse Effects

Short-term peri-operative use of glucocorticoids is generally well tolerated. Glucocorticoids may mask signs of infection and their immunosuppressive effects may lead to dissemination of infection. Increased risk of infection and delayed wound healing are major concerns with glucocorticoid therapy. There have been two cases of wound dehiscence reported in a randomized, nonblinded study after treatment with a combination of methylprednisolone IV, epidural analgesics, and IV indomethacin (Schulze et al., 1992). No evidence of these complications has been observed after short-term perioperative use of these agents in small, blinded randomized controlled trials (Frensilli et al., 1974; Skjelbred & Lokken 1982a; Curda, 1983; Holland, 1987; Glasser et al., 1993; Schulze et al., 1997; Rasmussen et al., 1998) or a retrospective case-control study with one-year follow-up (Vargas & Ross, 1989).

A recurrence of pain may occur when the anti-inflammatory and analgesic effects of glucocorticoid wear off (Wilkinson, 1984).

Intra-articular injections of glucocorticoids generally lack systemic adverse effects (Rozental & Sculco 2000); however, systemic and infectious complications are possible. Adrenosuppression has been reported (Wicki et al., 2000). In patients with osteoarthritis, frequent repeated doses of intra-articular glucocorticoids has been associated with joint damage (Parikh et al., 1993; Wada et al., 1993). The treatment course for a specific weight bearing joint should generally be limited to no more than 2 to 3 injections per year (Neustadt, 1992). Other adverse effects associated with intra-articular administration of glucocorticoids include osteonecrosis, tendon rupture, skin atrophy, and crystal-induced synovitis (postinjection flare) (Neustadt, 1992).

High doses or long-term use of glucocorticoids given **orally or parenterally** may be associated with potentially serious systemic and metabolic effects, including hyperglycemia, hypokalemia, adrenosuppression, immunosuppression, infection, myopathy, osteonecrosis, psychosis, depression, dermoatrophy, cataracts, and glaucoma. Agents with mineralocorticoid activity may also cause sodium and water retention (see Table GC1). Adrenosuppression has been reported in patients undergoing oral surgery who received a single dose of dexamethasone 8 mg IV to prevent postoperative complications. Adrenal function returned to normal after 7 days without overt symptoms of adrenal insufficiency, probably because of adequate glucocorticoid activity provided by dexamethasone (Williamson et al., 1980). In a retrospective review, 1 of 44 patients (2.3%) who received high-dose glucocorticoids after neurosurgery for cerebral aneurysm and who were available for follow-up developed osteonecrosis of the hips (Sambrook et al., 1984). Nosocomial infections have been associated with glucocorticoid-induced immunosuppression in neurosurgical patients (Dauch et al., 1994).

Adverse reactions associated with **neuraxial** injection of glucocorticoids peri-operatively have been rarely reported. Complications associated with nonsurgical use of epidural glucocorticoids include infection, dural tap, transient headache, and transient increase in pain (Carette et al., 1997). Infectious, aseptic, or chemical meningitis and adhesive arachnoiditis are also risks (Anonymous, 2000). Complications have occurred after intentional or inadvertent injection of glucocorticoids into the subarachnoid space (Nelson, 1993; Hodges et al., 1998). Although systemic absorption of epidurally administered glucocorticoids is thought to be negligible, adrenosuppression (Jacobs et al., 1983) and Cushing's syndrome (Knight & Burnell, 1980; Tuel et al., 1990) have been reported even after only single doses of methylprednisolone. The adrenosuppressive effects of epidural methylprednisolone acetate may be detectable for three weeks (Jacobs et al.,1983).

Dose and Route of Administration

Glucocorticoids differ in their duration of action, anti-inflammatory potency, and mineralocorticoid activity (Table GC1).

Table GC1: Comparison of Glucocorticoid Agents in Order of Increasing Potency and Duration

Glucocorticoid†	Approximate Equivalent Anti-inflammatory Dose (mg)	Relative Sodium Retaining Potency	Plasma half-life (min)	Biologic half-life (h)
Short-acting				
Cortisone	25	2	30	8 to 12
Hydrocortisone	20	2	80 to 118	8 to 12
Intermediate-acting				
Prednisone	5	1	60	18 to 36
Prednisolone	5	1	115 to 212	18 to 36
Methylprednisolone	4	0	78 to 188	18 to 36
Triamcinolone	4	0	≥ 200	18 to 36
Long-acting				
Dexamethasone	0.75	0	110 to 210	36 to 54
Betamethasone	0.60 to 0.75	0	≥ 300	36 to 54

Adapted from Drug Facts and Comparisons®, 2000(Anonymous 2000)

† Agents shown in **bold** are listed on the VA National Formulary (VANF, as of Dec. 2001); agents shown in *italic* are listed on the DoD Basic Core Formulary (BCF, as of 15 Nov. 2001); agents shown in ***bold italic*** are listed on both the VANF and BCF. Check listings for specific formulations and restrictions.

The more potent glucocorticoids (methylprednisolone, triamcinolone, dexamethasone, and betamethasone) have been the agents most frequently used in studies of postoperative pain control. These agents have a longer duration of action (biologic half-life) and lack mineralocorticoid activity.

Methylprednisolone, dexamethasone, and betamethasone are available as two types of parenteral preparations. One preparation is a solution with prompt onset that may be given IV (i.e., methylprednisolone sodium succinate [Solu-Medrol], dexamethasone sodium phosphate [Decadron phosphate], or betamethasone sodium phosphate [Celestone Phosphate]). The other preparation is a parenteral suspension with sustained activity that is not for IV use (i.e., methylprednisolone acetate [Depo-Medrol], dexamethasone acetate [Decadron-LA], or betamethasone sodium phosphate in combination with betamethasone acetate [Celestone Soluspan]). The betamethasone combination product provides prompt and sustained activities from the sodium phosphate and acetate salt components, respectively. Triamcinolone, as the acetonide, diacetate, or hexacetonide salt, is available only in long-acting parenteral suspensions not intended for IV use.

Many parenteral suspensions of methylprednisolone acetate contain polyethylene glycol, which has been associated with neurotoxicity (Nelson, 1993). Subarachnoid injection of methylprednisolone preparations containing polyethylene glycol should be avoided (Nelson, 1993). The only routes of administration approved for methylprednisolone acetate by the FDA are IM, IA, soft tissue, and intralesional.

Doses of the individual agents found to have postoperative analgesic efficacy in randomized controlled trials have varied according to indication, route, and site of administration (see Table GC2). Glucocorticoids may be given just before or immediately after surgery as single doses or as scheduled, tapering doses over several days postoperatively.

For prevention of PONV related to abdominal total hysterectomy, administration of dexamethasone before induction of anesthesia has been shown to be more effective than administration after anesthesia (Wang et al., 2000).

The doses of glucocorticoids when used for analgesic and antiemetic activity are shown in Table GC2 and Table GC3, respectively.

Table GC2: Dosing and Routes of Administration of Glucocorticoids with Postoperative Analgesic Efficacy (Randomized Controlled Trials)

Procedure	Glucocorticoid[†]	Dosing	Route(s)	Reference
Arthroscopic knee surgery	Methylprednisolone acetate	40 mg at end of surgery	IA	(Rasmussen et al., 1998)
	Triamcinolone acetonide	10 mg at end of surgery	IA	(Wang et al., 1998)
Lumbar disc surgery	Dexamethasone	6 mg before surgery and q6h after surgery for 4 doses, followed by tapering PO doses.[§]	IV then PO	(Watters et al., 1989)
	Methylprednisolone sodium succinate (MPSS) + Methylprednisolone acetate (MPA)	250 mg MPSS + 160 mg MPA at start of surgery, then fat graft soaked in 80 mg MPA applied to affected nerve root before wound closure	IV + IM then direct application	(Glasser et al., 1993)
	Methylprednisolone acetate	40 mg at end of surgery	ED	(McNeill et al., 1995)
Bunion surgery	Dexamethasone sodium phosphate	0.4 to 1.2 mg (depending on site) at end of surgery	IA	(Curda 1983)
Hallux valgus correction or Hemorrhoidectomy	Betamethasone disodium phosphate + acetate[‡]	12 mg, 30 min before surgery	IM	(Asaboe et al., 1998)
Molar extraction	Betamethasone disodium phosphate / acetate[‡]	9 mg before surgery or 3 h after surgery	IM	(Skjelbred & Lokken, 1982a) ; (Skjelbred & Lokken, 1982b)
	Betamethasone	1.2 mg on the evening before surgery, then 1.2 mg q.i.d. to a total of 14.4 mg	PO	(Hooley & Francis, 1969)
	Dexamethasone	4 mg, 5 to 10 min before surgery	IV	(Neupert et al., 1992)
	Methylprednisolone	40 mg before surgery or 125 mg before induction of anesthesia	IV	(Holland, 1987) (Beirne & Hollander, 1986)
	Methylprednisolone	32 mg, 12 h before and after surgery	PO	(Schultze-Mosgau et al., 1995)
Endodontic procedure	Methylprednisolone acetate	4 to 8 mg immediately after onset of local anesthesia	IL	(Kaufman et al., 1994)

ED = Epidural; IA = Intra-articular; IL = Intraligamentary; IT = Intrathecal; IM = Intramuscular; IV = Intravenous; MPA = Methylprednisolone acetate; MPSS = Methylprednisolone sodium succinate; PO = Per os (oral)

† Salt forms of glucocorticoids not shown in table were not specified. Concomitant analgesics or anesthesthetics not shown.

‡ Preparation consisted of 50% betamethasone disodium phosphate with fast onset and 50% betamethasone acetate with slower onset and longer duration.

§ Tapering regimen: 4 mg PO q6h for 4 doses, then 2 mg PO q6h for 4 doses.

Table GC3: Dosing and Administration of Glucocorticoids for Postoperative and Epidural Morphine-Related Nausea or Vomiting

Procedure	Agent†	Effective Dose	Route	Reference
Prevention of Postoperative Nausea or Vomiting				
Various surgeries	Dexamethasone	Usually 8 or 10 mg in adults, 1 or 1.5 mg/kg in children	IV	(Henzi et al., 2000)
Abdominal total hysterectomy or other gynecologic surgery	Dexamethasone	2.5 to 10 mg before induction of anesthesia‡	IV	(Liu et al., 1999) (Wang et al., 2000); (Wang et al., 2000) (Lopez-Olaondo et al., 1996)
Laparoscopic cholecystectomy	Dexamethasone	8 mg, 1 min before induction of anesthesia	IV	(Wang et al., 1999)
Thyroidectomy	Dexamethasone	10 mg, 1 min before induction of anesthesia	IV	(Wang et al., 1999)
Hallux valgus correction or Hemorrhoidectomy	Betamethasone disodium phosphate + acetate§	12 mg, 30 min before surgery	IM	(Asaboe et al., 1998)
Prevention of Nausea or Vomiting Due to Epidural Morphine				
Abdominal total hysterectomy	Dexamethasone	8 mg at end of surgery	IV	(Wang et al., 1999)

IM = Intramuscular; IV = Intravenous

† Salt forms of glucocorticoids not shown in table were not specified.

‡ One study found that administration of dexamethasone before induction of anesthesia was more effective in preventing PONV than administration after anesthesia (Wang et al., 2000).

§ Preparation consisted of 50% betamethasone disodium phosphate with fast onset and 50% betamethasone acetate with slower onset and longer duration.

Evidence

In a limited number of small studies, these agents have been shown to reduce postoperative pain following arthroscopic, lumbar disc, or other orthopedic surgery and oral surgery. Their role in management of postoperative pain needs further study.

EVIDENCE TABLE

	Intervention	Sources of Evidence	QE	R
1	Perioperative use of glucocorticoids as adjunctive analgesic therapy may be a consideration for arthroscopic surgery.	Rasmussen et al., 1998 Wang et al., 1998	I I	A A
2	There is less or weaker evidence supporting the perioperative use of glucocorticoids for prevention of pain following lumbar disc surgery.	Watters et al., 1989 King, 1984	I II-1	B B
3	There is less or weaker evidence supporting the perioperative use of glucocorticoids for prevention of pain following bunion surgery.	Curda, 1983	I	A
4	There is less or weaker evidence supporting the perioperative use of glucocorticoids for prevention of pain following hallux valgus correction surgery.	Asaboe et al, 1998	I	A
5	There is substantial evidence supporting the perioperative use of glucocorticoids for prevention of pain following third molar extraction.	Beirne & Hollander, 1986 Holland, 1987 Neupert et al., 1992 Skjelbred & Lokken, 1982a Schultze et al., 1995 Hooley & Francis, 1969	I I I I I I	A A A A B B
6	The use of epidural methylprednisolone acetate for preventing pain following surgery for spinal stenosis cannot be routinely recommended.	Nelson, 1993	III	D
7	In the case of intrathecal application of betamethasone for reducing pain after surgery for herniated disc, the risks associated with disruption of the dural barrier probably outweigh the analgesic benefits of this treatment.	Langmayr et al., 1995 Nelson, 1993	I III	D E

QE = Quality of Evidence; R = Recommendation (See Introduction)

Glucorticoids References

Anonymous. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Company; 2000.

Asaboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. Anesth Analg 1998; 87(2):319-23.

Beirne OR, Hollander B. The effect of methylprednisolone on pain, trismus, and swelling after removal of third molars. Oral Surg Oral Med Oral Pathol 1986; 61(2):134-8.

Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, Truchon R, Parent F, Levesque J, Bergeron V, Montminy P, Blanchette C. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med 1997; 336(23):1634-40.

Curda GA. Postoperative analgesic effects of dexamethasone sodium phosphate in bunion surgery. J Foot Surg 1983; 22(3):187-91.

Dauch WA, Krex D, Heymanns J, Zeithammer B, Bauer BL. Peri-operative changes of cellular and humoral components of immunity with brain tumour surgery. Acta Neurochir 1994; 126(2-4):93-101.

De Bosscher K, Vanden Berghe W, Haegeman G. Mechanisms of anti-inflammatory action and of immunosuppression by glucocorticoids: negative interference of activated glucocorticoid receptor with transcription factors. J Neuroimmunol 2000; 109(1):16-22.

Foulkes GD, Robinson JS, Jr. Intraoperative dexamethasone irrigation in lumbar microdiskectomy. Clin Orthop 1990; 261:224-8.

Frensilli FJ, Immergut MA, Gilbert EC. Use of methylprednisolone acetate in vasectomy. Urology 1974; 4(6):732-3.

Glasser RS, Knego RS, Delashaw JB, Fessler RG. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. J Neurosurg 1993; 78(3):383-7.

Hanretty KP, Davidson SE, Cordiner JW. Clinical evaluation of a topical anaesthetic preparation (pramoxine hydrochloride and hydrocortisone) in post-episiotomy pain relief. Br J Clin Pract 1984; 38(11-12):421-2.

Hargreaves KM, Costello A. Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther 1990; 48(2):168-78.

Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000; 90(1):186-94.

Hodges SD, Castleberg RL, Miller T, Ward R, Thornburg C. Cervical epidural steroid injection with intrinsic spinal cord damage. Two case reports. Spine 1998; 23(19):2137-42; discussion 41-2.

Hodges SD, Castleberg RL, Miller T, Ward R, Thornburg C. Cervical epidural steroid injection with intrinsic spinal cord damage. Two case reports. Spine 1998; 23(19):2137-42; discussion 41-2.

Holland CS. The influence of methylprednisolone on post-operative swelling following oral surgery. Br J Oral Maxillofac Surg 1987; 25(4):293-9.

Hooley JR, Francis FH. Betamethasone in traumatic oral surgery. J Oral Surg 1969; 27(6):398-403.

Jacobs S, Pullan PT, Potter JM, Shenfield GM. Adrenal suppression following extradural steroids. Anaesthesia 1983; 38(10):953-6.

Kaufman E, Heling I, Rotstein I, Friedman S, Sion A, Moz C, Stabholtz A. Intraligamentary injection of slow-release methylprednisolone for the prevention of pain after endodontic treatment. Oral Surg Oral Med Oral Pathol 1994; 77(6):651-4.

King JS. Dexamethasone--a helpful adjunct in management after lumbar discectomy. Neurosurgery 1984; 14(6):697-700.

Knight CL, Burnell JC. Systemic side-effects of extradural steroids. Anaesthesia 1980; 35(6):593-4.

Langmayr JJ, Obwegeser AA, Schwarz AB, Laimer I, Ulmer H, Ortler M. Intrathecal steroids to reduce pain after lumbar disc surgery: a double- blind, placebo-controlled prospective study. Pain 1995; 62(3):357-61.

Liden J, Rafter I, Truss M, Gustafsson JA, Okret S. Glucocorticoid effects on NF-kappaB binding in the transcription of the ICAM-1 gene. Biochem Biophys Res Commun 2000; 273(3):1008-14.

Liu K, Hsu CC, Chia YY. The effect of dose of dexamethasone for antiemesis after major gynecological surgery. Anesth Analg 1999; 89(5):1316-8.

Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996; 76(6):835-40.

McNeill TW, Andersson GB, Schell B, Sinkora G, Nelson J, Lavender SA. Epidural administration of methylprednisolone and morphine for pain after a spinal operation. A randomized, prospective, comparative study. J Bone Joint Surg Am 1995; 77(12):1814-8.

Muramoto T, Atsuta Y, Iwahara T, Sato M, Takemitsu Y. The action of prostaglandin E2 and triamcinolone acetonide on the firing activity of lumbar nerve roots. Int Orthop 1997; 21(3):172-5.

Nelson DA. Intraspinal therapy using methylprednisolone acetate. Twenty-three years of clinical controversy. Spine 1993; 18(2):278-86.

Neupert EA, Lee JW, Philput CB, Gordon JR. Evaluation of dexamethasone for reduction of postsurgical sequelae of third molar removal. J Oral Maxillofac Surg 1992; 50(11):1177-82; discussion 82-3.

Neustadt D. Osteoarthritis: Diagnosis and Medical/Surgical Management. Philadelphia: WB Sanders; 1992.

Parikh JR, Houpt JB, Jacobs S, Fernandes BJ. Charcot's arthropathy of the shoulder following intraarticular corticosteroid injections. J Rheumatol 1993; 20(5):885-7.

Rasmussen S, Larsen AS, Thomsen ST, Kehlet H. Intra-articular glucocorticoid, bupivacaine and morphine reduces pain, inflammatory response and convalescence after arthroscopic meniscectomy. Pain 1998; 78(2):131-4.

Rozental TD, Sculco TP. Intra-articular corticosteroids: an updated overview. Am J Orthop 2000; 29(1):18-23.

Sambrook PN, Hassall JE, York JR. Osteonecrosis after high dosage, short term corticosteroid therapy. J Rheumatol 1984; 11(4):514-6.

Schultze-Mosgau S, Schmelzeisen R, Frolich JC, Schmele H. Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 1995; 53(1):2-7; discussion -8.

Schulze S, Sommer P, Bigler D, Honnens M, Shenkin A, Cruickshank AM, Bukhave K, Kehlet H. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch Surg 1992; 127(3):325-31.

Skjelbred P, Lokken P. Post-operative pain and inflammatory reaction reduced by injection of a corticosteroid. A controlled trial in bilateral oral surgery. Eur J Clin Pharmacol 1982; 21(5):391-6.

Skjelbred P, Lokken P. Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. Eur J Clin Pharmacol 1982; 23(2):141-6.

Tuel SM, Meythaler JM, Cross LL. Cushing's syndrome from epidural methylprednisolone. Pain 1990; 40(1):81-4.

Vargas JH, Ross DG. Corticosteroids and anterior cruciate ligament repair. Am J Sports Med 1989; 17(4):532-4.

Wada J, Koshino T, Morii T, Sugimoto K. Natural course of osteoarthritis of the knee treated with or without intraarticular corticosteroid injections. Bull Hosp Jt Dis 1993; 53(2):45-8.

Wang JJ, Ho ST, Lee SC, Tang JJ, Liaw WJ. Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. Anesth Analg 1998; 87(5):1113-6.

Wang JJ, Ho ST, Liu HS, Ho CM. Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery. Br J Anaesth 2000; 84(4):459-62.

Wang JJ, Ho ST, Liu YH, Ho CM, Liu K, Chia YY. Dexamethasone decreases epidural morphine-related nausea and vomiting. Anesth Analg 1999; 89(1):117-20.

Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, Ho CM. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999; 83(5):772-5.

Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg 2000; 91(1):136-9.

Watters WC, Temple AP, Granberry M. The use of dexamethasone in primary lumbar disc surgery. A prospective, randomized, double-blind study. Spine 1989; 14(4):440-2.

Wicki J, Droz M, Cirafici L, Vallotton MB. Acute adrenal crisis in a patient treated with intraarticular steroid therapy. J Rheumatol 2000; 27(2):510-1.

Wilkinson H. Comments on Dexamethasone--A helpful adjunct in management after lumbar discectomy. Neurosurgery 1984; 14(6):700.

Williamson LW, Lorson EL, Osbon DB. Hypothalamic-pituitary-adrenal suppression after short-term dexamethasone therapy for oral surgical procedures. J Oral Surg 1980; 38(1):20-8.

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

EDUCATION FOR PAIN MANAGEMENT

Version 1.2

GENERAL PREOPERATIVE EDUCATION

Preoperative Questions:

1. What understanding do you have regarding the pain following this operation?
2. What experience do you have with postoperative pain relief?
3. Do you have a desire for a particular type of pain treatment postoperatively?
4. Do you have any questions about your anesthetic or postoperative pain management plan?
5. What are your concerns about pain medication and pain relief?

If unknown to patient and nurse, ascertain from the surgeon what type and route of analgesia will be used postoperatively to better focus pain education.

What is pain?
Pain is an uncomfortable feeling that tells you something may be wrong in your body. When there is an injury to your body (e.g., surgery, broken bones) or if you have a painful disease or condition (e.g., sickle-cell disease, arthritis, cancer), tiny nerve cells send messages to your brain. Pain medicine blocks or lessens these messages.

Why is pain control important?
Pain can affect your activity, appetite, sleep, energy, mood, and relationships. It can also affect your rate of recovery from the surgery. Pain relief allows you to start walking and doing your breathing exercises so that you can get your strength back faster and leave the hospital sooner after surgery. Pain relief helps you avoid problems such as pneumonia and blood clots, enjoy greater comfort while you heal, and may help you heal faster.

Can pain be relieved?
Pain in almost all cases can be controlled. Although pain is a common experience after surgery and with many types of illness, most patients with postoperative pain can be kept comfortable with simple treatment.

If I am taking pain medications already, does it make a difference?
Be sure to notify your health care provider if you are already taking pain medications. You may require a higher dose of pain medicine to relieve your pain.

How can I help the doctors and nurses "measure" my pain?
Use a pain scale to communicate your pain. For pain management to work, we need to have some way to help your doctors and nurses understand how much you are hurting. You will be asked to use a "pain rating scale" to do this. For example, on a scale of 0 to 10, with 0 being no pain, and 10 being the worst pain you can imagine, how much pain do you have right now?

Appropriate goal for pain relief:
Talk to your doctors and nurses about setting a pain control goal (such as having no pain that's worse than 3 on the scale and being able to turn, cough, take deep breaths, walk, take care of yourself at home etc.). The goal is to relieve your pain without causing too many side effects. It may not be possible to eliminate all your pain after surgery. Our goal is to control your pain so that you are able to function well enough to walk, cough, and deep breathe after surgery. This will allow you to recover more easily following surgery.

When should I ask for pain medication?
Ask for pain medication when your pain first begins. If you know your pain will worsen when walking or doing breathing exercises, ask for pain medication first. It is harder to ease pain once it has taken hold. This is a key step in proper pain control.

How soon after I take medicine should my pain be relieved?
Your pain should be relieved within 30-45 minutes of taking pain medication. If it is not relieved, report this to your nurse or physician so that they can make prompt adjustments to your pain treatment plan.

Will I become addicted to the pain medicine?
It is very unlikely that you will become addicted to pain medication when used as prescribed by your physician. Studies have shown that becoming addicted to pain medication is very rare unless you already have a problem with substance abuse.

How can my pain be controlled?
Both drug and non-drug methods can be successful in helping to prevent and control pain. The most common methods are described below. You, your doctor, and your nurse will decide which ones are right for you.

Medicines for Pain Relief:

NSAIDs: Acetaminophen (e.g., Tylenol) will relieve mild to moderate pain and soreness. Aspirin and ibuprofen (e.g., Motrin) will reduce swelling and soreness and relieve mild to moderate pain.
Benefits:

- These medicines can lessen or eliminate the need for stronger medicines (e.g., morphine or another opioid).

Risks:

- Most NSAIDs interfere with blood clotting. They may cause nausea, stomach bleeding, or kidney problems. For severe pain, an opioid usually must be added.

Opioids: Morphine, oxycodone, codeine, and other opioids are most often used for acute pain such as short-term pain after surgery.
Benefits:

- These medicines are effective for severe pain and they do not cause bleeding in the stomach or elsewhere.
- It is rare for a patient to become addicted as a result of taking opioids for postoperative pain.

Risks:

- Opioids may cause drowsiness, nausea, constipation, itching or interfere with breathing or urination.

Local anesthetics: These drugs (e.g., bupivacaine) are given either near the incision, near nerves, or through a small tube in your back to block the nerves that transmit pain signals.
Benefits:

- Local anesthetics are effective for severe pain.
- Injections or infusions at the incision site block pain from that site.
- There is little or no risk of drowsiness, constipation, or breathing problems.
- Local anesthetics reduce the need for opioid use.

Risks:

- Repeated injections or continuous infusions are needed to maintain pain relief.
- Average epidural doses may cause some patients to have weakness in their legs or dizziness.

Non-Drug Measures for Pain Relief:

Education: Learning about the operation and the pain expected afterwards may reduce anxiety and pain
Benefits:
Reduces anxiety; no equipment needed.

- There are no risks; however, patient attention and cooperation with staff are required.

Relaxation: Simple techniques such as abdominal breathing and jaw relaxation can help to increase your comfort after surgery.
Benefits:

- Relaxation techniques are easy to learn, and they can help to reduce anxiety.
- After instruction, you can use relaxation at any time.

- No equipment is needed.

Risks:

- There are no risks, but you will need instruction from your health care provider.

Example: Slow Rhythmic Breathing for Relaxation

1. Breathe in slowly and deeply.
2. As you breathe out slowly, feel yourself beginning to relax; feel the tension leaving your body.
3. Now breathe in and out slowly and regularly, at whatever rate is comfortable for you. You may wish to try abdominal breathing. If you do not know how to do abdominal breathing, ask your nurse for help.
4. To help you focus on your breathing and breathe slowly and rhythmically: Breathe in as you say silently to yourself, "in, two, three." Breathe out as you say silently to yourself: "out, two, three." Or:
5. Each time you breathe out, say silently to yourself a word such as 'peace' or 'relax'.
6. You may imagine that you are doing this in a place that is very calming and relaxing for you, such as lying in the sun at the beach.
7. Do steps 1 through 4 only once or repeat steps 3 and 4 for up to 20 minutes.
8. End with a slow deep breath. As you breathe out say to yourself, "I feel alert and relaxed."

Additional points: If you intend to do this for more than a few seconds, try to get in a comfortable position in a quiet place. You may close your eyes or focus on an object. This breathing exercise may be used for only a few seconds or for up to 20 minutes.

Physical Agents: Cold packs, support of surgical site while moving, mild exercise such as walking, massage, rest, heat, and TENS are some non-drug pain relief methods that might be used following surgery.

Benefits:

- In general, physical agents are safe and have no side effects.
- TENS, which stands for Transcutaneous Electrical Nerve Stimulation, is often helpful; it is quick to act and can be controlled by the patient.
- Walking is very beneficial in relieving gas pains.

Risks:

- There are few risks related to the use of physical techniques.
- Your physician should approve the use of heat or cold after surgery.
- If TENS is used, there is some cost and staff time involved for purchasing the machine and instructing patients in its use.

Distraction: Distraction prevents or lessens the perception of pain by focusing attention on sensations unrelated to pain. The goals of distraction are to increase pain tolerance and perceived control and to decrease pain intensity. This technique can involve all the senses.

Benefits:

- Distraction is safe and has no side effects.
- It can be individualized to each person's interest.
- It can include music, videos, reading, humor, and television.

Risks:

- There are no risks related to the use of distraction for pain control.

Hypnosis: Hypnosis is a state of focused attention to allow distraction from external stimuli. Induction of this state has been shown to improve pain management.

Benefits:

- Hypnosis is safe and decreases anxiety.

Risks:

- There is a need for a professional trained in hypnosis to assist this procedure.
- It does not work with all patients.

How are pain medicines given?

Oral Medication: Pills (tablets or capsules) and liquid taken by mouth.
Benefits:

- Tablets and liquids cause less discomfort than injections into muscle or fat, *and* they can work just as well.
- They are inexpensive, simple to give, and easy to use at home.

Risks:

- These medicines cannot be used if nothing can be taken by mouth or if you are nauseated or vomiting.
- There may be a delay in pain relief, since you must ask for the medicine and wait for it to be brought to you. Also, these medicines take time (30-60 minutes) to take full effect.

Intramuscular (IM)/Subcutaneous (SQ): An injection or "shot" of medicine given into a muscle or fat.
Benefits:

- Medicine given by injection into fat or muscle is effective even if you are nauseated or vomiting;
- Injections are simple to give.
- They don't require an intravenous access.
- This technique is successfully used to control moderate to severe pain in all regions of the body.

Risks:

- The injection site is usually painful for a short time.
- There are possibilities of infection, sterile abscess, or peripheral nerve injury.
- Medicines given by injection are more expensive than tablets or liquids.
- Pain relief may be delayed while you ask the nurse for medicine and wait for the shot to be drawn up and given.
- Due to the variable absorption and the time and staff necessary to administer, other routes are preferred.

IV PCA (Patient-Controlled Analgesia) / Intravenous (IV): IV is an injection or "shot" of medication given into a vein. IV PCA allows you to control when you get IV pain medication. When you begin to feel pain, you press a button to inject the pain medicine through the IV into your vein.
Benefits:

- Medicines given by injection into a vein are fully absorbed and act quickly.
- This method is well suited for relief of brief episodes of pain.
- When an IV PCA pump is used you can control your own doses of pain medicine.

Risks:

- A small tube must be inserted in a vein.
- You must want to use the pump and learn how and when to give yourself doses of medicine if you use IV PCA.

Regional Analgesia: Local anesthetics injections along a nerve that provide pain relief to a specific area of the body and a decrease in systemic side effects.
Benefits:

- Limiting the analgesia to a region of the body may allow for reducing or eliminating other types of pain medication.
- Reducing the need for other types of pain medication may reduce the incidence of adverse effects.

Risks:

- This technique requires knowledgeable providers and specialized equipment.
- If a single administration is used, there is a limited duration of action, so these patients may require some of the other methods of pain relief also.

Epidural/Spinal: Medication given by injection or through a small tube placed in your back (epidural space or into the spinal fluid). The tube may be connected to a pump, which delivers pain medicine. Some pumps allow you to press a button to inject the pain medicine while others provide continuous flow of medication.

Benefits:

- This method works well when you have chest surgery or an operation on the lower parts of your body.
- These methods provide excellent pain relief with minimal side effects from the medications because they are given in lower doses.

Risks:

- Staff must be specially trained to place a small tube in the back and to watch for problems that can appear hours after pain medicine is given.
- A spinal anesthetic may only provide relief for the duration of the operation and you may require medications by other routes after the operation.
- You may not be allowed to walk or required to walk with assistance only while an epidural catheter is in place.
- You may also experience difficulty urinating that may require a urinary catheter to be placed.

Rectal: Medication in a suppository placed into the rectum.

Benefits:

- This method is inexpensive, simple to give, and easy to use at home.

Risks:

- Some people do not like this route.
- There may be a delay in pain relief, since you must ask for the medicine and wait for it to be brought to you.
- Also, these medicines take time (30-60 minutes) to take full effect.

What to report to your physician or nurse:

1. Report previous drug reactions and allergies.
2. Report conditions such as stomach ulcers, kidney, heart or liver problems, and bleeding problems.
3. Tell us about all other medications you are taking, including over-the-counter medicines, herbal remedies, vitamins, and nutritional supplements.
4. Take your medication exactly as it is prescribed. If the pain medicine does not work as you want it to, TALK to your doctor, nurse, or pharmacist.
5. DO NOT drink alcohol or take other drugs that cause drowsiness without informing your doctor or nurse.
6. DO NOT drive if you are taking medications that produce drowsiness.
7. DO NOT drive after the operation until your doctor says it is safe to do so.
8. Report medication side effects immediately.

DISCHARGE EDUCATION:

Pain control is an important part of your recovery from surgery. Decreased pain will improve your ability to move and resume your normal activities. If your pain is not controlled enough for you to walk and participate in your own self-care, you need to report this to your physician. As you recover from the surgery, it is anticipated that the pain will gradually decrease over time. If the pain suddenly increases or does not decrease after several weeks, this should be reported to your physician.

You may need to modify your activities or home situation for a brief time as you recover from surgery. This may include changing location of sleeping to minimize stair climbing, assistance with household duties and even personal care. Discuss these needs with your health care provider prior to discharge.

You should continue to take the prescribed medication for your pain.

Medicines for Pain Relief:

Use your medication only as directed. If the pain is not relieved or if it gets worse, call your physician.

Remember that oral medications need time to work. Most oral pain relievers need at least 30 minutes to begin to take effect.

NSAIDs: Acetaminophen (e.g., Tylenol) will relieve mild to moderate pain and soreness. Aspirin and ibuprofen (e.g., Motrin) will reduce swelling and soreness and relieve mild to moderate pain. This medication is available both as a prescription and also over-the-counter. If you are taking a prescription, you should not take it over-the-counter. However, if you are not taking a prescription for an anti-inflammatory, you may take these over-the-counter medications for pain if approved by your physician.
Benefits:

- These medicines can lessen or eliminate the need for stronger medicines (e.g., morphine or another opioid).

Risks:

- Most NSAIDs interfere with blood clotting.
- NSAIDs may cause nausea, stomach bleeding, or kidney problems.
- For severe pain, an opioid usually must be added.

Opioids: Morphine, oxycodone, codeine, and other opioids are most often used for acute pain such as short-term pain after surgery.
Benefits:

- These medicines are effective for severe pain and they do not cause bleeding in the stomach or elsewhere.
- It is rare for a patient to become addicted as a result of taking an opioid for postoperative pain.

Risks:

- Opioids may cause drowsiness, nausea, constipation, itching, or interfere with breathing or urination.
- These medications can cause constipation. If you don't have a bowel movement in two days, please contact your physician. Remember to drink plenty of fluids (6-8 glasses of fluids a day unless you are on a fluid-restricted diet).
- These medications can cause drowsiness. Avoid driving or other activities that require alertness when taking opioid pain medications.
- Do not drink any alcohol beverages when you are taking opioid pain medication.

Local anesthetics: These drugs (e.g., bupivacaine) are given either near the incision or through a small tube in your back to block the nerves that transmit pain signals. During the time the surgical area is anesthetized, you will not be able to feel any additional injury to the area, just as you do not feel the pain from the surgery. You will need to be aware of injuring the area. As the medication wears off, the pain may increase. You will then need to use alternative means for pain control.
Benefits:

- Local anesthetics are effective for severe pain. Injections or infusions at the incision site block pain from that site.
- There is little or no risk of drowsiness, constipation, or breathing problems.
- Local anesthetics reduce the need for opioid use.

Risks:

- Repeated injections are needed to maintain pain relief.
- Average doses may cause some patients to have weakness in their legs or dizziness.

You may use the following methods for pain control while at home:

Relaxation: Simple techniques such as abdominal breathing and jaw relaxation can help to increase your comfort after surgery.
Benefits:

- Relaxation techniques are easy to learn, and they can help to reduce anxiety.
- After instruction, you can use relaxation at any time.

- No equipment is needed.

Risks:

- There are no risks, but you will need instruction from your nurse or doctor.

Example: Slow Rhythmic Breathing for Relaxation

1. Breathe in slowly and deeply.
2. As you breathe out slowly, feel yourself beginning to relax; feel the tension leaving your body.
3. Now breathe in and out slowly and regularly, at whatever rate is comfortable for you. You may wish to try abdominal breathing. If you do not know how to do abdominal breathing, ask your nurse for help.
4. To help you focus on your breathing and breathe slowly and rhythmically: Breathe in as you say silently to yourself, "in, two, three." Breathe out as you say silently to yourself, "out, two, three." Or:
5. Each time you breathe out, say silently to yourself a word such as 'peace' or 'relax.'
6. You may imagine that you are doing this in a place that is very calming and relaxing for you, such as lying in the sun at the beach.
7. Do steps 1 through 4 only once or repeat steps 3 and 4 for up to 20 minutes.
8. End with a slow deep breath. As you breathe out say to yourself, "I feel alert and relaxed."

Additional points: If you intend to do this for more than a few seconds, try to get in a comfortable position in a quiet place. You may close your eyes or focus on an object. This breathing exercise may be used for only a few seconds or for up to 20 minutes (McCaffery & Pasero, 1999).

Distraction: Distraction prevents or lessens the perception of pain by focusing attention on sensations unrelated to pain. The goals of distraction are to increase pain tolerance and perceived control and to decrease pain intensity. This technique can involve all the senses.

Benefits:

- Distraction is safe and has no side effects.
- It can be individualized to each person's interest.
- It can include music, videos, reading, humor, and television.

Risks:

- There are no risks related to the use of distraction for pain control.

Physical agents: Cold pack, support of surgical site while moving, mild exercise such as walking, massage, rest, heat, and TENS are some non-drug pain relief methods that might be used following surgery.

Benefits:

- In general, physical agents are safe and have no side effects.
- TENS, which stands for transcutaneous electrical nerve stimulation, is often helpful; it is quick to act and can be controlled by the patient.
- Walking is very beneficial in relieving gas pains.

*Risks***:**

- There are few risks related to the use of physical techniques. Your physician should approve the use of heat or cold after surgery.
- If TENS is used, there is some cost and staff time involved for purchasing the machine and instructing patients in its use. Also, there is only limited evidence to support the effectiveness of TENS for pain relief in certain situations.

EPIDURAL ANALGESIA

+

HOW DOES PAIN AFFECT THE BODY?

When you are injured, pain warns you to protect yourself and avoid further injury. However, unrelieved pain can be harmful, especially when you are sick or after surgery. Pain can make it difficult to take a deep breath and interferes with your ability to move and walk. This can result in complications and a long stay in the hospital.

HOW WILL OTHERS KNOW HOW MUCH PAIN YOU HAVE?

- Your nurses will check you often while you are receiving epidural analgesia. They will ask you to rate your pain on a 0 to 10 scale. A rating of 0 means you feel no pain at all, 5 means you feel a moderate amount of pain, and 10 means you feel the worst pain imaginable.
- Your comfort goal is a reasonable expectation of the degree of pain relief you need to achieve to perform the activities needed for a rapid recovery. If you are unable to maintain this level of comfort, especially during activities such as deep breathing and walking, let your nurse know. The dose of pain medicine usually can be increased to keep you as comfortable as possible without producing intolerable side effects.

WHAT ARE SOME OF THE GOALS OF PAIN MANAGEMENT WITH EPIDURAL ANALGESIA?

- To keep pain from becoming severe and out of control.
- To keep you comfortable so that you can sleep, deep breathe, walk, and visit with others.
- To decrease the length of time spent in the hospital.

HOW DOES EPIDURAL ANALGESIA WORK?

- Pain medicine will be given by a small pump through an epidural catheter, which is a tiny tubing the anesthesiologist will put in your back before surgery.
- The pump will give you a small amount of pain medicine continuously.
- The anesthesiologist may inject pain medicine into the catheter when you request it for pain management, *or*
- You MAY have a button that is attached to the pump that allows you to control the amount of pain medicine given. This is patient-controlled epidural analgesia (PCEA). You can press the button to give yourself a dose of pain medicine when you hurt.
    - The recovery room nurse will manage your pain for you when you arrive in the recovery room, then give you the PCEA button as soon as you are awake enough to manage the pain yourself. It is difficult to treat pain when it is severe, so it is important to "stay on top" of your pain. When you begin to feel some discomfort, press the PCEA button, then wait a few minutes to see if the dose helped to relieve the pain. If the pain has not been relieved, press the PCEA button again.

HOW IS THE EPIDURAL CATHETER PLACED?

- You will be positioned on your side or sitting up with your back arched out toward the anesthesiologist.
- Your back will be washed with a cool soap solution.
- The anesthesiologist will inject local anesthetic to numb the area where the catheter will go. This will feel like a bee sting.
- You will feel pressure against your back while the anesthesiologist advances a needle to find the epidural space.
- A very small catheter will be inserted through the needle into the epidural space, and then the needle will be removed.
- The catheter will be taped to your back and up to your shoulder where it will be connected to the pump.
- While the catheter is in place, you may lie on your back, turn, walk, and perform any activities your physician approves.

WHAT ARE THE SIDE EFFECTS OF EPIDURAL ANALGESIA?

- Itching is not an allergic reaction but is a fairly common side effect of the pain medicine. Ask the nurse for medicine to relieve the itching when necessary.
- Nausea can occur from pain medicine, and it also can be treated with medicine that has been prescribed.
- Some patients have difficulty urinating while they are receiving epidural analgesia. Reducing the dose of pain medicine helps relieve this side effect, and it usually resolves on its own within 48 hours. Often a urinary catheter is used to prevent this side effect.
- Pain medicine slows the bowel and can cause constipation. If your condition allows, the nurse will give you medicine to prevent constipation.
- Excessive drowsiness and respiratory depression are the most serious but least common side effects of pain medicine. Less than 1 percent of patients experience these effects. These two side effects develop slowly. Nurses will be checking your sedation and breathing frequently. If detected, both are easily treated and corrected by decreasing the dose of pain medicine.
- Numbness and tingling from the epidural local anesthetic is normal in and around the surgery incision area. Let your nurse know if numbness or tingling occurs in other areas. If you have difficulty feeling or moving your legs, stay in bed and call your nurse. This usually can be corrected by reducing the dose of pain medicine. Be sure to ask someone to help you up the first few times you walk.

IS EPIDURAL INJECTION SAFE?

- The pump will be programmed to give you an amount of pain medicine that is typically safe for someone your sex, size, age, and diagnosis or type of surgery. If this is too much, the dose of the pain medicine can be reduced.
- The pump will be programmed with a safe hourly limit and safe time between doses so you cannot give yourself too much pain medicine too often.
- You are the only person who will know when you are hurting and when it is necessary and safe to have a dose of pain medicine. Therefore, you are the only person who should press the PCEA button. Your family, visitors, physicians, and hospital personnel are not to press the PCEA button.
- Let the nurse know before you take any other medicines, including the ones you usually take at home.

HOW LONG WILL EPIDURAL ANALGESIA BE USED?

- As your condition improves, your pain will decrease. You will find that you need to press the PCEA button less often as you improve.
- The dose of pain medicine will be decreased gradually until the pump is no longer necessary and you are able to use a different method for taking pain medicine.
- Your nurse or physician will remove the epidural catheter. This is a simple and painless procedure.

May be duplicated for use in clinical practice (McCaffery 1999). In addition to talking with patients about opioids and their side effects, providing written information reinforces explanations about the method of opioid delivery and other important points the patient will need to remember.

IV PCA

HOW DOES PAIN AFFECT THE BODY?

When you are injured, pain warns you to protect yourself and avoid further injury. However, unrelieved pain can be harmful, especially when you are sick or after surgery. Pain can make it difficult to take a deep breath and interferes with your ability to move and walk. This can result in complications and a long stay in the hospital.

HOW WILL OTHERS KNOW HOW MUCH PAIN YOU HAVE?

Your nurses will check you often while you are receiving IV *PCA.* They will ask you to rate your pain on a 0 to 10 scale. *A* rating of 0 means you feel no pain at all, 5 means you feel a moderate amount of pain, and 10 means you feel the worst pain you can imagine.

Establish your comfort goal based on this rating. If you are unable to maintain this level of comfort, especially during activities such as deep breathing and walking, let your nurse know. The dose of pain medicine usually can be increased to keep you as comfortable as possible.

WHAT ARE SOME OF THE GOALS OF PAIN MANAGEMENT WITH 1V PCA?

- To keep pain from becoming severe and out of control.
- To keep comfortable so that you can sleep, deep breathe, walk, and visit with others.
- To decrease the length of time spent in the hospital.

HOW DOES IV PCA WORK?

- Pain medicine will be given by a small pump through your IV line. If you have surgery, the pump will be attached to your IV in the recovery room.
- You will have a *PCA* button that is attached to the pump. You can press the button to give yourself a dose of pain medicine when you hurt.
- You also may be given a small amount of pain medicine continuously.
- The recovery room nurse will manage your pain for you when you arrive in the recovery room, then give you the *PCA* button as soon as you are awake enough to manage the pain yourself.
- It is difficult to treat pain when it is severe, so it is important to "stay on top" of your pain. When you begin to feel some discomfort, press the *PCA* button, then wait a few minutes to see if the dose helped to relieve the pain. If the pain has not been relieved, press the PCA button again.

IS IV PCA SAFE?

The pump will be programmed to give you an amount of pain medicine that is typically safe for someone your sex, size, age, and diagnosis or type of surgery. If this is too much, the dose of the pain medicine can be reduced.

The pump will be programmed with a safe hourly limit and safe time between doses so you cannot give yourself too much pain medicine too often.

You are the only person who will know when you are hurting and when it is necessary and safe to have a dose of pain medicine. Therefore ***you are the only person who should press the PCA button.*** Your family, visitors, physicians, and hospital personnel are not to press the PCA button.

Let the nurse know before you take any other medicines, including the ones you usually take at home.

WHAT ARE THE SIDE EFFECTS OF IV PCA?

Itching is not an allergic reaction but is a fairly common side effect of pain medicine. Ask the nurse for medicine to relieve the itching when necessary.

Nausea can occur from pain medicine, and it also can be treated with medicine that has been prescribed.

Some patients have difficulty urinating while taking pain medicine. Reducing the dose of pain medicine helps relieve this side effect, and it usually resolves on its own within 48 hours. Pain medicine slows the bowel and can cause corutipation. If your condition allows, the nurse will give you medicine to prevent constipation.

Excessive drowsiness and respiratory depression are the most serious but least common side effects of pain medicine. Less than 1 % of our patients experience these effects. These two side effects develop slowly. Nurses will be checking your sedation and breathing frequently. If detected, both are easily treated and corrected by decreasing the dose of pain medicine.

HOW LONG WILL IV PCA BE USED?

- As your condition improves, your pain will decrease. You will find that you need to press the PCA button less often as you improve.
- The dose of pain medicine will be decreased gradually until the pump is no longer necessary and you are able to use a different method for taking pain medicine.

May be duplicated for use in clinical practice (McCaffery 1999). In addition to talking with patients about opioids and their side effects, providing written information reinforces explanations about the method of opioid delivery and other important points the patient will need to remember.

The Pain Trajectory Relative to the Operative Procedure

Type of Surgery	What does it feel like? (Quality)	How bad is it? (Severity w/o pain medication)	How long does it last? (Duration)	How can we control it? (Interventions)
Head & Neck Surgeries				
Eye (Opthalmic)	Little nociceptive pain. Enucleations & retinal surgeries produce both nociceptive & neuropathic.	Mild to Severe	Several days Phantom eye pain may develop following enucleation and last for months to years.	• *Regional* - preferred based on evidence • *IV/PO opioids* and *PO NSAIDs* - consensus • Oral pain medication-consensus
Craniotomies	Nociceptive in nature	Mild to Moderate	Lasts days	• *IM/IV opioids* and *NSAIDs* and *PO opioids* – consensus • Oral medicine (Codeine preferred because of its lessor effect on brain/blood flow) • NSAIDs – controversial • PCA - a consideration but controversial
Radical Neck Dissection	Nociceptive & Neuropathic	Moderate to severe	Days to years	• *PCA opioids* – consensus • Controlled with IM, IV, or PCA opiates
Oral-Maxillofacial	Nociceptive & neuropathic	Mild to severe	1-3 days (outpatients)	• *Cold, Immobilization* - preferred based on evidence • *Oral opioids, NSAIDs* - consensus • Oral opioids and NSAIDs - following surgery • IM or IV – if oral not effective
Thorax (Non-cardiac)				
Thoracotomy	Nociceptive & neuropathic Can develop chronic post-thoractomy pain syndrome	Moderate to severe	Days to weeks Months to years	• *Epidural, TENS* - preferred based on evidence • Thoracic epidural analgesia (opioid & local anesthetic) - greatest beneficial effects • PCA opioids improve pain control vs. IM opioids

Type of Surgery	What does it feel like? (Quality)	How bad is it? (Severity w/o pain medication)	How long does it last? (Duration)	How can we control it? (Interventions)
Mastectomy	Nociceptive & neuropathic Can develop chronic post-mastectomy pain syndrome	Moderate to severe	Days to weeks Months to years	• *IV NSAIDs, IV/PCA opioids* - consensus • IV/IM or PCA for 24 hours followed by PO opioids and NSAIDs
Thoracoscopy	Nociceptive and rarely neuropathic	Mild to moderate Occasionally severe	Days	• *IV opioids and NSAIDs* - consensus
Thorax (Cardiac)				
CABG	Nociceptive	Moderate to severe	Days to weeks	• *IV opioids, NSAIDs* - preferred based on evidence • IV rapidly transitioning to PCA or local
MID-CAB	Nociceptive	Mild to moderate	Days to weeks	• I*V opioids* and *NSAIDs* - consensus • IV rapidly transitioning to PCA or local
Upper Abdomen				
Laparotomy	Nociceptive (somatic and visceral) and neuropathic	Moderate to severe	Days to weeks	• *Epidural opioids*, *Regional*, *TENS* - preferred based on evidence • *PCA opioids*, *Exercise* – consensus
Laparoscopic Cholecystectomy	Nociceptive (somatic and visceral) and neuropathic	Mild to moderate	Days	• *PO, IM, IV NSAIDs, Opioids, TENS, exercise* – consensus
Nephrectomy	Nociceptive (somatic and visceral) and neuropathic	Mild to severe	Days to weeks	• *Epidural opioids, local* – preferred based on evidence • *Exercise* – consensus
Lower Abdomen/Pelvis				
Hysterectomy	Nociceptive and neuropathic	Mild to severe	Weeks	• *PCA opioids, exercise* – consensus • IM, IV/PCA or intraspinal drug administration, oral opioid or NSAID often sufficient once bowel function has returned • Epidural can also be considered for abdominal hysterectomy

Type of Surgery	What does it feel like? (Quality)	How bad is it? (Severity w/o pain medication)	How long does it last? (Duration)	How can we control it? (Interventions)
Radical Prostatectomy	Nociceptive	Moderate to severe	Weeks	• *Epidural opioid*, *exercise* – preferred based on evidence • IM, IV or PCA opiates, epidural analgesia may reduce pain for several subsequent weeks postoperative
Hernia	Nociceptive and neuropathic	Mild to severe	Weeks, neuropathic pain may last weeks to years	• *Regional* - preferred based on evidence • *PO opioids* – consensus • Regional anesthesia may prevent postoperative pain • Opioids combined with NSAIDS to treat pain
Extremities and Vascular				
Vascular	Nociceptive	Mild to moderate	Days to weeks	• *Epidural opioids*, *regional*, *exercise* - preferred based on evidence • Oral, IM IV/PCA, or intraspinal • Epidural may also be used for intra- and postoperative pain control
Total Hip Replacement	Nociceptive	Mild to Severe	Several days to weeks	• *Epidural opioids*, *regional*, *exercise*, *cold*, and *TENS* - preferred based on evidence • IM, IV/PCA, intraspinal opioids, local anesthetics, may be effective • Continue femoral and continuous epidural gives better pain relief with movement • If anticoagulation used, epidural may need to be removed postoperative day #1 or sooner
Total Knee Replacement	Nociceptive	Moderate to severe	Days to weeks	• *Regional*, *Exercise*, *Cold*, *TENS* - preferred based on evidence • *Epidural opioids* – consensus • Continuous epidural and regional or epidural/ femoral blocks have better pain control than IM, IV/PCA

Type of Surgery	What does it feel like? (Quality)	How bad is it? (Severity w/o pain medication)	How long does it last? (Duration)	How can we control it? (Interventions)
Knee arthroscopy/ Arthroscopic joint repair	Nociceptive	Mild to moderate	Days to weeks	• *Exercise, TENS, Cold* – preferred based on evidence
Amputation	Nociceptive and Neuropathic	Moderate to severe	Days to years	• *Exercise* - preferred based on evidence • *Epidural*, *Intrathecal opioids* and *local*, *regional* – consensus • Treat preoperative pain aggressively • Postoperative epidural, intraspinal, IV, IM PO may be effective • May use oral agents in 2-3 days
Shoulder	Nociceptive	Moderate to severe	Weeks	• *Exercise*, *TENS*, *Cold*, *Immobilization* - preferred based on evidence • *Regional* – consensus
Back / Spinal Surgery				
Laminectomy, Discetomy	Nociceptive and neuropathic	Mild to severe	Weeks	• *Exercise* - preferred based on evidence • *IV opioids*, *NSAIDs* – consensus • IV NSAIDs, PCA, IV, IM and PO, NSAIDs may be effective • Epidural can be used for superior pain control • Local infiltration may be helpful
Fusion	Nociceptive and neuropathic	Moderate to severe	Months	• *Exercise*, *Immobilization* – preferred based on evidence • *IV*, *PCA opioids* – consensus • PCA, VI IM with conversion to PO over days • Intraspinal morphine may be used to provide intra- and postoperative pain

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR
MANAGEMENT OF **POSTOPERATIVE PAIN**

APPENDIX A:
GUIDELINE DEVELOPMENT PROCESS

Version 1.2

Guideline Development Process

The present guideline is the product of a close collaboration between the VHA and the DoD, which started in May 2000. The DoD has participated with the VHA in developing and disseminating several CPGs. The guideline will be updated at two to three-year intervals or when relevant research results become available.

The current guideline for the management of postoperative pain represents hundreds of hours of diligent effort and consensus building among knowledgeable individuals from the VHA, DoD, academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary working group that included anesthesiologists, internists, nurses, pharmacists, and expert consultants in the field of guideline and algorithm development. Many of the experts involved in developing this guideline have previously participated in the development of other VHA/DoD clinical practice guidelines.

Development Process

The process of developing this guideline was evidence-based whenever possible. Where evidence is ambiguous or conflicting, or where scientific data are lacking, the clinical experience of the working group was used to guide the development of consensus-based recommendations. The developers incorporated information from several existing, evidence-based guidelines into a format that would maximally facilitate clinical decision-making (Woolf, 1992). This effort drew, among others, from the following sources:

- Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb 1992.
- VHA, Pain as the 5th Vital Sign Toolkit, Washington, DC: National Pain Management Coordinating Committee, October 2000.
- Pain Standards for 2001, Joint Commission on Accreditation of Healthcare Organizations, 2001, http://www.jcaho.org/standard/stds2001_mpfrm.html.

Finally, many guidelines focus on a single episode of care or a single situation (e.g., management of post-colectomy pain). This guideline was designed to cover a broad spectrum of inpatient and outpatient situations, and thereby provides an overview of treatment options as well as detail about specific clinical approaches.

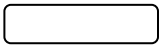
Format of the Guideline

The guideline is presented in an algorithmic format. There are indications that this format improves data collection and clinical decision-making and helps to change patterns of resource use. A clinical algorithm is a set of rules for solving a clinical problem in a finite number of steps. It allows the clinician to follow a linear approach to critical clinical information needed at the major decision points in the disease management process, and stepwise evaluation and management strategies that include the following:

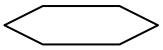
- Ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

The clinical experts subjected all decision points in the algorithms to simulated patients. Hypothetical "patients" were run through the algorithm to test whether it was likely to work in a real clinical situation. Based on these tests, the necessary changes were made to assure accurate clinical logic. Treatment must always reflect the unique clinical issues in an individual patient-clinician situation. Due to the nature of the algorithmic format, the specific therapies and preventive treatments are presented in separate boxes. It is recognized, however, that clinical practice often requires a nonlinear approach and concurrent processes that combine a number of different treatment modalities.

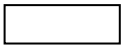
Algorithms
A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (SMDMC, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.



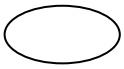
Rounded rectangles represent a clinical state or condition.



Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.



Rectangles represent an action in the process of care.



Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and the specific evidence tables.

The Evidence
The literature supporting the decision points and directives in this guideline is referenced in Evidence Tables and Discussions. The working group leaders were solicited for input on focal issues prior to a review of the literature, and a working list of questions was generated. Electronic searches of the Cochrane Controlled Trials Register (Cochrane Reviews) were undertaken. Full texts or abstracts of the Cochrane reviews were provided to the experts at the May 2000 meeting. In addition, a search was carried out using the National Library of Medicine's (NLM) MEDLINE database. Papers selected for further review were those published in English-language peer-reviewed journals between 1980 and 2000. Preference was given to papers based on randomized, controlled clinical trials, or nonrandomized case-control studies. Studies involving meta-analysis were also reviewed.

In addition, the assembled experts suggested numerous additional references. Copies of specific articles were provided to participants on an as-needed basis. This document includes references through the year 2000. More recent information will be included in the next guideline update.

A complete bibliography of all the sources used in the development of the annotations and discussions is provided.

Rating the Evidence
Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The working group reviewed the articles for relevance and graded the evidence using the rating scheme published in the U. S. Preventive Service Task Force Guide to Clinical Preventive Services, Second Edition (USPSTF, 1996), displayed in Table 1. The experts themselves formulated Quality of Evidence (QE) ratings after an orientation and tutorial on the evidence grading process. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal health care system. The QE rating is based on experimental design and overall quality. Randomized controlled trials (RCT) received the highest ratings (QE=I), while other well-designed studies received a lower score (QE=II-1, II-2, or II-3). The QE ratings are based on the quality, consistency, reproducibility, and relevance of the studies.

Table 1. Quality of Evidence Rating Scheme (USPSTF, 1996)

Quality of Evidence (QE)	
Grade	**Description**
I	Evidence is obtained from at least one properly randomized controlled trial (RCT).
II-1	Evidence is obtained from well-designed controlled trials without randomization.
II-2	Evidence is obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one center or research group.
II-3	Evidence is obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence.
III	Opinions of respected authorities are based on clinical experience, descriptive studies and case reports, or reports of expert committees.

The U. S. PSTF grading process suggests assigning a second grade that reflects the strength of the recommendation (SR) for each appraised study. The evidence grade score (i.e., the SR) reflects the significance of the evidence as drawn from the scientific studies, but does not always reflect the importance of the recommendation to individual patient care. Often, the most basic patient management questions and well-accepted care strategies are the most difficult to test through RCTs (i.e., QE = I), especially when experimental design puts patients at risk. For example, no RCTs have been conducted to quantify the value of administering supplemental oxygen to a patient who presents with an AMI.

In lieu of the SR rating, the recommendation rating (R), using a rating scale from A to E has been formulated. The specific language used to formulate each recommendation conveys panel opinion of both the clinical importance attributed to the topic and the strength of evidence available. When appropriate and necessary, expert opinion was formally derived from the working group panel to supplement or balance the conclusions reached after reviewing the scientific evidence.

The rating of R (displayed in Table 2) is influenced primarily by the significance of the scientific evidence. Other factors that were taken into consideration when making the R determination are standards of care, policy concerns, and cost of care, and potential harm.

Table 2. Recommendation Rating Scheme

Recommendation (R)	
Grade	**Description**
A	A strong recommendation, based on evidence or general agreement, that a given procedure or treatment is useful/effective, always acceptable, and usually indicated.
B	A recommendation, based on evidence or general agreement, that a given procedure or treatment may be considered useful/effective.
C	A recommendation that is not well established, or for which there is conflicting evidence regarding usefulness or efficacy, but which may be made on other grounds.
D	A recommendation, based on evidence or general agreement, that a given procedure or treatment may be considered not useful/effective.
E	A strong recommendation, based on evidence or general agreement, that a given procedure or treatment is not useful /effective, or in some cases may be harmful, and should be excluded from consideration.

This rating scheme is consistent with the rating system used in all ACC/AHA guidelines, as well as the system used by the VA Pharmacy Benefits Management (PBM) in the VHA/DoD Guideline for Pharmacologic Management of Chronic Heart Failure.

Appendix A: Guideline Development Process References

Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb 1992.

Cochrane Reviews, Cochrane Controlled Trials Register at http://www.update-software.com/cochrane.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Pain Standards for 2001, 2001, http://www.jcaho.org/standard/stds2001_mpfrm.html.

NHMRC, Commonwealth of Australia, National Health and Medical Research Council, Acute Pain Management: Scientific Evidence, 1999, http://www.health.gov.au/nhmrc/publicat/synopses/cp57syn.htm.

SMDMC, Proposal for clinical algorithm standards, Society for Medical Decision Making Committee on Standardization of Clinical Algorithms, In: Medical Decision Making, 12(2): 149-54.

USPSTF, Guide to Clinical Preventive Services. 2 ed. Baltimore: Williams and Wilkins; 1996.

VA 1996 External Peer Review Program. Contract No. V101(93) P-1369.

VHA Directive 96-053 (August 29, 1996). Roles and Definitions for Clinical Practice Guidelines and Clinical Pathways.

VHA, Pain as the 5th Vital Sign Toolkit, Washington, DC: National Pain Management Coordinating Committee, October 2000.

Woolf SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. Archives of Intern Med 1992;152: 947-948.

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APPENDIX B:
PARTICIPANT LIST

Version 1.2

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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **POSTOPERATIVE PAIN**

APPENDIX C:
BIBLIOGRAPHY

Version 1.2

BIBLIOGRAPHY

Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. AHCPR pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb 1992.

Agency for Health Care Policy and Research (AHCPR). AHCPR Clinical Practice Guideline, Acute Pain Management: Operative of Medical Procedures and Trauma. U. S. Department of Health and Human Services. 1992.

Agency for Health Care Policy and Research (AHCPR). Pain Control After Surgery-A Patient Guide. Rockville, Maryland: AHCPR, Public Health Services, U.S. Department of Health and Human Services, February 1992 Report No.: 92-0021.

American Hospital Formulary Service (AFHS) Drug Information. Bethesda: American Society of Health-System Pharmacists, Inc.; 2000.

Ahmad N, Grad HA, Haas DA, Aronson KJ, Jokovic A, Locker D. The efficacy of nonopioid analgesics for postoperative dental pain: a meta-analysis. Anesth Prog 1997; 44(4):119-26.

Ali J, Yaffe CS, Serrette C. The effect of transcutaneous electric nerve stimulation on postoperative pain and pulmonary function. Surgery 1981; 89(4):507-12.

Al-Kaisy A, McGuire G, Chan VW, Bruin G, Peng P, Miniaci A, Perlas A. Analgesic effect of interscalene block using low-dose bupivacaine for outpatient arthroscopic shoulder surgery. Reg Anesth Pain Med 1998; 23(5):469-73.

Allen JG, Denny NM, Oakman N. Postoperative analgesia following total knee arthroplasty: a study comparing spinal anesthesia and combined sciatic femoral 3-in-1 block. Reg Anesth Pain Med 1998; 23(2):142-6.

Amar, D. Prevention and management of dysrhythmias following thoracic surgery. Chest Surg Clin N Am 1997 Nov; 7(4):817 – 29.

American Society of Anesthesiologists, US House of Delegates, Standards for Postanesthesia Care, 1994, http://www.asahq.org/Standards/02.html#3.

American Society of Regional Anesthesia. Recommendations for Neuraxial Anesthesia and Anticoagulation 1998. Consensus Conference of the American Society of Regional Anesthesia. http://www.asra.com/items_of_interest/consensus_statements

Andrews JR. Posterolateral rotatory instability of the knee: surgery for acute and chronic problems. Phys Ther 1980; 60(12):1637-9.

Anonymous. Celebrex ™ Prescribing Information. Chicago, IL: G.D. Serle & Co.

Anonymous. Chirocaine Prescribing Information. Stanford, CT: Purdue Pharmacology LP.

Anonymous. Cocaine Hydrochloride Topical Solution Prescribing Information. Columbus, Ohio: Roxane Laboratories, Inc.

Anonymous. Drug Facts and Comparisons. St. Louis: A Wolters Kluwer Company; 2001.

Anonymous. Duranest Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. EMLA Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Injectable Local Anesthetics. In: T Burnham, RM Short, eds. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Co; 2000; 1000-5.

Anonymous. Naropin Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Nonsteroidal anti-inflammatory agents 28:08;04. In: GK McEvoy, ed. AHFS Drug Information. Bethesda. American Society of Health-System Pharmacists, 2001 (electronic version).

Anonymous. Nonsteroidal anti-inflammatory agents. In: Burnham TH, Short RM, eds. Drug Facts and Comparisons. St Louis: Wolters Kluwer Co., 2001: 836-848.

Anonymous. Physicians' Desk Reference. Montvale, New Jersey: Medical Economics Company; 2001.

Anonymous. Sensorcaine Prescribing Information. Wilmington, DE: AstraZeneca LP.

Anonymous. Vioxx ™ Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.

Anonymous. Xylocaine Prescribing Information. Wilmington, DE: AstraZeneca LP.

Asaboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. Anesth Analg 1998; 87(2):319-23.

Ashburn MA, Ready LB. Postoperative pain. In: JD Loeser, ed. Bonica's Management of Pain. New York: Lippincott Williams & Wilkins; 2000:765-779.

Atanassoff PG, Alon E, Weiss BM. Intercostal nerve block for lumpectomy: superior postoperative pain relief with bupivacaine. J Clin Anesth 1994; 6(1):47-51.

Atkinson RS, Rushman GB, Davies NJ.Surgical operations and choice of anesthetic. In: Lee's Synopisis of Anaesthesia. Oxford: Butterworth Heinman; 1993;441-602.

Austrup ML, Korean G. Analgesic agents for the postoperative period. Opioids. Surg Clin North Am 1999; 79(2):253-73.

Auvinet B, Ziller R, Appelboom T, Velicitat P. Comparison of the onset and intensity of action of intramuscular meloxicam and oral meloxicam in patients with acute sciatica. Clin Ther 1995; 17(6):1078-98.

Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988; 33(3):297-301.

Badner N. Epidural agents for postoperative analgesia. Anesth Clin North Am 1992; 10(2):321-37.

Ballantyne JC, Carr DB, Chalmers TC. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. J Clin Anesth 1993; 5(3):182-93.

Barber FA, McGuire DA, Click S. Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction. Arthroscopy 1998; 14(2):130-5.

Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet 1995; 345(8952):763-4.

Bardram L, Funch-Jensen P, Kehlet H. Rapid rehabilitation in elderly patients after laproscopic colonic resection. Br J Surg 2000; 87(11):1540-5.

Baron R, Wasner G, Lindner V. Optimal treatment of phantom limb pain in the elderly. Drugs Aging 1998; 12(5):361-76.

Barron DJ, Tolan MJ, Lea RE. A randomized controlled trial of continuous extra-pleural analgesia post-thoracotomy: efficacy and choice of local anaesthetic. Eur J Anaesthesiol 1999; 16(4):236-45.

Bartholdy J, Sperling K, Ibsen M, Eliasen K, Mogensen T. Preoperative infiltration of the surgical area enhances postoperative analgesia of a combined low-dose epidural bupivacaine and morphine regimen after upper abdominal surgery. Acta Anaesthesiol Scand 1994; 38(3):262-5.

Bastian H, Sollholm B, Marker P, Eckerdal A. Comparative study of pain control by cryotherrapy of exposed bone following extraction of wisdom teeth. Journal of Oral Science 1998; 40(3):109-13.

Basur R, Shepard E, Mouzas G. Wall and Melzack Textbook of Pain. 2nd ed. New York: Churchill Livingstone; 1976:932-41.

Baxter AD, Laganiere S, Samson B, Stewart J, Hull K, Goernert L. A comparison of lumbar epidural and intravenous fentanyl infusions for post-thoracotomy analgesia. Can J Anaesth 1994; 41(3):184-91.

Bednar DA. Analysis of factors affecting successful discharge in patients undergoing lumbar discectomy for sciatica performed on a day-surgical basis: a prospective study of sequential cohorts. J Spinal Disord 1999; 12(5):359-62.

Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157(14):1531-6.

Beirne OR, Hollander B. The effect of methylprednisolone on pain, trismus, and swelling after removal of third molars. Oral Surg Oral Med Oral Pathol 1986; 61(2):134-8.

Ben-David B, Baune-Goldstein U, Goldik Z, Gaitini L. Is preoperative ketorolac a useful adjunct to regional anesthesia for inguinal herniorrhaphy. Acta Anaesthesiol Scand 1996; 40(3):358-63.

Benzon HT, Wong HY, Belavic AM, Goodman I, Mitchell D, Lefheit T, Locicero J. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. Anesth Analg 1993; 76(2):316-22.

Berde CB, Strichartz GR. Local anesthetics. In: RD Miller, ED Miller, JG Reves, eds. Anesthesia. Philadelphia: Churchill Livingston; 2000:506-510 (electronic version).

Berti M, Fanelli G, Casati A, Lugani D, Aldegheri G, Torri G. Comparison between epidural infusion of fentanyl/bupivacaine and morphine/bupivacaine after orthopaedic surgery. Can J Anaesth 1998; 45(6):545-50.

Bloomfield EL, Schubert A, Secic M, Barnett G, Shutway F, Ebrahim ZY. The influence of scalp infiltration with bupivicaine on hemodynamics and post-operative pain in adult patients undergoing craniotomy. Anaesth Anal, Sep 1998, 87(3) 579-82

Boldt J, Thaler E, Lehmann A, Papsdorf M, Isgro F. Pain management in cardiac surgery patients: comparison between standard therapy and patient-controlled analgesia regimen. J Cardiothorac Vasc Anesth 1998; 12(6):654-8.

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000; 343(21):1520-8.

Bonica J. The Management of Pain. 3d ed. WA Wilkins, ed. Philadelphia: Lippincott; 2001:1805-31, 42-47

Borgeat A, Tewes E, Biasca N, Gerber C. Patient-controlled interscalene analgesia with ropivacaine after major shoulder surgery: PCIA vs PCA. Br J Anaesth 1998; 81(4):603-5.

Borgeat A. Interscalene block following shoulder surgery. Acta Anaesthesiol Scand 2000; 44(4):495.

Bost P, Commun F, Albuisson E, Guichard C, Mom T, Eschalier A, Gilian L. Postoperative pain assessment in head and neck cancer surgery: benefit of patient controlled analgesia (PCA). Ann Otolarygol Chir Cervicofac 1999; 3:154-61.

Bostrom BM, Ramberg T, Davis BD, Fridlund B. Survey of post-operative patients' pain management. J Nurs Manag 1997; 5(6):341-9.

Bourke DL, Smith B, Erickson J, Gwartz B. Textbook of Pain. 2d ed. W Melzack, ed. New York: Churchill Livingstone; 1984:884-96.

Bourke M, Hayes A, Doyle M, McCarroll M. A comparison of regularly administered sustained release oral morphine with intramuscular morphine for control of postoperative pain. Anesth Analg 2000; 90(2):427-30.

Bradley LA, McKendree-Smith NL. Assessment of psychological status using interviews and self-report instruments. In: DC Turk & R Melzack, eds., Handbook of Pain Assessment. 2nd ed. New York: Guilford Press; 2001:in press.

Brandsson S, Rydgren B, Hedner T, Eriksson BI, Lundin O, Sward L, Karlsson J. Postoperative analgesic effects of an external cooling system and intra- articular bupivacaine/morphine after arthroscopic cruciate ligament surgery. Knee Surg Sports Traumatol Arthrosc 1996; 4(4):200-5.

Brichon PY, Pison C, Chaffanjon P, Fayot P, Buchberger M, Neron L, Bocca A, Verdier J, Sarrazin R. Comparison of epidural analgesia and cryoanalgesia in thoracic surgery. Eur J Cardiothorac Surg 1994; 8(9):482-6.

Broscious S. Music: An intervention for pain during chest tube removal after open heart surgery. Am J Crit Care 1999(8):410-15.

Brown F. Anterior Cruciate Ligament Reconstruction as an Outpatient Procedure. Orthopeadic Nursing 1996; 15(1):15-21.

Bruehl, Carson C, McCubbin J. Two brief interventions for acute pain. Pain 1993(54):29-36.

Bruzga R, Speer K. Challenges of rehabilitation after shoulder surgery. Clinics in Sports Medicine 1999; 18(4):769-93.

Bucerius J, Metz S, Walther T, Doll N, Falk V, Diegeler A, Autschbach R, Mohr FW. Pain is significantly reduced by cryoablation therapy in patients with lateral minithoracotomy. Ann Thorac Surg 2000; 70(3):1100-4.

Buckley FP. Regional anesthesia with local anesthetics. In: JD Loeser, ed. Bonica's management of pain. New York: Lippincott Williams & Wilkins; 2001:1893-1952.

Burgess FW, Anderson DM, Colonna D, Cavanaugh DG. Thoracic epidural analgesia with bupivacaine and fentanyl for postoperative thoracotomy pain. J Cardiothorac Vasc Anesth 1994; 8(4):420-4.

Calenda E, Retout A, Muraine M. Peribulbar anesthesia for peroperative and postoperative pain control in eye enucleation or evisceration: 31 cases. J Fr Ophtalmol, May 1999, 22(4) 426-30.

Cambareri JJ, Afifi MS, Glass PS, Esposito BF, Camporesi EM. A-3665, a new short-acting opioid: a comparison with alfentanil. Anesth Analg 1993; 76(4):812-6.

Campbell JT. Anterior cruciate ligament reconstruction; Using patellar tendon grafts. AORN J 1990; 51(4):944-66.

Cannon CR. Patient-controlled analgesia (PCA) in head and neck surgery. Otolaryngol Head Neck Surg 1990; 103(5, Pt 1):748-51.

Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology 1999; 91(1):8-15.

Carabine UA, Gilliland H, Johnston JR, McGuigan J. Pain relief for thoracotomy. Comparison of morphine requirements using an extrapleural infusion of bupivacaine. Reg Anesth 1995; 20(5):412-7.

Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, Truchon R, Parent F, Levesque J, Bergeron V, Montminy P, Blanchette C. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med 1997; 336(23):1634-40.

Carretta A, Zannini P, Chiesa G, Altese R, Melloni G, Grossi A. Efficacy of ketorolac tromethamine and extrapleural intercostal nerve block on post-thoracotomy pain. A prospective, randomized study. Int Surg 1996; 81(3):224-8.

Carroll D, Tramer M, McQuay H, Nye B. Randomization is important in studies with pain outcomes; systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain. Br J Anaesth 1996(77):798-803.

Catala E, Casas JI, Unzueta MC, Diaz X, Aliaga L, Villar Landeira JM. Continuous infusion is superior to bolus doses with thoracic paravertebral blocks after thoracotomies. J Cardiothorac Vasc Anesth 1996; 10(5):586-8.

Cepeda MS, Uribe C, Betancourt J, Rugeles J, Carr DB. Pain relief after knee arthroscopy: intra-articular morphine, intra- articular bupivacaine, or subcutaneous morphine? Reg Anesth 1997; 22(3):233-8.

Chalmers TC, Berrier J, Hewitt P, Berlin J, Reitman D, Nagalingam R, Sacks H. Meta-analysis of randomized controlled trials as a method of estimating rare complications of non-steroidal anti-inflammatory drug therapy. Aliment Pharmacol Ther. 1988;2 Suppl 1:9-26.

Chan A, Dore CJ, Ramachandra V. Analgesia for day surgery: Evaluation of the effect of diclofenac given before or after surgery with or without bupivacaine infiltration. Anesthesia 1996; 51(6):592-5.

Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Intrathecal morphine for coronary artery bypass graft procedure and early extubation revisited. J Cardiothorac Vasc Anesth 1999; 13(5):574-8.

Chaney MA, Smith KR, Barclay JC, Slogoff S. Large-dose intrathecal morphine for coronary artery bypass grafting. Anesth Analg 1996; 83(2):215-22.

Chaplin JM, Morton RP. A prospective, longitudinal study of pain in head and neck cancer patients. Head Neck 1999; 21(6):531-7.

Checketts MR, Gilhooly CJ, Kenny GN. Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA. Br J Anaesth 1998; 80(6):748-51.

Chen L, Tang J, White PF. The effect of location of transcutaneous electrical nerve stimulation on postoperative opiod analgesic requirement; acupoint versus nonacupoint stimulation. Anesth Analg 1998; 87(1129-34).

Chen PP, Chui PT, Gin T. Comparison of ondansetron and metoclopramide for the prevention of post-operative nausea and vomiting after major gynaecological surgery. Eur J Anaesthesiol 1996 Sep;13(5):485-91

Cherian MN, Mathews MP, Chandy MJ. Local wound infiltration with bupivacaine in lumbar laminectomy. Surg Neurol 1997; 47(2):120-2; discussion 2-3.

Chisakuta AM, George KA, Hawthorne CT. Postoperative epidural infusion of a mixture of bupivacaine 0.2% with fentanyl for upper abdominal surgery. A comparison of thoracic and lumbar routes. Anaesthesia 1995; 50(1):72-5.

Choyce A, Chan VW, Middleton WJ, Knight PR, Peng P, McCartney CJ. What is the relationship between paresthesia and nerve stimulation for axillary brachial plexus block? Reg Anesth Pain Med 2001; 26(2):100-4.

Christensen O, Christensen P, Sonnenschein C, Nielsen PR, Jacobsen S. Analgesic effect of intraarticular morphine. A controlled, randomised and double-blind study. Acta Anaesthesiol Scand 1996; 40(7):842-6.

Christopherson R, Beattie C, Frank SM, Norris EJ, Meinert CL, Gottlieb SO, Yates H, Rock P, Parker SD, Perler BA, et al. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 1993; 79(3):422-34.

Chung F, Lane R, Spraggs C, McQuade B, Jacka M, Luttropp HH, Alahuta S, Rocherieux S, Roy M, Duvaldestin P, Curtis P. Ondansetron is more effective than metoclopramide for the treatment of opioid-induced emesis in post-surgical adult patients. Ondansetron OIE Post-Surgical Study Group. Eur J Anaesthesiol 1999; 16(10):669-77.

Cleeland CS. The impact of pain on the patient with cancer. Cancer 1984; 54(11 Suppl)):2635-41.

Cleeland CS, Gonin R, Hatfield AK. Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994; 330(9):592-6.

Cleeland CS, Nakamura Y, Mendoza TR, Edwards KR, Douglas J, Serlin RC. Dimensions of the impact of cancer pain in a four country sample: new information from multidimensional scaling. Pain 1996; 67(2-3):267-73.

Cleeland CS, Syrjala KL. How to assess cancer pain. In: Turk DC & MR Melzack, eds. Handbook of Pain Assessment. New York: The Guilford Press; 1992:362-87.

Cobby TF, Crighton IM, Kyriakides K, Hobbs GJ. Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. Br J Anaesth 1999; 83(2):253-6.

Cobby TF, Reid MF. Wound infiltration with local anaesthetic after abdominal hysterectomy. Br J Anaesth 1997; 78(4):431-2.

Cochrane Reviews, Cochrane Controlled Trials Register at http://www.update-software.com/ccweb/cochrane/revabstr/ccabout.htm

Cockings E, Moore P, Lewis R. Transarterial brachial plexus blockade using high doses of 1.5% mepivacaine. Reg Anesth 1987; 12:159-64.

Cohen BE, Hartman MB, Wade JT, Miller JS, Gilbert R, Chapman TM. Postoperative pain control after lumbar spine fusion. Patient-controlled analgesia versus continuous epidural analgesia. Spine 1997; 22(16):1892-6; discussion 6-7.

Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR. Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 1992; 75(5):747-52.

Cohn B, Draeger R, Jackson D. The effects of cold therappy in the postoperative management of pain in patients undergoing anterior cruciate ligament reconstruction. American Journal of Sports Medicine 1989; 17:344.

Cole PJ, Craske DA, Wheatley RG. Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. Br J Anaesth 2000; 85(2):233-7.

Colwell Jr. CW, Morris BA. Patient-controlled analgesia compared with intramuscular injection of analgesics for the management of pain after an orthopaedic procedure. J Bone Joint Surg Am 1995; 77(5):726-33.

Conceptual framework and item selection. Med Care 1992; 30(6):473-83.

Conway C. Neurological Anesthesia. In: Churchill-Davidson HC, ed. A Practice of Anesthesia. 5 ed. London: Lloyd Luke; 1984:765-92.

Cooperman A, Hall B, Mikalacki K, Hardy R. Use of Transcutaneous Electrical Stimulation in the Control of Postoperative Pain. Am Journal of Surgery 1977; 133:185-7.

Cornell P, Lopez A, Malofsky H. Pain reduction with transcutaneous electrical nerve stimulation after foot surgery. The Journal of Foot Surgery 1984; 23(4):326-33.

Coutts F, Hewetson D, Matthews J. Continuous passive motion of the knee joint: Use at the Royal National Orthopaedic Hospital, Stanmore. Physiotherapy 1989; 75(7):427-31.

Cox CR, Checketts MR, Mackenzie N, Scott NB, Bannister J. Comparison of S(-)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 1998; 80(5):594-8.

Crome P, Gain R, Ghurye R, Flanagan RJ. Pharmacokinetics of dextropropoxyphene and nordextropropoxyphene in elderly hospital patients after single and multiple doses of distalgesic. Preliminary analysis of results. Hum Toxicol 1984; 3 Suppl:41S-8S.

Curda GA. Postoperative analgesic effects of dexamethasone sodium phosphate in bunion surgery. J Foot Surg 1983; 22(3):187-91.

D'Alessio JG, Rosenblum M, Shea KP, Freitas DG. A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. Reg Anesth 1995; 20(1):62-8.

Dalsgaard J, Felsby S, Juelsgaard P, Froekjaer J. Low-dose intra-articular morphine analgesia in day case knee arthroscopy: a randomized double-blinded prospective study. Pain 1994; 56(2):151-4.

Danielsen J, Johnsen R, Kibsgaard S, Hellevik E. Early aggressive exercise for postoperative rehabilitation after discectomy. Spine. 2000; 25(8):1015-20.

Danou F, Paraskeva A, Vassilakopoulos T, Fassoulaki A. The analgesic efficacy of intravenous tenoxicam as an adjunct to patient-controlled analgesia in total abdominal hysterectomy. Anesth Analg 2000; 90(3):672-6.

Dauch WA, Krex D, Heymanns J, Zeithammer B, Bauer BL. Peri-operative changes of cellular and humoral components of immunity with brain tumour surgery. Acta Neurochir 1994; 126(2-4):93-101.

Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer 1982; 50(9):1913-8.

Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 1996; 31(6):410-22.

de Leon-Casasola OA, Lema MJ, Karabella D, Harrison P. Postoperative yocardial ischemia: epidural versus intravenous patient-controlled analgesia. A pilot project. Reg Anesth 1995; 20(2):105.12.

DeBenedittis G, Lorenzetti A, Migliore M, Spagnoli D, Tibiero F, Villani R. Postoperative pain in neurosurgery: A pilot study in brain surgery clinical study. Neurosurgery 1996; 38:4666-70.

DeBosscher K, Vanden Berghe W, Haegeman G. Mechanisms of anti-inflammatory action and of immunosuppression by glucocorticoids: negative interference of activated glucocorticoid receptor with transcription factors. J Neuroimmunol 2000; 109(1):16-22.

Deyo RA. Conservative therapy for low back pain. Distinguishing useful from useless therapy. JAMA 1983; 250(8):1057-62.

Ding Y, White PF. Post-herniorrhaphy pain in outpatients after pre-incision ilioinguinal-hypogastric nerve block during monitored anaesthesia care. Can J Anaesth 1995; 42(1):12-5.

Donnelly A, Shafer A. Perioperative Care in Applied Therapeutics: The Clinical Use of Drugs. LY Young & MA Koda-Kimble, eds. Vancouver: Applied Therapeutics Inc.; 1995.

Doyle CE. Pre-operative strategies for managing postoperative pain at home after day surgery. J Perianesth Nurs 1999; 14(6):373-9.

Dunbar P, Visco E, Lam A. Craniotomy procedures are associated with less analgesic requirements than other surgical procedures. Anesth Anal Feb 1999; 88(2): 335-40.

DuPen S, DeRidder M. Cynergy Group Opioid Conversion Calculator 2000 [cited 2000 15 December 2000].

Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 1993; 79(5):881-92.

Egbert AM, Parks LH, Short LM, Burnett ML. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. Arch Intern Med 1990; 150(9):1897-903.

Eisenberg et al. Efficacy and safety of non-steroidal anti-inflammatory drugs for cancer pain: A meta-analysis. *J Clin Oncol* 1994; 12:2756-2765.

Elizaga AM, Smith DG, Sharar SR, Edwards WT, Hansen Jr. ST. Continuous regional analgesia by intraneural block: effect on postoperative opioid requirements and phantom limb pain following amputation. J Rehabil Res Dev 1994; 31(3):179-87.

Elta GH, Barnett JL. Meperidine need not be proscribed during sphincter of Oddi manometry. Gastrointest Endosc 1994; 40(1):7-9.

Engberg G. Respiratory performance after upper abdominal surgery. A comparison of pain relief with intercostal blocks and centrally acting analgesics. Acta Anaesthesiol Scand 1985; 29(4):427-33.

Enneking FK, Scarborough MT, Radson EA. Local anesthetic infusion through nerve sheath catheters for analgesia following upper extremity amputation. Clinical report. Reg Anesth 1997; 22(4):351-6.

Eriksson-Mjoberg M, Kristiansson M, Carlstrom K, Olund A, Eklund J. Infiltration of morphine into an abnormal wound; effects on pain relief and endocrine/immune response. Pain 1997; 73(3):355-60.

Eriksson-Mjoberg M, Svensson JO, Almkvist O, Olund A, Gustafsson LL. Extradural morphine gives better pain relief than patient-controlled I.V. morphine after hysterectomy. Br J Anaesth 1997; 78(1):10-6.

Fabling JM, Gan TJ, El-Moalem HE, Warner DS, Borel CO. A randomized, double-blinded comparison of ondansetron, droperidol, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy, Anesth Analg 2000; 91(2):358-61.

Faymonville M, Mambourg P, Joris J, Vrijens B. Psychological approaches during conscious sedation. Hypnosis versus stress reducing strategies: a prospective randomized study. Pain 1997; 73(3):361-7.

Feeley TW, and Macario A: Chapter 68: The Postanesthesia Care Unit. In: RD Miller, ed. Anesthesia. 5 ed. Philadelphia: Churchill Livingston; 2000.

Fezza JP, Klippenstien KA, Wesley RE. Use of an orbital catheter to control pain after orbital implant surgery. Archiv Ophthamol June 1999; 117(6):784-8

Finsen V, Persen L, Lovlien M, Veslegaard EK, Simensen M, Gasvann AK, Benum P. Transcutaneous electrical nerve stimulation after major amputation. J Bone Joint Surg Br 1988; 70(1):109-12.

Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg 1987; 66(8):723-30.

Flory N, Van-Gessel E, Donald F, Hoffmeyer P, Gamulin Z. Does the addition of morphine to brachial plexus block improve analgesia after shoulder surgery? Br J Anaesth 1995; 75(1):23-6.

Fogarty DJ, Carabine UA, Milligan KR. Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. Br J Anaesth 1993; 71(5):661-4.

Fogarty DJ, O'Hanlon JJ, Milligan KR. Intramuscular ketorolac following total hip replacement with spinal anaesthesia and intrathecal morphine. Acta Anaesthesiol Scand 1995; 39(2):191-4.

Foster R, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anesthetic. Drugs 2000 2000; 59(3):551-79.

Foulkes GD, Robinson JS, Jr. Intraoperative dexamethasone irrigation in lumbar microdiskectomy. Clin Orthop 1990; 261:224-8.

France JC, Jorgenson SS, Lowe TG, Dwyer AP. The use of intrathecal morphine for analgesia after posterolateral lumbar fusion: a prospective, double-blind, randomized study. Spine 1997; 22(19):2272-7.

Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A. Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. Anesth Analg 1994; 79(1):152-4.

Fredman B, Olsfanger D, Flor P, Jedeikin R. Ketorolac does not decrease postoperative pain in elderly men after transvesical prostatectomy. Can J Anaesth 1996; 43(5 Pt 1):438-41.

Frensilli FJ, Immergut MA, Gilbert EC. Use of methylprednisolone acetate in vasectomy. Urology 1974; 4(6):732-3.

Freysz M, Beal JL, D'Athis P, Mounie J, Wilkening M, Escousse A. Pharmacokinetics of bupivacaine after axillary brachial plexus block. Int J Clin Pharmacol Ther Toxicol 1987; 25(7):392-5.

Fromm MF, Eckhardt K, Li S, Schanzle G, Hofmann U, Mikus G, Eichelbaum M. Loss of analgesic effect of morphine due to coadministration of rifampin. Pain 1997; 72(1-2):261-7.

Frost EA. Complications in the postanesthetic care unit. Middle East J Anesthesiology 1992; 11(6):525-47.

Gabbott DA, Cohen AM, Mayor AH, Niemiro LA, Thomas TA. The influence of timing of ketorolac administration on post-operative analgesic requirements following total abdominal hysterectomy. Eur J Anaesthesiol. 1997 Nov;14(6):610-5.

Gaeta RR, Macario A, Brodsky JB, Brock-Utne JG, Mark JB. Pain outcomes after thoracotomy: lumbar epidural hydromorphone versus intrapleural bupivacaine. J Cardiothorac Vasc Anesth 1995; 9(5):534-7.

Gal TJ, Cooperman LH. Hypertension in the immediate postoperative period. Br J Anesth; 1975; 47(1):70-4.

Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R. Opioid-sparing effects of a low-dose infusion of naloxone in patient- administered morphine sulfate. Anesthesiology 1997; 87(5):1075-81.

Ganapathy S, Sandhu HB, Stockall CA, Hurley D. Transient neurologic symptom (TNS) following intrathecal ropivacaine. Anesthesiology 2000; 93(6):1537-9.

Gardner JS, Blough D, Drinkard CR, Shatin D, Anderson G, Graham D, Alderfer R. Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy 2000; 20(12):1423-31.

Gasse C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 2000; 20(6):629-34.

Gedney JA, Liu LE. Side-effects of epidural infusions of opioid bupivacaine mixtures. Anaesthesia 1998; 53(12):1148-55.

Gentili M, Juhel A, Bonnet F. Peripheral analgesic effect of intra-articular clonidine. Pain 1996; 64(3):593-6.

George K, Wright P, Chisakuta A. Continuous thoracic epidural fentanyl for post-thoracotomy pain relief: with or without bupivacaine? Anaesthesia 1991; 46(9):732-6.

George KA, Wright PM, Chisakuta AM, Rao NV. Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. Acta Anaesthesiol Scand 1994; 38(8):808-12.

Gersh M. Transcutaneous electrical nerve stimulation (TENS) for management of pain and sensory pathology. Philadelphia: Davis; 1992 (Electrotherapy in Rehabilitation).

Glasser RS, Knego RS, Delashaw JB, Fessler RG. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. J Neurosurg 1993; 78(3):383-7.

Glassman SD, Rose SM, Dimar JR, Puno RM, Campbell MJ, Johnson JR. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine 1998; 23(7):834-8.

Good M, Stanton-Hicks, Grass JA, Choi C. Relief of postoperative pain with jaw relaxation, music and their combination. Pain 1999; 83:163-72.

Good M. Effects of music and relaxation on postoperative pain: A review. Journal of Advanced Nursing 1996; 24:905-14.

Gottschalk A, Smith DS, Jobes DR, Kennedy SK, Lally SE, Noble VE, Grugan KF, Seifert HA, Cheung A, Malkowicz SB, Gutsche BB, Wein AJ. Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. JAMA 1998; 279(14):1076-82.

Gotzche P. Non-steroidal anti-inflammatory drugs. In: Clinical Evidence. 4 ed: British Medical Journal Publishing Group; 2000.

Gotzche PC. Meta-analysis of NSAIDs: contribution of drugs, doses, trial designs and meta-analytic techniques. *Scand J Rheumatol* 1993; 22:255-260.

Grass JA, Sakima NT, Valley M, Fischer K, Jackson C, Walsh P, Bourke DL. Assessment of ketorolac as an adjuvant to fentanyl patient-controlled epidural analgesia after radical retropubic prostatectomy. Anesthesiology 1993; 78(4):642-8; discussion 21A.

Greif R, Wasinger T, Reiter K, Chwala M, Neumark J. Pleural bupivacaine for pain treatment after nephrectomy. Anesth Analg 1999; 89(2):440-3.

Griffith JP, Whiteley S, Gough MJ. Prospective randomized study of a new method of providing postoperative pain relief following femoropopliteal bypass. Br J Surg 1996; 83(12):1735-8.

Guinard JP, Mavrocordatos P, Chiolero R, Carpenter RL. A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. Anesthesiology 1992; 77(6):1108-15.

Gupta S, Francis JD, Tillu AB, Sattirajah AI, Sizer J. The effect of pre-emptive acupuncture treatment on analgesic requirements after day-case knee arthroscopy. Anaesthesia 1999; 54(12):1204-7.

Haak-van der Lely F, van Kleef JW, Burm AG, Bovill JG. An intra-operative comparison of lumbar with thoracic epidural sufentanil for thoracotomy. Anaesthesia 1994; 49(2):119-21.

Hadjistavropoulos T, Von Baeyer C, Craig KD. Pain assessment in persons with limited ability to communicate. In: Turk D.C.& R. Melzack eds. Handbook of Pain Assessment. 2d ed. New York: Guilford Press; 2001 in press.

Hamza MA, White PF, Ahmed HE, Ghoname EA. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. Anesthesiology 1999; 91(5):1232-8.

Hanretty KP, Davidson SE, Cordiner JW. Clinical evaluation of a topical anaesthetic preparation (pramoxine hydrochloride and hydrocortisone) in post-episiotomy pain relief. Br J Clin Pract 1984; 38(11-12):421-2.

Hansen T, Ilett K, Lim S. Pharmacokinetics and clinical efficacy of long-term epidural ropivacaine infusion in children. Br J Anaesth 2000; 85(3):347-53.

Hansson P, Ekblom A, Thomsson M, Fjellner B. Influence of naloxone on relief of acute oro-facial pain by transcutaneous electrical nerve stimulation (TENS) or vibration. Pain 1986; 24(3):323-9.

Hansten P, Horn J. Drug Interactions: Analysis and Management. In: G McEvoy, ed. Facts and Comparisons, 2000. St.Louis, MO: 2000.

Hargreaves A, Lander J. Use of transcutaneous electrical nerve stimulation for postoperative pain. Nurs Res 1989; 38(3):159-61.

Hargreaves KM, Costello A. Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther 1990; 48(2):168-78.

Harley EH, Dattolo RA. Ibuprofen for tonsillectomy pain in children: efficacy and complications. Otolaryngol Head Neck Surg 1998; 119(5):492-6.

Harvie K. A major advance in the control of postoperative knee pain. Orthopedics 1979; 2(26).

He JP, Friedrich M, Ertan AK, Muller K, Schmidt W. Pain-relief and movement improvement by acupuncture after ablation and axillary lymphadenectomy in patients with mammary cancer. Clin Exp Obstet Gynecol 1999; 26(2):81-4.

Healy WL, Seidman J, Pfeifer BA, Brown DG. Cold compressive dressing after total knee arthroplasty. Clin Orthop 1994(299):143-6.

Heffline MS. Exploring nursing interventions for acute pain in the postanesthesia care unit. J Post Anesth Nurs 1990; 5(5):321-8.

Helmy SA. Prophylactic anti-emetic efficacy of ondansetron in laparoscopic cholecystectomy under total intravenous anaesthesia. A randomised, double-blind comparison with droperidol, metoclopramide and placebo. Anaesthesia 1999; 54(3):266-71.

Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta- analysis. BMJ 1996; 312(7046):1563-6.

Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000; 90(1):186-94.

Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. Anesthesiology 1985; 62(2):124-9.

Hines R, Barash PG, Watrous G, O'Connor T. Complications occurring in the postanesthesia care unit: A survey. Anesth Analg 1992; 74(4):503-9.

Hodges SD, Castleberg RL, Miller T, Ward R, Thornburg C. Cervical epidural steroid injection with intrinsic spinal cord damage. Two case reports. Spine 1998; 23(19):2137-42; discussion 41-2.

Hoe-Hansen C, Norlin R. The clinical effect of ketoprofen after arthroscopic subacromial decompression: a randomized double-blind prospective study. Arthroscopy 1999; 15(3):249-52.

Holland CS. The influence of methylprednisolone on post-operative swelling following oral surgery. Br J Oral Maxillofac Surg 1987; 25(4):293-9.

Hooley JR, Francis FH. Betamethasone in traumatic oral surgery. J Oral Surg 1969; 27(6):398-403.

Horta ML, Ramos L, Goncalves ZD, deOliveira MA, Tonellotto D, Teixeira JP, deMelo PR. Inhibition of epidural morphine-induced pruritus by intravenous droperidol. The effect of increasing the doses of morphine and of droperidol. Reg Anesth 1996; 21(4):312-7.

Hughes LC, Hodgson NA, Muller P, Robinson LA, McCorkle R. Information needs of elderly postsurgical cancer patients during the transition from hospital to home. J Nurs Scholarsh 2000; 32(1):25-30.

Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76(3):334-41.

Hymes A. Acute pain control by electrostimulation; A preliminary report. Advanced Neurology 1974; 4:761.

Iacono RP, Linford J, Sandyk R. Pain management after lower extremity amputation. Neurosurgery 1987; 20(3):496-500.

Ibrahim AW, Farag H, Naguib M. Epidural morphine for pain relief after lumbar laminectomy. Spine 1986; 11(10):1024-6.

Injectable local anesthetics. In: TH Burnham, RM Short, eds. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Co.; 2000:1000-1005.

Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: JG Hardman, LE Limbird, eds.-in-chief. Goodman and Gilman's The Pharmacologic Basis of Therapeutics 9th Edition. New York: McGraw-Hill; 1996:617-757.

Jackson, MR, Diagnosis and management of venous thrombosis in the surgical patient. Semin Thromb Hemost. 1998; 24 (Suppl 1):67-76.

Jacobs S, Pullan PT, Potter JM, Shenfield GM. Adrenal suppression following extradural steroids. Anaesthesia 1983; 38(10):953-6.

Jacobs V. Informational needs of surgical patients following discharge. Appl Nurs Res 2000 Feb; 13(1):12-8.

Jahangiri M, Jayatunga AP, Bradley JW, Dark CH. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl 1994; 76(5):324-6.

Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: A comparison of six methods. Pain 1986; 27(1):117-26.

Jensen MP, Karoly P, O'Riordan EF, Bland F, Burns RS. The subjective experience of acute pain. An assessment of the utility of 10 indices. Clin J Pain 1989; 5(2):153-9.

Jensen MP, Turner JA, Romano JM. Chronic pain coping measures: individual vs. composite scores. Pain 1992; 51(3):273-80.

Jick H, Derby LE, Vasilakis C, Fife D. The risk of seizures associated with tramadol. Pharmacotherapy 1998; 18(3):607-11.

Joehl RJ, Koch KL, Nahrwold DL. Opioid drugs cause bile duct obstruction during hepatobiliary scans. Am J Surg 1984; 147(1):134-8.

Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta- analysis. Ann Intern Med 1994; 121(4):289-300.

Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Pain Standards for 2001. http://www.jcaho.org/standard/stds2001_mpfrm.html

Jorgensen JO, Gillies RB, Hunt DR, Caplehorn JR, Lumley T. A simple and effective way to reduce postoperative pain after laparoscopic cholecystectomy. Aust N Z J Surg 1995; 65(7):466-9.

Joris J. Efficacy of non-steroidal anti-inflammatory drugs in post-operative pain. Acta Anaesthesiol Belg 1996; 47(3):115-23.

Joshi GP, McCarroll SM, O'Rourke K. Postoperative analgesia after lumbar laminectomy: epidural fentanyl infusion versus patient-controlled intravenous morphine. Anesth Analg 1995; 80(3):511-4.

Jurf JB, Nirschl AL. Acute postoperative pain management: a comprehensive review and update. Crit Care Nurs Q 1993; 16(1):8-25.

Kallis P, Tooze JA, Talbot S, Cowans D, Bevan DH, Treasure T. Pre-operative aspirin decreases platelet aggregation and increases post- operative blood loss--a prospective, randomised, placebo controlled, double-blind clinical trial in 100 patients with chronic stable angina. Eur J Cardiothorac Surg 1994; 8(8):404-9.

Kam PC, Calcroft RM. Peri-operative stroke in general surgical patients. Anesthesia 1997; 52(9):879-83.

Kampe S, Weigand C, Kaufmann J, Klimek M, Konig DP, Lynch J. Postoperative analgesia with no motor block by continuous epidural infusion of ropivacaine 0.1% and sufentanil after total hip replacement. Anesth Analg 1999; 89(2):395-8.

Kanbak M, Akpolat N, Ocal T, Doral MN, Ercan M, Erdem K. Intraarticular morphine administration provides pain relief after knee arthroscopy. Eur J Anaesthesiol 1997; 14(2):153-6.

Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, Howell S, Smith RL. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 1995; 83(5):968-75.

Kart T, Walther-Larsen S, Svejborg S. Comparison of continuous epidural infusion of fentanyl and bupivacaine with intermittent epidural administration of morphine for postoperative pain management in children. Acta Anaesthesiol Scand 1997; 41(4):461-5.

Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996; 12(1):50-5.

Kaufman E, Heling I, Rotstein I, Friedman S, Sion A, Moz C, Stabholtz A. Intraligamentary injection of slow-release methylprednisolone for the prevention of pain after endodontic treatment. Oral Surg Oral Med Oral Pathol 1994; 77(6):651-4.

Kehlet H, Mogensen T. Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. Br J Surg 1999 Feb; 86(2):227-30

Kenady DE, Wilson JF, Schwartz RW, Bannon CL, Wermeling D. A randomized comparison of patient-controlled versus standard analgesic requirements in patients undergoing cholecystectomy. Surg Gynecol Obstet 1992; 174(3):216-20.

Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain 1985; 23(4):345-56.

King JS. Dexamethasone--a helpful adjunct in management after lumbar discectomy. Neurosurgery 1984; 14(6):697-700.

Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy--video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. J Thorac Cardiovasc Surg 1995; 109(5):997-1001; discussion-2.

Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intraarticular, epidural, and intravenous analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 1999; 43(10):1021-6.

Klein JR, Heaton JP, Thompson JP, Cotton BR, Davidson AC, Smith G. Infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy has no opioid-sparing effect. Br J Anaesth 2000; 84(2):248-9.

Knight CL, Burnell JC. Systemic side-effects of extradural steroids. Anaesthesia 1980; 35(6):593-4.

Komatsu H, Matsumoto S, Mitsuhata H, Abe K, Toriyabe S. Comparison of patient-controlled epidural analgesia with and without background infusion after gastrectomy. Anesth Analg 1998; 87(4):907-10.

Koo P. Pain. Applied Therapeutics; The Clinical Use of Drugs. In: LY Young & MA Koda-Kimble, eds. Vancouver: Applied Therapeutics Inc.; 1995:7-1 to 7-28.

Kruger M, McRae K. Pain management in cardiothoracic practice. Surg Clin North Am 1999; 79(2):387-400.

Kundra P, Gurnani A, Bhattacharya A. Preemptive epidural morphine for postoperative pain relief after lumbar laminectomy. Anesth Analg 1997; 85(1):135-8.

Lacy CF, Armstrong LL, et al., eds. Drug Information Handbook, 7th edition. Hudson, OH: Lexi-Comp; 1999-2000.

Lai C, Yang P, Yang K, Chaung L, Chen T. Evaluation of peribulbar anesthesia in encircling scleral buckle surgery and its post-operative pain course. Chang Keng I Hseueh Tsa Chih (China republic: 1949-). Dec 1999; 22(4):609-14.

Lane GE, Lathrop JC, Boysen DA, Lane RC. Effect of intramuscular intraoperative pain medication on narcotic usage after laparoscopic cholecystectomy. Am Surg 1996; 62(11):907-10.

Langmayr JJ, Obwegeser AA, Schwarz AB, Laimer I, Ulmer H, Ortler M. Intrathecal steroids to reduce pain after lumbar disc surgery: a double- blind, placebo-controlled prospective study. Pain 1995; 62(3):357-61.

Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100(10):1043-9.

Lee A et al. Effects of non-steroidal anti-inflammatory drugs on post-operative renal function in adults (Cochrane Review). *Cochrane Database Syst Rev* 2000, 4 pCD002765.

Lehtipalo S, Koskinen LO, Johansson G, Kolmodin J, Biber B. Continuous interscalene brachial plexus block for postoperative analgesia following shoulder surgery. Acta Anaesthesiol Scand 1999; 43(3):258-64.

Lerner EB, Billittier AJ, Moscati RM. The effects of neutral positioning with and without padding on spinal immobilization of healthy subjects. Prehosp Emerg Care 1998; 2(2):112-6.

Lessard LA, Scudds RA, Amendola A, Vaz MD. The efficacy of cryotherapy following arthroscopic knee surgery. J Orthop Sports Phys Ther 1997; 26(1):14-22.

Levy A, Marmar E. The role of cold compression dressings in the postoperative treatment of total knee arthroplasty. Cl Ortho and Related Research. 1992; 297:174-8.

Liden J, Rafter I, Truss M, Gustafsson JA, Okret S. Glucocorticoid effects on NF-kappaB binding in the transcription of the ICAM-1 gene. Biochem Biophys Res Commun 2000; 273(3):1008-14.

Lieou FJ, Lee SC, Ho ST, Wang JJ. Interpleural bupivacaine for pain relief after transthoracic endoscopic sympathectomy for primary hyperhidrosis. Acta Anaesthesiol Sin 1996; 34(1):21-5.

Lindberg F, Bergqvist D, Rasmussen I. Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature. Surg Laparosc Endosc 1997; 7(4):324-31.

Liu K, Hsu CC, Chia YY. The effect of dose of dexamethasone for antiemesis after major gynecological surgery. Anesth Analg 1999; 89(5):1316-8.

Liu M, Rock P, Grass JA, Heitmiller RF, Parker SJ, Sakima NT, Webb MD, Gorman RB, Beattie C. Double-blind randomized evaluation of intercostal nerve blocks as an adjuvant to subarachnoid administered morphine for post-thoracotomy analgesia. Reg Anesth 1995; 20(5):418-25.

Local anesthetics 72:00. In: GK McEvoy, ed. AHFS Drug Information. Bethesda: American Society of Health-System Pharmacists; 2000 (electronic version).

Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. Br J Anaesth 1996; 76(6):835-40.

Lovstad R, Halvorsen P, Raeder J. A post-operative epidural analgesia with low dose fentanyl, adrenaline and bupivacaine in children after major orthopaedic surgery. A prospective evaluation of efficacy and side effects. Eur J Anaesthesiol 1997; 14(6):583-9.

MacKersie A. Anesthesia for Pediatric Surgery. In Walters FJM, Ingram GS (eds) Anesthesia and intensive care for the neurosurgical patient, 2nd edn. Oxford: Blackwell Scientific Publications, 1993; 345-72.

Madden C, Singer G, Peck C, Nayman J. The effect of EMG biofeedback on postoperative pain following abdominal surgery. Anaesth Intensive Care 1978; 6(4):333-6.

Mahon SV, Berry PD, Jackson M, Russell GN, Pennefather SH. Thoracic epidural infusions for post-thoracotomy pain: a comparison of fentanyl-bupivacaine mixtures vs. fentanyl alone. Anaesthesia 1999; 54(7):641-6.

Maidatsi P, Gorgias N, Zaralidou A, Ourailoglou V, Giala M. Intercostal nerve blockade with a mixture of bupivacaine and phenol enhance the efficacy of intravenous patient-controlled analgesia in the control of post-cholecystectomy pain. European Journal of Anaesthesiology 1998; 15:529.

Malmstrom K, Daniels S, Kotey P, Seidenberg BC, Desjardins PJ. Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in post-operative dental pain: a randomized, placebo and active-comparator-controlled clinical trial. *Clin Ther* Oct 1999, 21(10) 1653-63.

Management: Scientific Evidence, 1999. http://www.health.gov.au/nhmrc/publications/synopses/cp57syn.htm

Mann C, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G, Domergue J, Millat B, Colson P. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. Anesthesiology 2000; 92(2):433-41.

Mannheimer J, Lampe G. Clinical Transcutaneous Electrical Nerve Stimulation. Philadelphia: F.A. Davis Company; 1984: 17-27, 509.

Manninen PH, Burke SJ, Wennberg R, Lozano AM, El Beheiry H. Intraoperative localization of an epileptogenic focus with alfentanil and fentanyl. Anesth Analg 1999; 88(5):1101-6.

Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. American Journal of Medicine 1998; 105(5):380-4.

Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. Pain 1986; 24(1):57-65.

Mauerhan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. J Arthroplasty 1997; 12(5):546-52.

Mayer D. Acupuncture: an evidence-based review of the clinical literature. Annu Rev Med 2000; 51:49-63.

McBride WJ, Dicker R, Abajian JC, Vane DW. Continuous thoracic epidural infusions for postoperative analgesia after pectus deformity repair. J Pediatr Surg 1996; 31(1):105-7; discussion 7-8.

McCaffery M, Beebe A. Pain: Clinical Manual for Nursing Practice. St. Louis, MO: CV Mosby Company; 1989.

McCaffery M, Pasero C, eds. Assessment: Underlying Complexities, Misconceptions, and Practical Tools. In: Pain: Clinical Manual, 2d ed. St. Louis, MO: CV Mosby Company; 1999:35-75, 291-292.

McCallum MI, Glynn CJ, Moore RA, Lammer P, Phillips AM. Transcutaneous electrical nerve stimulation in the management of acute postoperative pain. Br J Anaesth 1988; 61(3):308-12.

McCammon RL, Stoelting RK, Madura JA. Effects of butorphanol, nalbuphine, and fentanyl on intrabiliary tract dynamics. Anesth Analg 1984; 63(2):139-42.

McCarthy MR, Yates CK, Anderson MA, Yates-McCarthy JL. The effects of immediate continuous passive motion on pain during the inflammatory phase of soft tissue healing following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 1993; 17(2):96-101.

McGlade DP, Kalpokas MV, Mooney PH, Chamley D, Mark AH, Torda TA. A comparison of 0.5% ropivacaine and 0.5% bupivacaine for axillary brachial plexus anaesthesia. Anaesth Intensive Care 1998; 26(5):515-20.

McLeod DH, Wong DH, Claridge RJ, Merrick PM. Lateral popliteal sciatic nerve block compared with subcutaneous infiltration for analgesia following foot surgery. Can J Anaesth 1994; 41(8):673-6.

McMahon AJ, Russell IT, Ramsay G, Sunderland G, Baxter JN, Anderson JR, Galloway D, O'Dwyer PJ. Laparoscopic and minilaparotomy cholecystectomy: a randomized trial comparing postoperative pain and pulmonary function. Surgery 1994; 115:533-9.

McNally MA, Cooke EA, Mollan RA. The effect of active movement of the foot on venous blood flow after total hip replacement. J Bone Joint Surg Am 1997; 79(8):1198-201.

McNeill TW, Andersson GB, Schell B, Sinkora G, Nelson J, Lavender SA. Epidural administration of methylprednisolone and morphine for pain after a spinal operation. A randomized, prospective, comparative study. J Bone Joint Surg Am 1995; 77(12):1814-8.

McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day- case surgery: a systematic review. Health Technol Assess 1998; 2(12):1-236.

McSwiney M, Cooper J, Karadia S, Campbell M. Intravenous regional analgesia using morphine. The effect on postoperative pain following total knee arthroplasty. Acta Anaesthesiol Scand 1997; 41(3):345-7.

Meeker MH, Rothrock JC. Alexander's Care of the Patient in Surgery. Mosby, St. Louis; 1999.

Melzack R, Guite S, Gonshor A. Relief of dental pain by ice massage of the hand. Can Med Assoc J 1980; 122(2):189-91.

Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975; 1(3):277-99.

Melzack R. The short-form McGill Pain Questionnaire. Pain 1987; 30(2):191-7.

Merrill DC. Clinical evaluation of FasTENS, an inexpensive, disposable transcutaneous electrical nerve stimulator designed specifically for postoperative electroanalgesia. Urology 1989; 33(1):27-30.

Mersky H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2d ed. Seattle, WA: International Association for the Study of Pain, IASP Press; 1994.

Michalets EL. Update: clinically significant cytochrome P-450 drug interactions. Pharmacotherapy 1998; 18(1):84-112.

Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 1996; 82:44-51.

Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. J Cardiothorac Vasc Anesth 1993; 7(5):529-34.

Miro J, Raich RM. Effects of a brief and economical intervention in preparing patients for surgery: does coping style matter? Pain 1999; 83(3):471-5.

Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: JD Loeser,ed. Bonica's Management of Pain. New York: Lippincott Williams & Wilkins; 2000:1682-1709.

Moiniche S, Mikkelsen S, Wetterslev J, Dahl JB. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth 1998; 81(3):377-83.

Mollmann M, Cord S, Holst D, Auf der Landwehr U. Continuous spinal anaesthesia or continuous epidural anaesthesia for post-operative pain control after hip replacement? Eur J Anaesthesiol 1999; 16(7):454-61.

Mom T, Commun F, Derbal C, Dubray C, Eschalier A, Bost P, Avan P, Bazin J, Gilian L. Post-operative pain evaluation in the surgery of head and neck cancers. Rev Laryngol Otol Rhinol (Bord) 1996; 177(2) 93-6.

Moore C, Cardea J. Vascular Changes in leg trauma. In: W Melzack, ed. Textbook of Pain 2d ed. New York: Churchill Livingstone; 1977:932-41.

Moore KN, Estey A. The early post-operative concerns of men after radical prostatectomy. J Adv Nurs 1999; 29(5):1121-9.

Moser AR, Hurt ME, Easter DW. Surgical complications. In: DC Sabiston, ed. Textbook of Surgery: The Biological Basis of Modern Surgical Practice. 15th ed. Philadelphia: W.B. Saunders: 1997.

Morgan J, Wells N, Robertson E. Effects of preoperative teaching on postoperative pain. A replication and expansion. International Journal of Nursing Studies 1985; 22:267-80.

Morris J. The Value of Continuous Passive Motion in Rehabilitation Following Total Knee Replacement. Physiotherapy 1995; 81(9):557-62.

Mulroy MF. Epidural opioid delivery methods: bolus, continuous infusion, and patient-controlled epidural analgesia. Reg Anesth 1996; 21(6 Suppl):100-4.

Munro AJ, Long GT, Sleigh JW. Nurse-administered subcutaneous morphine is a satisfactory alternative to intravenous patient-controlled analgesia morphine after cardiac surgery. Anesth Analg 1998; 87(1):11-5.

Muramoto T, Atsuta Y, Iwahara T, Sato M, Takemitsu Y. The action of prostaglandin E2 and triamcinolone acetonide on the firing activity of lumbar nerve roots. Int Orthop 1997; 21(3):172-5.

Myles PS, Buckland MR, Cannon GB, Bujor MA, Langley M, Breaden A, Salamonsen RF, Davis BB. Comparison of patient-controlled analgesia and nurse-controlled infusion analgesia after cardiac surgery. Anaesth Intensive Care 1994; 22(6):672-8.

National Center for Complementary and Alternative Medicine. National Institutes of Health. Acupuncture Information and Resources, 2001. http://nccam.nih.gov/ fcp/factsheets/acupuncture/acupuncture.htm

National Institutes of Health. Acupuncture, NIH Consensus Statement, Nov 3-5 1997. http://odp.od.nih.gov/consensus/cons/107/107_intro.htm

Nelson DA. Intraspinal therapy using methylprednisolone acetate. Twenty-three years of clinical controversy. Spine 1993; 18(2):278-86.

Neupert EA, Lee JW, Philput CB, Gordon JR. Evaluation of dexamethasone for reduction of postsurgical sequelae of third molar removal. J Oral Maxillofac Surg 1992; 50(11):1177-82; discussion 82-3.

Neustadt DH. Intra-articular steroid therapy. In: RW Moskowitz, DS Howell , VM Goldberg, HJ Mankin, eds. Osteoarthritis: Diagnosis and Medical/Surgical Management. 2d ed. Philadelphia, Pa: WB Saunders Co; 1992.

NHMRC, Commonwealth of Australia, National Health and Medical Research Council, Acute Pain, 1999.

Nicodemus H, Ferrer M, Cristobal V, deCastro L. Bilateral infraorbital block with 0.5% bupivicaine as post-operative analgesia following chelioplasty in children. Scand J Plast Reconstr Surg Hand Surg (Sweden) 1991; 25(3):253-7.

Nicol DL, Smithers BM. Related Articles: Laparoscopic approach to the left kidney avoiding colonic mobilization. J Urol 1994; 152(6 Pt 1):1967-9.

Nicolodi M, Frezzott R, Diadori A, Scuteri F. Phantom eye: Features and prevalence. The predisposing role of headache. Cephalgia (Norway) Jun 1997; 17(4):501-4.

Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet 1997; 350(9088):1353-7.

Obata H, Saito S, Fujita N, Fuse Y, Ishizaki K, Goto F. Epidural block with mepivacaine before surgery reduces long-term post- thoracotomy pain. Can J Anaesth 1999; 46(12):1127-32.

O'Halloran P, Brown R. Patient-controlled analgesia compared with nurse-controlled infusion analgesia after heart surgery. Intensive Crit Care Nurs 1997; 13(3):126-9.

Omoigui, S. The Pain Drugs Handbook. St. Louis: Mosby-Year Book, Inc.; 1995.

Owen H, McMillan V, Rogowski D. Post-operative pain therapy: a survey of patients' expectations and their experiences. Pain 1990; 41(3):303-7.

Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery 1994; 35(6):1061-4; discussion 4-5.

Palve H, Kirvela O, Olin H, Syvalahti E, Kanto J. Maximum recommended doses of lignocaine are not toxic. Br J Anaesth 1995; 74(6):704-5.

Parikh JR, Houpt JB, Jacobs S, Fernandes BJ. Charcot's arthropathy of the shoulder following intraarticular corticosteroid injections. J Rheumatol 1993; 20(5):885-7.

Parker RK, Holtmann B, White PF. Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. Anesthesiology 1992; 76(3):362-7.

Parker RK, Sawaki Y, White PF. Epidural patient-controlled analgesia: influence of bupivacaine and hydromorphone basal infusion on pain control after cesarean delivery. Anesth Analg 1992; 75(5):740-6.

Passchier J, Rupreht J, Koenders ME, Olree M, Luitwieler RL, Bonke B. Patient-controlled analgesia (PCA) leads to more postoperative pain relief, but also to more fatigue and less vigour. Acta Anaesthesiol Scand 1993; 37(7):659-63.

Pastor J, Morales P, Cases E. Evaluation of intercostal cryoanalgesia versus conventional analgesia in postthoracotomy pain. Respiration 1996; 63(4):241-5.

Paulos L, Rusche K, Johnson C, Noyes FR. Patellar malalignment: a treatment rationale. Phys Ther 1980; 60(12):1624-32.

Perttunen K, Nilsson E, Kalso E. I.V. diclofenac and ketorolac for pain after thoracoscopic surgery. Br J Anaesth 1999; 82(2):221-7.

Picard PR, Tramer MR, McQuay HJ, Moore RA. Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomised controlled trials. Pain 1997; 72(3):309-18.

Pico L, Hernot S, Negre I, Samii K, Fletcher D. Peroperative titration of morphine improves immediate postoperative analgesia after total hip arthroplasty. Can J Anaesth 2000; 47(4):309-14.

Pike PM. Transcutaneous electrical stimulation. Its use in the management of postoperative pain. Anaesthesia 1978; 33(2):165-71.

Pinzur MS, Garla PG, Pluth T, Vrbos L. Continuous postoperative infusion of a regional anesthetic after an amputation of the lower extremity. A randomized clinical trial. J Bone Joint Surg Am 1996; 78(10):1501-5.

Pitkanen MT, Numminen MK, Tuominen MK, Rosenberg PH. Comparison of metoclopramide and ondansetron for the prevention of nausea and vomiting after intrathecal morphine. Eur J Anaesthesiol 1997; 14(2):172-7.

Puntillo KA. Effects of interpleural bupivacaine on pleural chest tube removal pain: a randomized controlled trial. Am J Crit Care 1996; 5(2):102-8.

Quebec Task Force Report on Spinal Disorders. Spine 1981; 12(75)S:1-59.

Quiney N, Cooper R, Stoneham M, Walters F. Pain after craniotomy. A time for reappraisal? Br J Neurosurg 1996; 10(3):295-9.

Radnay PA, Duncalf D, Novakovic M, Lesser ML. Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol, and naloxone. Anesth Analg 1984; 63(4):441-4.

Raffin L, Fletcher D, Sperandio M, Antoniotti C, Mazoit X, Bisson A, Fischler M. Interpleural infusion of 2% lidocaine with 1:200,000 epinephrine for postthoracotomy analgesia. Anesth Analg 1994; 79(2):328-34.

Ragazzo PC, Galanopoulou AS. Alfentanil-induced activation: a promising tool in the presurgical evaluation of temporal lobe epilepsy patients. Brain Res Brain Res Rev 2000; 32(1):316-27.

Rasmussen S, Larsen AS, Thomsen ST, Kehlet H. Intra-articular glucocorticoid, bupivacaine and morphine reduces pain, inflammatory response and convalescence after arthroscopic meniscectomy. Pain 1998; 78(2):131-4.

Rawal N. Epidural and spinal agents for postoperative analgesia. Surg Clin North Am 1999; 79(2):313-44.

Ready LB, Chadwick HS, Ross B. Age predicts effective epidural morphine dose after abdominal hysterectomy. Anesth Analg 1987; 66(12):1215-8.

Ready LB. Acute Perioperative Pain. In: RD Miller, ed. Anesthesia 5th ed. Philadelphia: Churchill Livingstone; 2000.

Reinhart DJ, Wang W, Stagg KS, Walker KG, Bailey PL, Walker EB, Zaugg SE. Postoperative analgesia after peripheral nerve block for podiatric surgery: clinical efficacy and chemical stability of lidocaine alone versus lidocaine plus clonidine. Anesth Analg 1996; 83(4):760-5.

Reuben S, Connely N. Post-operative analygesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000; 91(5):1221-5.

Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesth Analg 1998; 87(1):98-102.

Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. Br J Anaesth 1999; 83(3):387-92.

Richardson J, Sabanathan S, Mearns AJ, Shah RD, Goulden C. A prospective, randomized comparison of interpleural and paravertebral analgesia in thoracic surgery. Br J Anaesth 1995; 75(4):405-8.

Ritchie ED, Tong D, Chung F, Norris AM, Miniaci A, Vairavanathan SD. Suprascapular nerve block for postoperative pain relief in arthroscopic shoulder surgery: a new modality? Anesth Analg 1997; 84(6):1306-12.

Ritschel WA, Hoffmann KA, Willig JL, Frederick KA, Wetzelsberger N. The effect of age on the pharmacokinetics of pentazocine. Methods Find Exp Clin Pharmacol 1986; 8(8):497-503.

Robiony M, Demitri V, Costa F, Politi M. Percutaneous maxillary nerve block anesthesia in maxillofacial surgery. Minerva Stomatol 1999; 48(1-2):9-14.

Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321(7275):1493.

Rogers JE, Fleming BG, Macintosh KC, Johnston B, Morgan-Hughes JO. Effect of timing of ketorolac administration on patient-controlled opioid use. Br J Anaesth 1995; 75(1):15-8.

Romsing J, Ostergaard D, Drozdziewicz D, Schultz P, Ravn G. Diclofenac or acetaminophen for analgesia in paediatric tonsillectomy outpatients. Acta Anaesthesiol Scand 2000; 44(3):291-5.

Rose DK, Cohen MM, Wigglesworth DF. Critical respiratory events in the postanesthesia care unit: Patient, surgical and anesthetic factors. Anesthesiology 1994; 81(2):410-8.

Rosenberg M, Curtis L, Bourke DL. Transcutaneous electrical nerve stimulation for the relief of postoperative pain. Pain 1978; 5(2):129-33.

Rosenhow D, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998; 86(5):1045-50.

Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982; 56(2):93-6.

Rosted P. Adverse reaction after acupuncture: A review. Critical Rev Phys Rehabil Med 1997; 9(3&4):245-64.

Rowe WL, Goodwin AP, Miller AJ. The efficacy of pre-operative controlled-release indomethacin in the treatment of post-operative pain. Curr Med Res Opin 1992; 12(10):662-7.

Rozental TD, Sculco TP. Intra-articular corticosteroids: an updated overview. Am J Orthop 2000; 29(1):18-23.

Rusy LM, Houck CS, Sullivan LJ, Ohlms LA, Jones DT, McGill TJ, Berde CB. A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. Anesth Analg 1995; 80(2):226-9.

Rygnestad T, Zahlsen K, Bergslien O, Dale O. Focus on mobilisation after lower abdominal surgery. A double-blind randomised comparison of epidural bupivacaine with morphine vs. lidocaine with morphine for postoperative analgesia. Acta Anaesthesiol Scand 1999; 43(4):380-7.

Ryu, Johns Hopkins Health System et al. Clinical recognition of pulmonary embolism: problem of unrecognized and asymptomatic cases. Mayo Clin Proc. 1998; 73(9):873-9

Sabile M, Mallory T. The management of postoperative pain in total joint replacement; Transcutaneous electrical nerve stimulation is evaluated in total hip and knee patients. Orthopeadic Review 1978(7):121.

Sambrook PN, Hassall JE, York JR. Osteonecrosis after high dosage, short term corticosteroid therapy. J Rheumatol 1984; 11(4):514-6.

Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G, Katz J, Klein J. A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief. Analgesic, pharmacokinetic, and respiratory effects. Anesthesiology 1992; 77(4):626-34.

Sansone V, De Ponti A, Fanelli G, Agostoni M. Combined sciatic and femoral nerve block for knee arthroscopy: 4 years' experience. Arch Orthop Trauma Surg 1999; 119(3-4):163-7.

Santambrogio L, Nosotti M, Bellaviti N, Mezzetti M. Videothoracoscopy versus thoracotomy for the diagnosis of the indeterminate solitary pulmonary nodule. Ann Thorac Surg 1995; 59(4):868-70; discussion 70-1.

Savoie FH, Field LD, Jenkins RN, Mallon WJ, Phelps RA. The pain control infusion pump for postoperative pain control in shoulder surgery. Arthroscopy 2000; 16(4):339-42.

Scher KS. Unplanned re-operation for bleeding. *Am Surg* Jan 1996, 62(1) p52-5.

Scherhag A, Kleemann PP, Vrana S, Stanek A, Dick W. Plasma concentrations of bupivacaine for continuous peridural anesthesia in children. Anaesthesist 1998; 47(3):202-8.

Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet 1996; 31(4):275-92.

Schug SA, Burrell R, Payne J, Tester P. Pre-emptive epidural analgesia may prevent phantom limb pain. Reg Anesth 1995; 20(3):256.

Schulze S, Andersen J, Overgaard H, Norgard P, Nielsen HJ, Aasen A, Gottrup F, Kehlet H. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg 1997; 132(2):129-35.

Schultze-Mosgau S, Schmelzeisen R, Frolich JC, Schmele H. Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 1995; 53(1):2-7; discussion 8.

Schulze S, Sommer P, Bigler D, Honnens M, Shenkin A, Cruickshank AM, Bukhave K, Kehlet H. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch Surg 1992; 127(3):325-31.

Sebel PS, Hoke JF, Westmoreland C, Hug Jr. CC, Muir KT, Szlam F. Histamine concentrations and hemodynamic responses after remifentanil. Anesth Analg 1995; 80(5):990-3.

See WA, Fuller JR, Toner ML. An outcome study of patient-controlled morphine analgesia, with or without ketorolac, following radical retropubic prostatectomy. J Urol 1995; 154(5):1429-32.

Seers K, Carroll D. Relaxation techniques for acute pain management; A systematic review. Journal of Advanced Nursing 1998; 27:466-75.

Seino H, Watanabe S, Tanaka J, Koyama K, Naito H, Nakagawa H, Mitsui K. Cryoanalgesia for postthoracotomy pain. Masui 1985; 34(6):842-5.

Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995; 61(2):277-84.

Sethi GK, Copeland JG, Goldman S, Moritz T, Zadina K, Henderson WG. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. J Am Coll Cardiol 1990; 15(1):15-20.

Shacham S, Dar R, Cleeland CS. The relationship of mood state to the severity of clinical pain. Pain 1984; 18(2):187-97.

Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991; 74(1):53-63.

Sharf I, Kornmesser H, Hahnemann A. Pain-sensation following classic neck-dissection. Laryngol Rhin Otol (Stutt) 1977; Jun 56(6):546-52.

Shende D, Sadhasivam S, Madan R. Effects of peribulbar bupivacaine as an adjunct to general anaesthesia on peri-operative outcome following retinal detachment surgery. Anaesthesia 2000; 55(10):970-5.

Shir Y, Raja SN, Frank SM. The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. Anesthesiology 1994; 80(1):49-56.

Shroff A, Rooke GA, Bishop MJ. Effects of intrathecal opioid on extubation time, analgesia, and intensive care unit stay following coronary artery bypass grafting. J Clin Anesth 1997; 9(5):415-9.

Silvasti M, Pitkanen M. Continuous epidural analgesia with bupivacaine-fentanyl versus patient- controlled analgesia with I.V. morphine for postoperative pain relief after knee ligament surgery. Acta Anaesthesiol Scand 2000; 44(1):37-42.

Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti- inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284(10):1247-55.

Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 1998; 87(1):88-92.

Singelyn FJ, Gouverneur JM. Extended "three-in-one" block after total knee arthroplasty: continuous versus patient-controlled techniques. Anesth Analg 2000; 91(1):176-80.

Singh H, Bossard RF, White PF, Yeatts RW. Effects of ketorolac versus bupivacaine coadministration during patient- controlled hydromorphone epidural analgesia after thoracotomy procedures. Anesth Analg 1997; 84(3):564-9.

Sist T, Miner M, Lema M. Characteristics of postradical neck pain syndrome: a report of 25 cases. J Pain Symptom Manage 1999; 18(2):95-102.

Skjelbred P, Lokken P. Post-operative pain and inflammatory reaction reduced by injection of a corticosteroid. A controlled trial in bilateral oral surgery. Eur J Clin Pharmacol 1982a; 21(5):391-6.

Skjelbred P, Lokken P. Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. Eur J Clin Pharmacol 1982b; 23(2):141-6.

Slappendel R, Weber EW, Dirksen R, Gielen MJ, van Limbeek J. Optimization of the dose of intrathecal morphine in total hip surgery: a dose-finding study. Anesth Analg 1999; 88(4):822-6.

SMDMC, Proposal for clinical algorithm standards, Society for Medical Decision Making Committee on Standardization of Clinical Algorithms, In: Medical Decision Making, 12(2): 149-54.

Smidt W, Clark C, Smidt G. Short-term strength and pain changes in total hip arthroplasty patients. JOSPT 1990; 12(1):16-23.

Smith CM, Guralnick MS, Gelfand MM, Jeans ME. The effects of transcutaneous electrical nerve stimulation on post- cesarean pain. Pain 1986; 27(2):181-93.

Sochart DH, Hardinge K. The relationship of foot and ankle movements to venous return in the lower limb. J Bone Joint Surg Br 1999; 81(4):700-4.

Solomon RA, Viernstein MC, Long DM. Reduction of postoperative pain and narcotic use by transcutaneous electrical nerve stimulation. Surgery 1980; 87(2):142-6, 884-96.

Song D, Greilich NB, White PF, Watcha MF, Tongier WK. Recovery profiles and costs of anesthesia for outpatient unilateral inguinal herniorrhaphy. Anesth Analg 2000; 91(4):876-81.

Speer KP, Warren RF, Horowitz L. The efficacy of cryotherapy in the postoperative shoulder. J Shoulder Elbow Surg 1996; 5(1):62-8.

Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage MM, Anderson DL. Prospective multicenter evaluation of tramadol exposure. J Toxicol Clin Toxicol 1997; 35(4):361-4.

Stage J, Jensen JH, Bonding P. Post-tonsillectomy haemorrhage and analgesics. A comparative study of acetylsalicylic acid and paracetamol. Clin Otolaryngol 1988; 13(3):201-4.

Staritz M, Poralla T, Manns M, Meyer Zum Buschenfelde KH. Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. Gut 1986; 27(5):567-9.

Steen M, Cooper K, Marchant P, Griffiths-Jones M, Walker J. A randomised controlled trial to compare the effectiveness of ice-packs and Epifoam with cooling maternity gel pads at alleviating postnatal perineal trauma. Midwifery 2000; 16(1):48-55.

Stein C, Comisel K, Haimerl E, Yassouridis A, Lehrberger K, Herz A, Peter K. Analgesic effect of intraarticular morphine after arthroscopic knee surgery. N Engl J Med 1991; 325(16):1123-6.

Stenseth R, Bjella L, Berg EM, Christensen O, Levang OW, Gisvold SE. Effects of thoracic epidural analgesia on pulmonary function after coronary artery bypass surgery. Eur J Cardiothorac Surg 1996; 10(10):859-65.

Stevens DS, Edwards WT. Management of pain in intensive care settings. Surg Clin North Am 1999; 79(2):371-86.

Stevens RD, Van Gessel E, Flory N, Fournier R, Gamulin Z. Lumbar plexus block reduces pain and blood loss associated with total hip arthroplasty. Anesthesiology 2000; 93(1):115-21.

Stevenson D. Drug hypersensitivity: adverse reactions to non-steroidal anti-inflammatory drugs. Imunol Aller Clin North Amer 1998; 18(4):773-98.

Stoneham MD, Cooper R, Quiney NF, Walters FJ. Pain following craniotomy: a preliminary study comparing PCA morphine with intramuscular codeine phosphate. Anaesthesia 1996; 51(12):1176-8.

Stoneham MD, Walters FJ. Post-operative analgesia for craniotomy patients: current attitudes among neuroanaesthetists. Eur J Anaesthesiol 1995; 12(6):571-5.

Swenson JD, Hullander RM, Bready RJ, Leivers D. A comparison of patient controlled epidural analgesia with sufentanil by the lumbar versus thoracic route after thoracotomy. Anesth Analg 1994; 78(2):215-8.

Syrjala KL. Integrating medical and psychological treatments for cancer pain. In: CR Chapman, KM Foley, eds. Current and emerging issues in cancer pain: research and practice. New York: Raven Press, Ltd.; 1993: 393-409.

Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 1999; 37(1):17-40.

Tempelhoff R, Modica PA, Bernardo KL, Edwards I. Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. J Neurosurg 1992; 77(2):201-8.

Thune A, Baker RA, Saccone GT, Owen H, Toouli J. Differing effects of pethidine and morphine on human sphincter of Oddi motility. Br J Surg 1990; 77(9):992-5.

Tittle M, McMillan SC. Pain and pain-related side effects in an ICU and on a surgical unit: nurses' management. Am J Crit Care 1994; 3(1):25-30.

Tobias JD, Deshpande JK, Wetzel RC, Solca M. Intrathecal morphine as an adjunct to anesthesia for head and neck surgery. South Med J 1990; 83(6):649-52.

TRICARE, Office of the Assistant Secretary of Defense (Health Affairs) and the TRICARE Management Activity, TRICARE Management Activity Statistical Report - Care in Fiscal Year 2000, 2001, http://www.tricare.osd.mil/Reports/HR/2000/15month/reg999.pdf.

Tsang J, Brush B. Patient-controlled analgesia in postoperative cardiac surgery. Anaesth Intensive Care 1999; 27(5):464-70.

Tuel SM, Meythaler JM, Cross LL. Cushing's syndrome from epidural methylprednisolone. Pain 1990; 40(1):81-4.

Tuman KJ, McCarthy RJ, March RJ, DeLaria GA, Patel RV, Ivankovich AD. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 1991; 73(6):696-704.

Turk D, Okifuji A. Textbook of Pain. In: PD Wall, R Melzack, eds. London: Churchill-Livingstone; 2000.

Turk DC, Okifuji A. Assessment of patients' reporting of pain: an integrated perspective. Lancet 1999; 353(9166):1784-8.

Tycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. J Pain Symptom Manage 1996; 12(5):273-82.

Tyler E, Caldwell C, Ghia JN. Transcutaneous electrical nerve stimulation: an alternative approach to the management of postoperative pain. Anesth Analg 1982; 61(5):449-56.

Uhrbrand B, Jensen TT, Bendixen DK, Hartmann-Andersen JF. Perioperative analgesia by 3-in-one block in total hip arthroplasty. Prospective randomized blind study. Acta Orthop Belg 1992; 58(4):417-9.

Urban MK, Urquhart B. Evaluation of brachial plexus anesthesia for upper extremity surgery. Reg Anesth 1994; 19(3):175-82.

USPSTF, Guide to Clinical Preventive Services. 2 ed. Baltimore: Williams and Wilkins; 1996.

VA 1996 External Peer Review Program. Contract No. V101(93) P-1369.

Vargas JH, Ross DG. Corticosteroids and anterior cruciate ligament repair. Am J Sports Med 1989; 17(4):532-4.

Varrassi G, Marinangeli F, Agro F, Aloe L, Cillis PD, Nicola AD, Giunta F, Ischia S, Ballabio M, Stefanini S. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. Anesth Analg 1999; 88(3):611-6.

Vassilakopoulos T, Mastora Z, Katsaounou P, Doukas G, Klimopoulos S, Roussos C, Zakynthinos S. Contribution of pain to inspiratory muscle dysfunction after upper abdominal surgery: A randomized controlled trial. Am J Respir Crit Care Med 2000; 161(4 Pt 1):1372-5.

VHA Directive 96-053 (August 29, 1996). Roles and Definitions for Clinical Practice Guidelines and Clinical Pathways.

VHA Patient Care Services, 2001.

VHA. Pain as the 5th Vital Sign Toolkit. Washington, DC: National Pain Management Coordinating Committee, October 2000.

Voshall B. The effects of pre-operative teaching on post-operative pain. Top Clin Nurs 1980; 2(1):39-43.

Wada J, Koshino T, Morii T, Sugimoto K. Natural course of osteoarthritis of the knee treated with or without intraarticular corticosteroid injections. Bull Hosp Jt Dis 1993; 53(2):45-8.

Walker DJ, Zacny JP. Subjective, psychomotor, and analgesic effects of oral codeine and morphine in healthy volunteers. Psychopharmacology (Berl) 1998; 140(2):191-201.

Wall P, Melzack R. Textbook of Pain. New York: Chruchill Livingstone; 1989. 884-96, 932-63.

Walsh W. The effect of transcutaneous electrical nerve stimulation on pain after thoracotomy. Textbook of Pain. 2 ed. W Melzack, editor. New York: Churchill Livingstone; 1980. 952-63.

Wang JJ, Ho ST, Liu HS, Ho CM. Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery. Br J Anaesth 2000; 84(4):459-62.

Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg 2000; 91(1):136-9.

Wang JJ, Ho ST, Liu YH, Ho CM, Liu K, Chia YY. Dexamethasone decreases epidural morphine-related nausea and vomiting. Anesth Analg 1999; 89(1):117-20.

Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, Ho CM. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Br J Anaesth 1999; 83(5):772-5.

Wang JJ, Ho ST, Lee SC, Tang JJ, Liaw WJ. Intraarticular triamcinolone acetonide for pain control after arthroscopic knee surgery. Anesth Analg 1998; 87(5):1113-6.

Wang JJ, Ho ST, Hu OY. Comparison of intravenous nalbuphine infusion versus saline as an adjuvant for epidural morphine. Reg Anesth 1996; 21(3):214-8.

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30(6):473-83.

Warfield CA, Stein JM, Frank HA. The effect of transcutaneous electrical nerve stimulation on pain after thoracotomy. Ann Thorac Surg 1985; 39(5):462-5.

Warner MA, Hosking MP, Gray JR, Squillace DL, Yunginger JW, Orszulak TA. Narcotic-induced histamine release: a comparison of morphine, oxymorphone, and fentanyl infusions. J Cardiothorac Vasc Anesth 1991; 5(5):481-4.

Wassef MR, Randazzo T, Ward W. The paravertebral nerve root block for inguinal herniorrhaphy--a comparison with the field block approach. Reg Anesth Pain Med 1998; 23(5):451-6.

Waterman H, Leatherbarrow B, Slater R, Waterman C. Post-operative pain, nausea and vomiting: qualitative perspectives from telephone interviews. J Adv Nurs 1999; 29(3):690-6.

Watters WC, Temple AP, Granberry M. The use of dexamethasone in primary lumbar disc surgery. A prospective, randomized, double-blind study. Spine 1989; 14(4):440-2.

Webb JM, Williams D, Ivory JP, Day S, Williamson DM. The use of cold compression dressings after total knee replacement: a randomized controlled trial. Orthopedics 1998; 21(1):59-61.

Weller R, M Rosenblum, P Conard, JB Gross. Comparison of epidural and patient-controlled intravenous morphine following joint replacement surgery. Can J Anaesth 1991; 38(5):582-6.

Wellwood J, Sculpher MJ, Stoker D, Nicholls GJ, Geddes C, Whitehead A, Singh R, Spiegelhalter D. Randomised controlled trial of laparoscopic versus open mesh repair for inguinal hernia: outcome and cost. BMJ 1998; 317(7151):103-10.

Whalley DG, Berrigan MJ. Anesthesia for radical prostatectomy, cystectomy, nephrectomy, pheochromocytoma, and laparoscopic procedures. Anesthesiol Clin North America 2000; 18(4):899-917, x.

Wheatley RG, Shepherd D, Jackson IJ, Madej TH, Hunter D. Hypoxaemia and pain relief after upper abdominal surgery: comparison of I.M. and patient-controlled analgesia. Br J Anaesth 1992; 69(6):558-61.

Whitelaw GP, DeMuth KA, Demos HA, Schepsis A, Jacques E. The use of the Cryo/Cuff versus ice and elastic wrap in the postoperative care of knee arthroscopy patients. Am J Knee Surg 1995; 8(1):28-30; discussion -1.

Whitford A, Healy M, Joshi GP, McCarroll SM, O'Brien TM. The effect of tourniquet release time on the analgesic efficacy of intraarticular morphine after arthroscopic knee surgery. Anesth Analg 1997; 84(4):791-3.

Wicki J, Droz M, Cirafici L, Vallotton MB. Acute adrenal crisis in a patient treated with intraarticular steroid therapy. J Rheumatol 2000; 27(2):510-1.

Wiebalck A, Brodner G, Van Aken H. The effects of adding sufentanil to bupivacaine for postoperative patient-controlled epidural analgesia. Anesth Analg 1997; 85(1):124-9.

Wierod FS, Frandsen NJ, Jacobsen JD, Hartvigsen A, Olsen PR. Risk of haemorrhage from transurethral prostatectomy in acetylsalicylic acid and NSAID-treated patients. Scand J Urol Nephrol 1998; 32(2):120-2.

Wilkinson H. Comments on Dexamethasone--A helpful adjunct in management after lumbar discectomy. Neurosurgery 1984; 14(6):700.

William MJ. Local anesthetics. In: PP Raj, ed. Pain medicine-a comprehensive review. St Louis, MO: Mosby Year Book, Inc.; 1996:162-175.

Williams D. Acute Pain Management. In: R Gatchel and D Turk, eds. Psychological Approaches to Pain Management. New York: Guilford; 1996:65-6.

Williams N, Strunin A, Heriot W. Pain and vomiting after vitreoretinal surgery: a potential role for local anaesthesia. Anaesth Intensive Care 1995; 23(4):444-8.

Williamson LW, Lorson EL, Osbon DB. Hypothalamic-pituitary-adrenal suppression after short-term dexamethasone therapy for oral surgical procedures. J Oral Surg 1980; 38(1):20-8.

Woolf SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. Archives of Intern Med 1992;152: 947-948.

Wulf H, Biscoping J, Beland B, Bachmann-Mennenga B, Motsch J. Ropivacaine epidural anesthesia and analgesia versus general anesthesia and intravenous patient-controlled analgesia with morphine in the perioperative management of hip replacement. Ropivacaine Hip Replacement Multicenter Study Group. Anesth Analg 1999; 89(1):111-6.

Yeh CC, Yu JC, Wu CT, Ho ST, Chang TM, Wong CS. Thoracic epidural anesthesia for pain relief and postoperation recovery with modified radical mastectomy. World J Surg 1999; 23(3):256-60; discussion 60-1.

Zimmerman L, Nieveen J, Barnason S, Schmaderer M. The effects of music interventions on postoperative pain and sleep in coronary artery bypass graft (CABG) patients. Sch Inq Nurs Pract 1996; 10(2):153-70; discussion 71-4.