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CE Information

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Target Audience

This activity is intended for nurses and other clinicians who care for patients with acute pain.

Goal

The goal of this activity is to provide nurses and other clinicians with an overview of pain management and the nursing role, focusing on interventional techniques and management of pain in the opioid-tolerant individual.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Summarize factors that promote the success of nurse-led pain management programs in the acute inpatient setting
2. Outline a multimodal approach to the management of acute pain in the opioid-tolerant individual
3. Identify appropriate interventional pain management therapies in the oncology patient

Credits Available

Nurses - 1 *ANCC* (0.5 contact hours are in the area of pharmacology)

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Disclosure: Debra B. Gordon, RN, MS, FAAN, has disclosed that she has served as an advisor or consultant to Cephalon and Ortho-McNeil.

From Medscape Nurses

Acute Pain Management in the Opioid-Tolerant Individual

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Posted: 10/15/2008

Opioid Use for Acute Pain

Despite controversies surrounding the risks and benefits of opioid use in chronic (noncancer) pain conditions, few would question the appropriateness of using opioids for the treatment of moderate to severe pain following major surgery. A primary factor constraining opioid use for acute pain has been dose-limiting side effects that can be problematic in opioid-naive patients. Recent increases in licit and illicit opioid use have produced a growing population of patients in the United States with opioid tolerance. This trend has resulted in a new challenge in perioperative pain management -- how to treat acute pain in the opioid-tolerant individual.

What Is Tolerance?

Distinct from addiction or physical dependence, tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of 1 or more of the drug's effects over time.[1] In pain management, it is vital to differentiate the different types of analgesic tolerance. Tolerance may develop to the analgesic effects of opioids, the side effects of opioids, or both. Although tolerance is considered a normal physiological adaptation, the development of tolerance is variable in individuals, and different types of tolerance develop at different rates. The dose of opioid and the duration of exposure required to produce tolerance are unknown, but tolerance to side effects (which is often beneficial) may develop as quickly as 2 weeks after beginning treatment.[2] Tolerance to the pain-relieving effects of opioids appears to be a less common and predictable clinical phenomenon. With analgesic tolerance, a higher dose is required to obtain the same amount of pain relief of previous lower doses.

Quoting a paper from *The New England Journal of Medicine*,[3] Kathleen Colfer, MSN, RN-BC, Clinical Nurse Specialist, Anesthesiology Pain Service at Thomas Jefferson Hospital in Philadelphia, Pennsylvania, described the differences between *associative* (learned) tolerance and *nonassociative* (adaptive) tolerance.[4] Associative tolerance is related to environmental clues and psychological factors that may, in some situations, help explain why tolerance is different in animals and humans. An example of associative tolerance may be seen in patients with addiction disease who exhibit less tolerance when opioids are used for pain treatment compared with doses that they may have used for their addiction. Nonassociative tolerance, on the other hand, is an adaptive cellular and receptor response.

What Do We Know About Opioid Tolerance?

Scientists are only now beginning to unravel the complex cellular processes involved in tolerance. Much of what we know comes from animal studies that are difficult to extrapolate to humans. A number of complex mechanisms have been linked to tolerance, including the desensitization of opioid receptors and a reduction in the turn-over rate and number of opioid receptors.[3] This process involves molecular and cellular mechanisms including alterations in gene expression, synaptic function, receptor coupling, and activity of neuronal circuits.[5,6]

Growing evidence suggests that opioid administration can actually produce pain through neuroplastic changes that involve a number of substrate systems and endogenous mediators (Table).[7] These changes stimulate a complex chain of events that increases the descending facilitation of pain in the central nervous system (Figure 1). Investigations are beginning to examine whether particular compounds that block some of these substrate systems and mediators, such as the N-methyl D-aspartate receptor, cholecystokinin, and dynorphin, might effectively prevent abnormal pain and response to opioids. In short, tolerance is a poorly understood and highly complex process that can limit the effectiveness of opioids for acute pain.

Table. Potential Mechanisms That Facilitate Pain in Chronic Opioid Dosing

•Increased DRG neurotransmitter content
•Increased primary afferent neurotransmitter release
•Increased spinal sensitivity to nociceptive neurotransmitters
•Increased spinal dynorphin activity
•Enhanced descending facilitation from the rostral ventromedial medulla
•Activation of NMDA receptors
•Enhanced monoxide signaling (NO/CO)
•Activation of protein kinase C

•Cytokine activation

CO = carbon monoxide; DRG = dorsal root ganglion; NMDA = N-methyl D-aspartate; NO = nitrous oxide
Reprinted from Reg Anesth Pain Med, 29, Carroll IR, Angst MS, Clark JD. Management of perioperative pain in patients chronically consuming opioids, 576-591. Copyright 2004, with permission from Elsevier

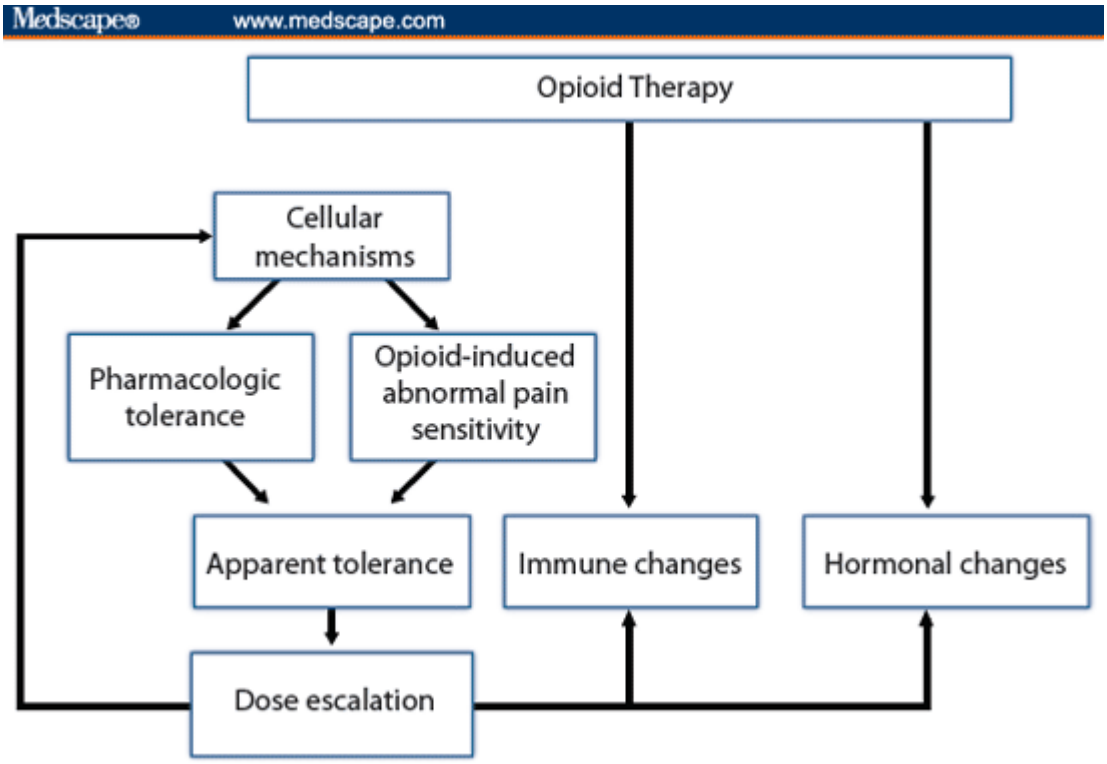

Figure 1. Possible adverse effects of prolonged opioid therapy. Prolonged opioid therapy can lead to cellular and intracellular changes, including activation of N-methyl-D-aspartate receptors. Such changes may contribute to pharmacologic opioid tolerance, increased sensitivity to pain (manifested as "apparent" opioid tolerance), or both, as well as the need for dose escalation. Prolonged opioid treatment may also result in hormonal changes and may alter immune function. These effects may be exacerbated by dose escalation in some circumstances.
Source: Ballantyne JC, Mao J. Opioid management for chronic pain. *NEJM 2003;349(20):1943-1953.*

What's a Clinician to Do?

I recently spoke with a number of anesthesiologists and pain scientists about this issue, asking what data were available to guide treatment of the opioid-tolerant individual in the perioperative setting. I was surprised by the lack of available data. It seems we are at a point in time when all we can say is, "Houston, we have a problem."

Early studies[8,9] characterized tolerance as a rightward displacement of the analgesic dose-response curve, so the simplest clinical approach has been to increase the opioid dose. However, a number of clinical studies[2,10] reported that patients who chronically consumed opioids before surgery experienced increased postoperative pain despite receiving a 3- to 4-fold greater amount of opioid than patients who were considered opioid-naive. These results have added to our appreciation that "uni-modal" treatment, particularly with just an opioid, is not the best approach for postoperative pain.

Multimodal Perioperative Analgesia

Lois Pizzi, BSN, RN-BC, Inpatient Pain Management Coordinator at the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, discussed implementation of a preemptive and multimodal approach to treat postoperative pain.[11] A concept that has quickly become a buzz-phrase in acute pain is *multimodal analgesia*. Rooted in the practice of anesthesiology,[12] the term simply implies combining 2 or more analgesic agents with different mechanisms of action to provide additive, if not synergistic, pain relief. There are many variations of multimodal analgesia, but a classic example is combining a nonsteroidal anti-inflammatory drug (NSAID) with an opioid analgesic following surgery.

Multimodal analgesic agents. Drugs commonly used for multimodal analgesia in acute pain include opioids, nonopioids, and a variety of adjuvant analgesics. Combinations of analgesics are chosen based on a mechanistic

approach that targets the pain pathway in both the peripheral and central nervous system (Figure 2). Although head-to-head comparisons of multimodal regimens are limited, evidence suggests that this approach can improve pain control while at the same time producing an opioid-sparing effect (reducing the amount of opioid required), and reducing analgesic side effects.[13] Another approach is a single agent with dual mechanisms of action.

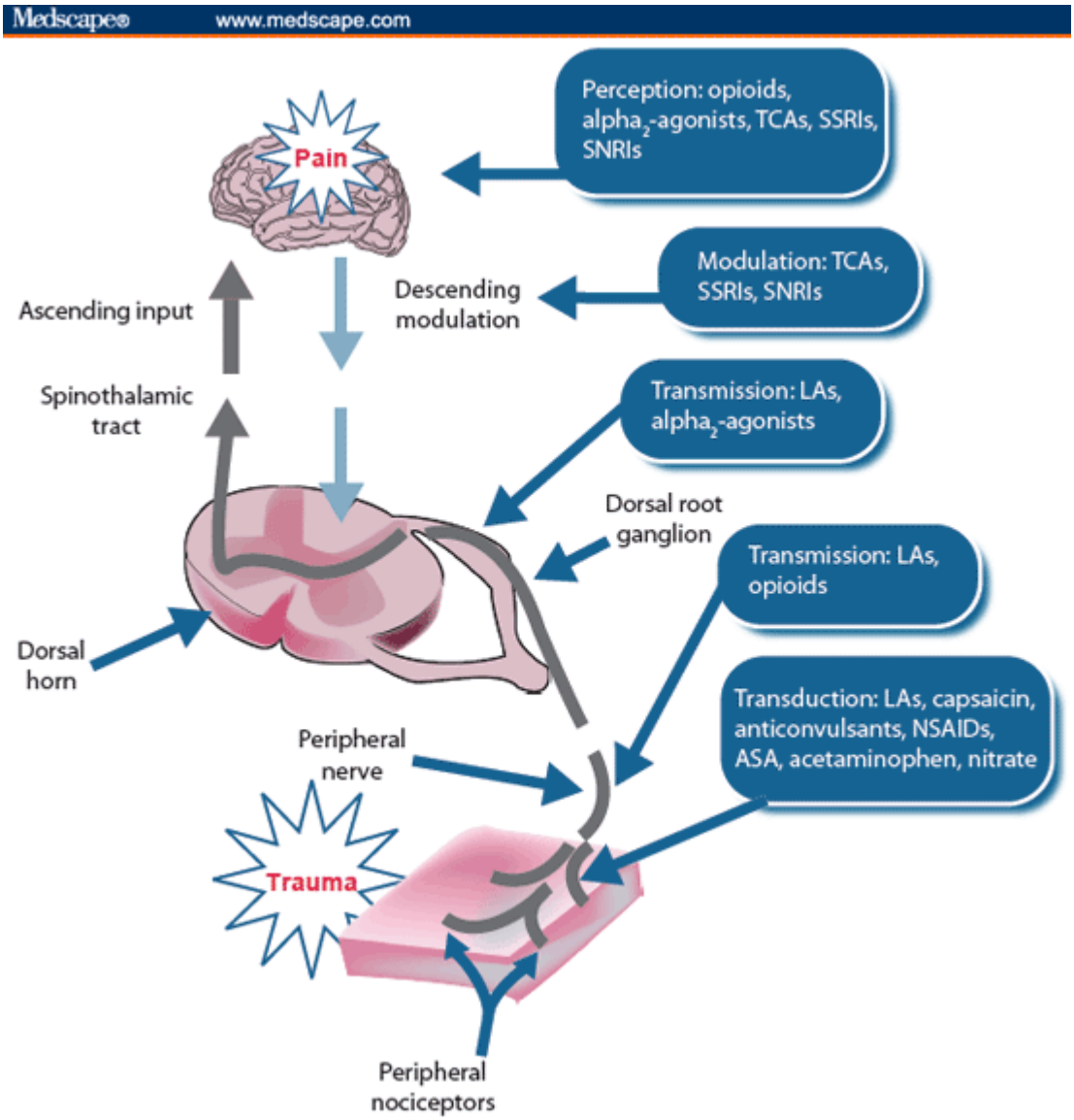

Figure 2. Multimodal analgesic approach to pain management. *ASA = aspirin; LAs = local anesthetics; NSAIDs = nonsteroidal anti-inflammatory drugs; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.*
Source: Kehlet H, Dahl JB. *Anesth Analg.* 1993;77:1048-1056.

The first agent in this class was tramadol, which produces analgesia by acting on opioid receptors as well as serotonin and norepinephrine receptors. The newest dual-mechanism agent in the pipeline is tapentadol. In phase 2 clinical trials, tapentadol has shown promise by producing fewer gastrointestinal side effects than conventional opioids, and it may be associated with less tolerance.[14,15]

The multimodal approach has been endorsed by many professional organizations including the American Society of Anesthesiologists[16] and the American Pain Society.[17] Of note, many of the approaches currently used in clinical practice are off-label. Whatever the regimen, multimodal analgesia should be rational and tailored to an individual patient's needs and risks.

Patient assessment. A first step for every patient is a thorough assessment, followed by frequent reassessments throughout the perioperative period. Patients may have skipped regular doses of medication prior to surgery and be at risk for opioid withdrawal. Nurses should be aware of, and help clarify, exactly what opioid and nonopioid analgesics (and doses) a patient was using before surgery. Team discussions that include the patient and family to address expectations and determine realistic goals are essential to successful pain management.

Treatment Approaches for Patients With Opioid Tolerance

Because we are only just beginning to understand tolerance, our knowledge about how to treat pain in the presence of opioid tolerance is extremely limited. A number of clinical reviews[18-22] have suggested the use of a multimodal approach for all stages of perioperative care including preoperative, intraoperative, and postoperative transition periods.

Preoperative Care

Discussion and preoperative education with the patient and family about:

- Previous effective pain management strategies;
- The patient's chronic baseline opioid requirements;
- Patient fears and expectations; and
- Plans for a balanced, multimodal regimen postoperatively.

Initiation of appropriate preoperative medications:

- Continuation of the preoperative opioid regimen on the day of surgery;
- Consideration of acetaminophen 1000 mg 1 to 2 hours before surgery;
- Consideration of a selective cyclooxygenase (COX-2) inhibitor such as celecoxib 1 to 2 hours before surgery; and
- Consideration of a single preoperative dose of gabapentin or pregabalin.

Intraoperative Care

Administration of opioids to meet the following requirements:

- Chronic requirements to avoid withdrawal issues;
- Intraoperative surgical stimulation; and
- Anticipated postoperative pain requirements.

Administration of adjuvant medications:

- Ketamine 0.5 mg/kg intravenous (IV) bolus followed by 2 µg/kg/minute infusion[23,24];
- Ketorolac 30 mg IV (if NSAID or COX-2 not started preoperatively); and
- Acetaminophen 1000 mg rectally if not started preoperatively
    - Institution of appropriate regional technique such as nerve block or epidural analgesia.

Postoperative Care

Understand that no predictions of opioid requirements can be made for individual patients. Patients who use even modest opioid doses (< 50 mg/day oral morphine equivalent) before surgery often require their baseline opioid dose plus 2 or more times the amount of opioids typically used for adequate pain control in opioid-naive patients.

During the acute phase of postoperative care, continue adjunct "multimodal" analgesics:

- Acetaminophen 1000 mg every 6 hours;
- And/or an NSAID or COX-2 inhibitor for several days with attention to renal function and risk of bleeding;
- Ketamine,[23,24] if started in the operating room, or consider instituting a ketamine infusion if pain proves refractory to other measures;
- Consider gabapentin; and
- Consider alpha-2 agonists.

During the transition phase of postoperative care:

- Transition from regional and parenteral techniques to oral opioids/adjuvants;
- Allow as-needed use of a short-acting opioid every 3 hours in sufficient quantity to provide the remaining required opioid dose;
- Plan to taper from postoperative opioid doses toward preoperative doses and discuss with the patient and outpatient care providers; and

- Determine whether there is a need for specialty follow-up if the regimen is particularly complex.

Summary and Take-Home Points

Surprisingly, few data exist to understand tolerance in humans. Tolerance is complex and can be both innate and acquired. The development of tolerance can be affected by many physiological processes and psychological issues. Development of tolerance is variable and may develop to side effects and analgesia. A growing population of opioid-tolerant patients creates new challenges in the management of postoperative pain. A multimodal approach combining analgesics with complementary, if not synergistic, mechanisms of action throughout the perioperative period seems to be our current best approach to managing acute pain in the opioid-tolerant individual.

This activity is supported by an independent educational grant from PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals Inc., administered by Ortho-McNeil Janssen Scientific Affairs, LLC.

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