

Pain Management and End-of-Life Care CME Program

Module 3

Registration: The registration page and test questions are at the end of this article (pages 68-70). The ten questions must be answered and submitted to the CSA in order to receive the CME credit. The full text of each module of this CME program, along with references, also will be accessible through the CSA Web Site, www.csahq.org.

Fees: This is a free service for CSA members. Non-members will be charged \$25 per CME credit hour. Your CME certificate will be mailed from the CSA office.

Availability: This module is available from September 15, 2004, until September 30, 2007.

Target Audience: California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. This module fulfills one credit hour of CME toward that requirement. This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in pain management.

Faculty and Disclosures for Module 3:

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Dr. Palmer is on the speaker's bureau for Pfizer, Merck and Medtronic. The article is not biased by her involvement with these companies.

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Evaluation: An evaluation of Module 3 of this series is offered after the test questions. Please fill in your responses to the questions and return them to the CSA office.

Objectives:

1. Understand the various reasons underlying opioid dose escalation;
2. Become familiar with the important issues of debate regarding the clinical use of opioids; and
3. Be aware of the general basic science theories regarding the mechanisms underlying opioid tolerance.

Resources: These materials are offered online at the CSA Web Site www.csahq.org also. The questions and answers are also available online. Please fill out the registration form, answer the questions, fill out the evaluation form and fax or mail these to the CSA office. Our fax number is (650) 345-3691; our new address is 951 Mariner's Island Boulevard #270, San Mateo, CA 94404.

Concepts in Opioid Tolerance

By Pamela Pierce Palmer, M.D., Ph.D.

Dr. Palmer received her M.D. and Ph.D. degrees from Stanford University in 1992, after which she completed her anesthesiology residency and fellowship in pain management at UCSF. She became the Medical Director of the UCSF Pain Management Center in 1999. Dr. Palmer also heads an NIH-funded basic science laboratory at UCSF, focusing her studies on mechanisms underlying inflammation and opioid tolerance. She has been a frequent and major contributor to a number of CSA's Educational Programs.

-Joshua Prager, M.D., Coordinator, CSA Bulletin Pain Management Series

Introduction

There is no question that the treatment of pain has become a priority of clinical medicine in the past decade. The concept of pain as the fifth vital sign, aggressive use of opioids in patients dying of cancer, and focusing on ways to assess and treat pain better in the pediatric population all are examples of

important steps towards reducing the suffering of patients. While there are still many examples of undertreatment of pain due to lack of education or inexperience of the treating physicians and nurses, or resistance on the part of the patient to ask for pain medication, there is another problem that may loom as an even bigger obstacle to effective management of chronic pain conditions—the problem of opioid tolerance.

There is active debate as to whether opioid tolerance is a significant clinical issue in patients with chronic pain. That is not surprising because, although we all have seen patients escalate their use of opioids over time, there are many variables, such as underlying disease progression or addictive behavior that may be the culprit. However, with the use of opioids as a treatment of chronic non-malignant pain having significantly increased in the past few decades, the issue of opioid tolerance needs to be more thoroughly addressed.

Whether chronic opioid use results in sustainable pain relief for chronic non-malignant pain conditions is a critical and complex subject that is not as straightforward as it might appear. The issue in many patients may not be whether their pain is being appropriately treated or being ignored, but whether the drugs that are being used to treat their pain can continue to provide pain relief in the long term. There is evidence to suggest that some, but not all, patients require rapid dose escalation to maintain opioid efficacy, suggesting that opioid tolerance may be a clinical problem in a subset of patients. For example, studies of chronic administration of systemic or intrathecal opioids suggest that while prolonged pain relief can be obtained in many patients, there are patients with non-malignant pain who tend to require escalating doses of opioids over time.^{1, 2} The study by Paice demonstrated over a 600% increase in intrathecal morphine dosing in non-malignant pain patients over a two-year period.¹ Mystakidou reports some patients escalating from 75 mcg/hr or less of transdermal fentanyl patches up to 250 mcg/hr within 18 months.²

Opioid escalation can occur for a variety of reasons, including underlying disease progression, psychological addiction and pharmacologic tolerance. We have diagnostic tools to identify disease progression and there are guidelines in the literature to identify and manage pain patients who might be drug-seeking or have a history of substance abuse.³ However, there are no guidelines in the literature to identify patients that may be poor candidates for long-term opioid treatment due to their development of rapid opioid tolerance, one that results in an inability to sustain long-term pain relief. This is an area where the basic science of opioid tolerance mechanisms has greatly outpaced clinical research.

Cellular Mechanisms of Tolerance

Complex cellular and molecular mechanisms are involved in the development of opioid tolerance. Endogenous opioid peptides and multiple opioid receptors have been identified. Opioid agonists activate classic G protein-coupled receptor signaling pathways via the mu-, delta- and kappa-opioid receptors, yet the mechanisms of opioid tolerance have proven particularly complicated. Underlying mechanisms involve second-messenger systems, kinases, receptor-G protein uncoupling and changes in membrane surface opioid receptors, including down-regulation and internalization.

Mu-opioid receptor down-regulation is reflected as an overall decrease in the level of receptor protein, or messenger RNA (mRNA) on the transcriptional level. Studies of the central nervous systems of animals exposed to opioids suggest that mu-opioid receptor down-regulation cannot by itself explain opioid tolerance. Most studies demonstrate no change in mu-opioid receptor mRNA levels in brains of morphine tolerant rats. However, a down-regulation of mu-opioid receptor mRNA has been found in the mediobasal hypothalamus of morphine tolerant guinea pigs, but without changes in other brain regions.

Up-regulation of the cyclic AMP (cAMP) pathway, as well as activation and inactivation of protein kinases, such as cAMP-dependent protein kinase, protein kinase C, G protein-coupled receptor kinases and Ca²⁺/calmodulin-dependent kinases have been observed after chronic opioid administration and/or withdrawal. Involvement of other receptors (such as the n-methyl-D-aspartate (NMDA) receptor), proteins and anti-opioid peptides are also well established. While a large body of evidence supports a role for each of these pathways and molecules in opioid tolerance development, there remain many unanswered questions.

New hypotheses are being proposed based on recent studies, including the concept that rapid morphine tolerance is the consequence of its inability to induce mu-opioid receptor internalization by endocytosis. The theory is that the mu-opioid receptor is chronically exposed to morphine and not allowed to internalize and become re-expressed and re-coupled to the G-protein. Although receptor internalization is common with G-protein-coupled receptors, morphine has not been shown to significantly stimulate the internalization of mu-opioid receptors. It is this lack of receptor internalization that is thought to be one of the reasons for the more rapid tolerance development with morphine. The mathematical ratio of relative agonist signaling versus endocytosis (RAVE) is proposed to assess the potential of an opioid agonist for induction of tolerance.⁴ The concept is that the mu- opioid receptor is chronically exposed to morphine

and not allowed to internalize and become re-expressed and re-coupled to the G-protein.

Receptor internalization and re-expression occurs constantly and does not result in an overall decrease in the number of expressed mu-opioid receptors. Receptor internalization is different from down-regulation of opioid receptors which, as mentioned above, does result in an overall decrease in the number of opioid receptors expressed on the neuronal surface. Because opioids in general do not appear to significantly down-regulate surface receptors in the central nervous system, recent research has focused more on receptor internalization as an important mechanism of opioid tolerance.

The above notwithstanding, a recent study of rats treated with chronic morphine demonstrates that the mu-opioid receptor mRNA is down-regulated in the peripheral nervous system, suggesting that receptor down-regulation may play a role in peripheral mu-opioid receptor tolerance.⁵

Mu-opioid agonists other than morphine, such as methadone, appear to have a stronger ability to promote receptor internalization by endocytosis. It has been suggested that chronic use of this agonist may result in less rapid tolerance development, although there are no definitive clinical studies demonstrating this to be true. It is possible that more effective opioid drugs will be developed which may more optimally interact with opioid receptors and reduce tolerance development.

Although the research of delta- and kappa-agonists for clinical use has lagged behind mu-agonists, advances in the field of kappa-agonists may allow more utilization of these drugs in the clinical setting. There is little known about kappa-agonist tolerance development because these drugs have been limited by their lack of analgesia for severe pain conditions.

In addition to the specific opioid agonist used, the type of pain condition being treated may also affect opioid tolerance development. Some animal studies have shown that neuropathic injury in rats results in less rapid tolerance to the analgesic effects of opioids compared with inflammatory injury models. A few human clinical studies have hinted at similar findings. Because neuropathic pain mechanisms involve similar molecules as opioid tolerance mechanisms (for example, the NMDA receptor), a relationship between type of pain and rate of tolerance is plausible.

Cellular Plasticity

Regardless of the cellular mechanisms of tolerance, there is no question that in order to develop tolerance, nociceptive neurons require significant cellular plasticity, such as modulation of NMDA channels and translocation of protein kinase C (PKC) from the cytosol to the membrane. Interestingly, the function of these molecules deteriorates with age of the neuron, suggesting that neuronal plasticity declines with age. Aged rodents display reductions in the protein expression of multiple subunits of the NMDA receptor. Aging also appears to diminish the ability of PKC to move from the cytosol to the membrane by impeding the ability of the PKC molecule to effectively anchor to the membrane.^{6, 7} While there are numerous reports studying the effects of age on pharmacokinetic parameters of opioids, clinical pharmacodynamic tolerance to long-term chronic daily opioids has not been studied in an age-dependent manner. The vast majority of clinical studies analyze patients from 18-80 (mean 50-60) years as a single group.

A single study in rats has suggested that the development of tolerance to daily morphine administration occurs more rapidly in young rats.⁸ In agreement with this finding is a study of 46 chronic pain patients taking sustained-relief oral morphine up to 60 mg twice a day.⁹ This is one of the few chronic pain studies in which the patient population was fairly young, averaging only 40 years of age. Once the dose-escalation phase was completed over the initial three weeks, patients, during the six-week evaluation on stable morphine dosing, reported an almost complete loss of pain relief by the end of the six weeks. There was no functional improvement in patients on opioid therapy in this study. Similarly, our laboratory has completed both an animal and human study on age-dependent tolerance and found that tolerance development to opioids decreases with age (in press).

Therefore, there are multiple variables when assessing opioid escalation in a chronic pain patient. Underlying disease progression, psychological addiction, and the development of opioid tolerance are some of the more important issues to consider. As discussed, there are additional variables when considering opioid tolerance, such as the type of opioid used, the type of pain condition being treated and neuronal plasticity (which appears to be less in older patients). When treating cancer pain we tend to escalate opioids as needed regardless of the underlying reason because long-term issues are not relevant. However, for chronic non-malignant pain, the long-term consequences of high-dose opioid therapy are receiving more attention. Ballantyne and Mao suggest that the practice of rapid continuous opioid escalation in non-malignant pain appears unjustified.¹⁰ They suggest that chronic high-dose opioid therapy, while

attempting to decrease the burden of medical care in complex pain patients, may in fact be increasing it by enhancing opioid tolerance, opioid-induced hypersensitivity, hormonal effects and immunosuppression. While this may be considered an extreme view by some physicians, there is no question that simply prescribing ever-escalating doses of opioids to chase tolerance development in chronic non-malignant pain is not the answer to this difficult problem.

Summary

Although it is crucial to continue the fight for more aggressive treatment of pain in all patients around the world, the limits of the drugs available today cannot be overlooked. The molecular and cellular changes that occur in neurons resulting in opioid tolerance development are complex. Variables such as age, type of pain and type of opioid must be evaluated. Further understanding of these mechanisms may allow development of therapies that can prolong opioid efficacy over time and truly result in long-term pain relief.

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To complete Module 3 for CME credit, please fill out the registration form on page 68, answer the test questions and the evaluation questions on pages 68-70, and send copies of all these pages to the CSA office by fax or mail.

Registration

To register for the CSA CME Course in Pain Management and End-of-Life Care, Module 2, fill out this form. Then make copies of the test and evaluation. Once you have answered the questions, **mail or fax** the form, the test answers and the evaluation to the CSA office at:

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Questions

1. The use of opioids for chronic non-malignant pain conditions has not increased much in the past two decades.
 - a. True
 - b. False
2. Opioid escalation is always a sign of opioid tolerance development.
 - a. True
 - b. False
3. Studies evaluating the escalating doses of opioids in chronic non-malignant pain patients show that some patients escalate by over 200% within two years or less.
 - a. True
 - b. False
4. Clinical research has outpaced basic science research in determining mechanisms underlying opioid tolerance development.
 - a. True
 - b. False
5. Mu opioid receptor down-regulation is one of the most important cellular mechanism underlying opioid tolerance development in the central nervous system.
 - a. True
 - b. False
6. Opioid tolerance mechanisms are complex and involve alterations in function at the receptor, G-protein and second-messenger system levels.
 - a. True
 - b. False
7. Which of the following molecules are thought to be important in pharmacodynamic opioid tolerance mechanisms?
 - a. NMDA receptors
 - b. protein kinase C
 - c. liver enzymes
 - d. Both A and B
8. The RAVE theory of determining the potential of a mu opioid agonist to promote tolerance development involves all but which of the following mechanisms?

- a. receptor endocytosis
 - b. receptor internalization
 - c. G-protein uncoupling
 - d. receptor desensitization
9. Age may influence the rate of pharmacodynamic tolerance development by:
- a. enhancing the anchoring mechanisms of PKC
 - b. decreasing cellular plasticity
 - c. increasing addictive behaviors
 - d. increasing the metabolism of morphine
10. Important variables involved in opioid dose escalation include which of the following?
- a. increased tumor burden
 - b. opioid tolerance development
 - c. psychological craving for the drug
 - d. all of the above

Evaluation of Module 3

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

3. How would you rate this program overall?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

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