Journal of Opioid Management™

A medical journal for proper and adequate use

Volume 2, Number 5 | SEPTEMBER/OCTOBER 2006 | ISSN 1551-7489

Official Journal of Opioid Management Society

CONTENTS

PAIN CARE PROTOCOL

Just 1 in 4 patients receives treatment to adequately alleviate suffering.

- *Insta-Cup*
- *Laboratory Screen*
- *Confirmation*
- *MRO*
- *Web Results*

Greater than 50% of doctors knowingly under-treat pain out of fear of opioid side effects and addiction, legal consequences with the use of controlled substances and reprisal from regulators. They risk investigation by Federal and State authorities for potential, inappropriate prescribing of pain medicine. Yet, they are just as much at risk of being accused of under treating pain if they are not willing to take the appropriate steps.

Routine and random toxicology tests are an essential element in the treatment of pain and limiting physician liability.

Accurate, Fast Results

Calloway controls each step of the drug testing process, minimizing possible delays and errors. We closely monitor each specimen throughout the testing lifecycle until results are reviewed and reported to the physician. Results are made available with MRO comments on our HIPAA-compliant web site.

In-House Confirmation – GC/MS

Calloway's initial lab screen is performed within 24 hours and then retested using one of the most advanced confirmation tests available: Gas Chromatography /Mass Spectrometry (GC/MS). Most labs send specimens to third parties, often taking weeks to deliver GC/MS results. Calloway is one of the few U.S. labs to perform GC/MS as an in-house test, representing the "gold standard" of drug testing confirmation and quantification.

Third-Party Billing

Calloway handles all billing through 3rd party insurance carriers, eliminating the need for physicians to bill for lab testing. This means the benefits of Calloway's Pain Care Protocol are available without administrative effort or financial obligation.

Medical Review Officer (MRO)

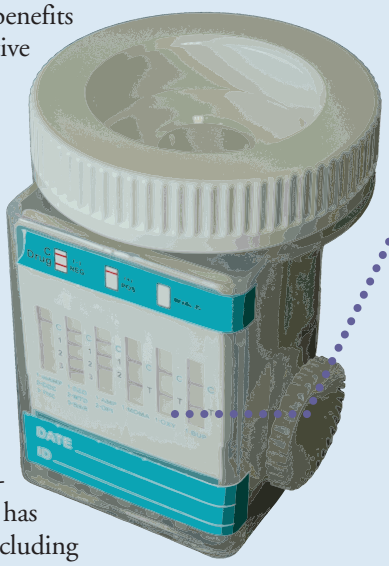
Calloway offers a unique MRO process specifically developed for our Pain Care Protocol. Unlike commonly preformed medical reviews, our MRO does not simply look for positive results, but also identifies any inconsistencies between toxicology results and the drugs prescribed by the ordering physician. The MRO process is fully integrated into our reporting process so that physicians receive MRO comments with each test.

Tools, Resources & Training

Training office staff and educating patients is one of the most important components of a successful Pain Care Protocol. Calloway has developed a full program to implement screening programs, including hands-on training, recommended forms & procedures, and FAQ's for both the office staff and patients.

Calloway's INSTA-CUP

Calloway's Pain Care Protocol includes a unique split chamber instant-read prescreening cup for preliminary results in less than five minutes, allowing for early identification of possible problems with patients undergoing pain management treatment. This prescreening is then confirmed with quantitative results at the Calloway lab.



Tests for 11 Drugs

- *Amphetamine*
- *Barbiturates*
- *Benzodiazepines*
- *Buprenorphine*
- *Cocaine*
- *Methadone*
- *Methamphetamine*
- *MDMA (Ecstasy)*
- *Opiates*
- *Oxycodone*
- *THC*

Rapid delivery of accurate answers to critical questions

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Call for manuscripts

Editorial Policy

The mission of the ***Journal of Opioid Management*** is to educate and promote, through scientifically rigorous research, the adequate and safe use of opioids in the treatment of pain as well as the legal and regulatory issues surrounding abuse, addiction, and prescription practices (both over- and under-prescribing). Original articles, case studies, literature reviews, editorials, and letters to the editor concerning all aspects of opioid management will be considered for publication. All submissions, excluding editorials and letters to the editor, are subject to peer review by the editorial board prior to acceptance.

Manuscript Submission

Electronic manuscript submission is preferred. Attach articles in MS Word, WordPerfect, or rich text (.rtf) format to the journal email address at *jom@pnpco.com.* If submitting via regular mail, please supply your article on a 3-1/2 inch IBM-PC format floppy disk or CD in MS Word 6.0 or greater, WordPerfect, or rich text format (.rtf). Manuscripts and all correspondence should be addressed to the Managing Editor, Journal of Opioid Management, 470 Boston Post Road, Weston, MA 02493. Submit one paper copy of the manuscript, typed and double-spaced, with the floppy disk or CD. As a general guideline, text should be 1,500 to 2,500 words (seven to 12 pages for a research paper, three to five manuscript pages for editorials or book reviews).

Manuscript Format

The cover page should indicate the article's title, the full name, highest pertinent academic degrees, institutional affiliations, and current address of each author, contact information for the author handling all correspondence, telephone number, fax number, and, if the manuscript was orally presented at a meeting, the name of the organization, place, and date it was read. The first use of an uncommon abbreviation should be preceded by the full name. Brief definitions of key terms may be appended to the manuscript and can be presented in parentheses after the term within the article. With the exception of forum articles, book reviews, or letters to the editor, manuscripts should include the following five sections: Abstract, Introduction, Methods, Results, and Discussion. Subheads should be inserted at suitable levels. Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (available online at *http://www.icmje.org).*

Figures & Tables

The ***Journal*** welcomes illustrations, charts, and photographs to accompany articles. Figures should be titled and numbered consecutively according to the citation in the text. Information presented in figures and tables should be explained in the text. If data have been published previously, an appropriate reference should be included.

Short, descriptive legends should be provided on a separate page. Legends for figures previously published should include a complete reference to the original publication, with the copyright designation. Copies of the publisher's and author's permission to use the figure must be provided. Photographs should include legends and should be numbered consecutively according to the citation in the text and labeled on the back. Tables, photos, and figures must be submitted in the following formats: TIFF, JPEG, or EPS.

Manuscript review

Manuscripts are received with the understanding that they are submitted solely to ***Journal of Opioid Management*** and that, apart from abstracts, none of the material contained in the manuscript has been published previously or is under consideration for publication elsewhere. Authors should secure all necessary clearances and approvals prior to submission.

Journal of Opioid Management is a refereed journal. All manuscripts are generally subject to review by at least two members of the editorial advisory board who are noted experts in the appropriate subject area. The ***Journal*** reserves the right to make editorial revisions prior to publication.

All manuscripts are acknowledged immediately, and every effort will be made to advise contributors of the status of their submissions within 60 days.

References

References are organized in AMA format; that is, they are to be cited numerically in the text and in consecutive order, including the first three authors followed by et al., and listed at the end of the article in the following format:

Journal articles—

1. Mudd P, Smith JG, Allen AZ, et al.: High ideals and hard cases: The evolution of opioid therapy for cancer pain. *Hastings Cent Rep*. 1982; 12(2):11-14.

Books—

1. Bayles SP (ed.): *Nutritional Supplements and Interactions with Analgesics*. Boston: GK Hall & Co., 1978.

Book chapters—

1. Martin RJ, Post SG: Introducing alternative prescribing strategies. In Smith J, Howard RP, and Donaldson P (eds.): *The Oncology Management Handbook*. Madison, WI: Clearwater Press, 1998, pp. 310-334.

Web sites—

Health Care Financing Administration: HCFA Statistics at a glance. Available at: www.hcfa/gov/stats/stahili.htm. Accessed December 27, 2002.

Ethics

Style should conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" prepared by the International Committee of Medical Journal Editors and published in *Ann Intern Med* 1997; 126: 36-47, and available on the web at *http:www.acponline.org/journals/annals/01jan97/unifreqr.htm.*

The ***Journal*** expects authors to disclose any commercial or financial associations that might pose a conflict of interest in connection with the submitted article. All funding sources supporting the work should be acknowledged on the title page.

Manuscripts and all correspondence regarding them should be addressed to the Managing Editor, ***Journal of Opioid Management***, 470 Boston Post Road, Weston, MA 02493.

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(See Call for manuscripts)

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Editor-in-Chief, Robert E. Enck, MD

Professor of Medicine, Assistant Division Chief for Clinical Activities, Division of Medical Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania.

Editorial Review Board

CALENDAR

Opioid Management Society
Journal of Opioid Management
Opioid Education Program
Philadelphia: October 7-8, 2006
Miami: October 28-29, 2006
Houston: November 11-12, 2006

For registration information, contact:
Opioid Management Society
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Weston, Massachusetts 02493
Tel: 781-899-2702 ext. 103
E-mail: *jom@pnpco.com*
Web site: *http://www.opioidmanagementsociety.org*

University of Rochester School of Medicine & Dentistry
International Association for the Study of Pain (IASP)
9th International Conference on the Mechanisms and Treatment of Neuropathic Pain
November 2-4, 2006
The Fairmont South Hampton, Bermuda

For more information, contact:
Neuropathic Pain 2006 Conference Secretariat
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, New York 14642-8677
Tel.: 585-275-4392 / Fax 585-275-3721
E-mail: *office@cpe.rochester.edu*
Web site: *http://www.neuropathicpain.org*

David Geffen School of Medicine at UCLA
Anesthesiology Update 2006
November 4, 2006
Tom Bradley International Hall, UCLA
Los Angeles, California

For registration information, contact:
David Geffen School of Medicine
Office of Continuing Medical Education
Tel.: 310-794-2620 / Fax: 310-794-2624
Web site: www.cme.ucla.edu/courses/event-description?event_id=198769

Pain Free Africa
2nd African Congress on Pain
November 16-19, 2006
Dat El Imad Complex
Tripoli, Libya

For registration information, contact:
Dr. Husni R. Ajaj
Tel.: 218-91-313-8074
Fax: 218-21-361-9736
E-mail: info@pain-free-africa.com
Web site: www.pain-free-africa.com

American Society of Regional Anesthesia and Pain Medicine
2006 Annual Fall Pain Meeting and Workshops
November 16-19, 2006
San Francisco Marriott
San Francisco, California

For registration information, contact:
American Society of Regional Anesthesia and Pain Medicine
Tel.: 847-825-7246
Fax: 847-825-5658
E-mail: asrameetings@asahq.org
Web site: www.asra.com

University of Toronto Faculty of Medicine
Toronto Sunnybrook
13th Annual Conference: The Science & Art of Pain and Symptom Management
November 17-18
The Old Mill Inn
Toronto, Ontario, Canada

For registration Information, contact:
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Continued inside




OPIOID EDUCATION PROGRAM

For all physicians and pharmacists

"Any healthcare professional involved in pain management should attend this program!"

– Dr. Ralph F. Rashbaum, Texas Back Institute

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OPIOID MANAGEMENT SOCIETY™

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CONFERENCE LEADER

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Professor of Medicine, Assistant Division Chief for Clinical Activities, Division of Medical Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania

FALL 2006

Chicago: Sept. 16 – 17
Philadelphia: Oct. 7 – 8
Miami: Oct. 28 – 29
Houston: Nov. 11 – 12

This intensive, 2-day program, led by a renowned group of specialists, is designed to inform primary care physicians, pain specialists, pharmacists, and other opioid prescribers in the uses, abuses, and legal ramifications of opioids. The Society will issue a certificate of attendance verifying completion of the entire program.

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kentucky College of Medicine and the Opioid Management Society. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 14.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The University of Kentucky College of Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

Pharmacy

The University of Kentucky College of Pharmacy is approved by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This program has been assigned ACPE # 022-999-06-074-l01 and will award up to 17.1 contact hours (1.71 CEUs) of continuing pharmacy education credit in states that recognize ACPE providers. Statements of credit will indicate hours and CEUs based on participation. The College complies with the Criteria for Quality for continuing education programming.

Disclosure Statement

Faculty presenters of continuing education programs sponsored by the University of Kentucky Colleges of Pharmacy and Medicine are expected to disclose any real or perceived conflict of interest. Copies of faculty disclosures are included in participant program materials or given prior to the lecture.

REGISTER EARLY AND SAVE!

Registration fee is $695. Early registration is $645.

Register 6 weeks prior to program date (below) and save $50!

Chicago: September 16-17–Thorne Auditorium, Northwestern University

Philadelphia: October 7-8–Sheraton University City

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Houston: November 11-12–Marriott Houston Medical Center

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WEB: **www.opioidmanagementsociety.org**

Fee: Payment for this conference is due with registration form. Payments may be made by check, Visa, MasterCard, Discover, or American Express. Please make all checks payable to the "Opioid Management Society" and write the name of the delegate(s) on the face of the check.

Hotel Reservations:

Go to *www.opioidmanagementsociety.org* for your conference hotel information. A discounted rate will be available at the conference hotel under the name "Opioid Education Program" (or OEP) for all registrants. Hotel room space is limited, so make your reservation early. A credit card number is required at the time of reserving your room. Hotel rates are based upon availability.

Cancellations and Substitutions:

Should you be unable to attend for any reason, please inform us in writing two full weeks prior to the conference date, and a full refund less a 25% nonrefundable deposit will be issued. No refunds or credits will be given for cancellations received less than two weeks to the conference date. Substitutions of enrolled registrants must be made in writing. If, for any reason, the Opioid Management Society (OMS) decides to cancel this conference, OMS does not accept responsibility for covering airfare, hotel, or other costs incurred by registrants.

The Opioid Management Society and the University of Kentucky Colleges of Pharmacy and Medicine Continuing Education Office reserve the right to cancel or make substitutions in this activity.

Any individual requiring special physical arrangements or diet to attend this conference should notify the Opioid Management Society at least 3 weeks prior to the conference in writing by faxing to 781-899-4900.

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BOSTON

WHAT ATTENDEES HAD TO SAY ABOUT THE INAUGURAL OPIOID EDUCATION PROGRAM

"Any healthcare professional involved in pain management should attend this program!"
–Dr. Ralph F. Rashbaum, surgeon, Texas

"A first-rate educational experience with specific applications for my own work. I would highly recommend it to anyone involved in the prescription or management of opioids."
–Dr. David Raper, hospice and palliative medicine, Kentucky

"The standard of all the speakers was excellent. It was very educational."
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Day Two* – Sunday 8:00 AM – 4:30 PM

History of Opioids

Although there is universal recognition of the potent analgesic effects of opioids, many physicians are reluctant to employ them due to the risk of addiction. Over the last few decades, the benefits of opioid use in the acute post-operative period and in cancer patients has become evident. Despite that, the controversy between lay people, regulatory authorities, and physicians remains regarding the use of opioid analgesics for chronic non-cancer pain. While the debate stays open, millions of patients with acute and chronic pain suffer the consequences. To better understand the cultural and regulatory barriers that surround the medical use of opioids, it is instructive to analyze the historical context about their use and abuse.

Opioids: Types and Uses

There are many types of opioids and they are classified in many ways. For example: 1) Natural vs. semi-synthetic vs. synthetic. 2) Strong vs. weak. 3) Duration of action- a. short vs. medium; b. immediate release vs. controlled release. 4) Analgesic vs. non-analgesic. 5) By federal schedule (CI-CV). 6) By receptor affinity. 7) Legal vs. illegal. 8) Agonist vs. partial agonist vs. antagonist. There are many uses for opioids. The major focus here is, of course, on analgesia. But there are other, often fascinating, uses which will be covered: anesthesia, antitussive, antidiarrheal, antispasmodic, drug abuse, opioid maintenance treatment, opioid detoxification, vasodilatation/smooth muscle relaxation, and even antiterror.

Risk Management and Related Medico-Legal Issues with the Practice of Chronic Opioid Therapy

Risk management and related micro-legal issues are reviewed with respect to clinicians who undertake chronic opioid therapy in their practice. Risk factors are discussed with reference to typical malpractice claims, medical board complaints, and reports in medico-legal literature. Specific issues include guideline and Model Pain Policies implementation, scope of practice, record keeping/documentation, patient abandonment, communication with co-treating clinicians, and particular risks within solo versus group practice. The relative risk of undertaking chronic opioid therapy is contrasted to risks inherent in other pharmacotherapy or interventional treatments.

Rotation of Opioids

Escalating opioid requirements can be a consequence of either progression of disease or tolerance. There is increasing awareness among pain specialists that there may be a ceiling effect on the opioid dosing above which hyperalgesia, sedation, cognitive dysfunction, myoclonus or other side-effects may limit further upward titration. Opioid rotation takes advantage of incomplete opioid cross-tolerance which implies that an equianalgesic dose of a different opioid—one to which the patient has not been exposed before—will be much lower than expected. This may result in a 40% reduction in dosage while maintaining the same or better analgesia. Providers can use opioid rotation to reduce side-effects or improve efficacy in opioid tolerant individuals.

Judicious Screening: Psychosocial Issues with Chronic Opioid Therapy

Assessment of chronic pain is discussed with a focus on psychosocial evaluation and screening. Screening issues are addressed with respect to chronic opioid therapy with commentary on behavioral strategies intended to maximize adherence to the medical treatment regimen. The integration of nonpharmacologic strategies into the treatment regimen is discussed with a brief review of cognitive and relaxation interventions. Evidence-based interdisciplinary treatment is emphasized with additional discussion on barriers to effective treatment.

Interventional Techniques Used in Pain Management

There are various interventional techniques that can be used in pain management. One important consideration is the use of image guidance in the performance of said interventional techniques and differential diagnosis between certain types of pain. Back, neck, and head pain all have common causes. Possible interventional techniques to treat these three conditions include sacroiliac injection, facet/medial branch injection, sympathetic blocks, discography, radiofrequency, IDET, percutaneous disc decompression, vertebroplasty, Botox® injection, and implantables (nerve stimulators and intrathecal pumps). The indications, contraindications, and possible side effects of these techniques will be discussed.

Identification and Treatment of Opioid Dependence

Opioid dependence is a brain disease which will affect a certain percentage of patients treated with opioid analgesics for pain. It is crucial for physicians treating pain with opioids to be able to identify and treat these patients in a timely and effective manner. In 2002, the Drug Addiction Treatment Act gave all physicians (including pain management, family practice and internal medicine practitioners) the legal right to treat their patients for opioid dependence in the privacy of their own office. This introductory presentation will cover the following topics: overview of opioid dependence, in-office treatment options for opioid dependence, opioid dependence in chronic and acute pain patients, patient assessment and treatment/referral process, and available clinical tools.

Urine Drug Testing: Which Patient, Which Drug, Why

Opioid toxicology in various disease states will be discussed, along with the issue of rotation, the use of adjunctive medications, and how to taper and increase dosing in a safe manner. The treatment of side effects will be considered. Drug screening will cover use and misuse of opioids and what testing is most helpful. Urine testing, although not totally accurate, is a quick, practical, and cost-effective way of making sure which patients are or are not taking medications and to protect physician and patient from the problem of diversion.

**Program and faculty subject to change*

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Call for Abstracts

For International Conference on Opioids at Conference Center at Harvard Medical April 2007

SETTING THE STANDARDS FOR OPIOIDS

Purpose

For a variety of reasons, physicians often underprescribe opioids for the treatment of acute and chronic pain. This under-treatment of pain leads to significant social and economic costs including needless suffering, lost productivity, and excessive healthcare expenditures.

The Opioid Management Society in association with the *Journal of Opioid Management* believe that these impediments to the proper and compassionate use of opioids—which include concerns about addiction, negative side effects, tolerance, diversion, and fear of regulatory action—can be overcome through effective training and education, not only for the practitioners who prescribe and manage these drugs but also for other health professionals, regulators, policymakers, and the public.

A critical step in this educational process includes the establishment of a set of standards for the proper use and management of opioids in effective pain therapies. To create these clinical guidelines, the Opioid Management Society in association with the *Journal of Opioid Management* is inviting contributions for the international conference in April 2007 in Boston: "Setting the Standards for Opioids."

Abstracts will be reviewed by the OMS Conference Planning Committee for selection as an oral presentation or poster presentation. Attendees to OMS conferences are primarily medical clinicians and academic researchers at the medical professional level, and abstracts should reflect this level of experience and expertise. It is anticipated that this event will be accredited for continuing medical education for physicians. Abstracts selected will be published in the conference syllabus.

Scope

Topics could include, but not be limited to cancer pain, neuropathic pain, trauma pain, arthritis pain, addiction issues, legal and regulatory concerns, and end-of-life management.

Abstracts

- Abstracts should be non-commercial and focus on one or more of the areas indicated above.
- Submitted electronically preferably in MS Word but could be submitted in the body of an email.
- One page in length (single spaced, 12-point font), including all authors with presenting author listed first and in bold, institution(s) and include Objectives, Method, Results and Conclusion.
- Include presenting authors full name, academic credentials, mailing address, city, state, zip code, and email address.

Submission Process

1. Please email abstracts to *chris_rowland@ pnpco.com* no later than November 1, 2006.

2. Presenting author will be contacted by November 21st and advised if their abstract is approved with the type of presentation specified.

3. If selected, presenting author will be required to provide a Curriculum Vitae and complete necessary forms as directed in order to comply with AACME requirements for accreditation. Authors will be advised of the date and time of their presentation.

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COMMENTARY

Malignant pain or malignant patients?

Michael Weaver, MD

There is a difference in approach to patients with pain between professionals who specialize in palliative care and those who treat chronic nonmalignant pain (CNMP). This reflects not only the differences in the presentation of patients with malignant versus nonmalignant pain but also the differences in orientation of physicians who provide palliative care compared to those who treat CNMP. The use of opioid analgesics differs when the approach is palliation versus management of CNMP. This article contrasts the differing approaches to patients receiving palliative care versus those with CNMP with regard to the use of opioid analgesics.

Palliative care is the coordinated service offered to a patient with a progressive disease and his or her family when the illness is no longer curable, with the aims of maximizing quality of life and alleviating distressing symptoms.[1] Malignant pain is usually associated with terminal diagnoses; most often it is a result of cancer and/or complications of the treatment, but it may occur with other conditions such as AIDS and neurologic diseases. Management of malignant pain with opioid analgesics has gained wide acceptance within the field of palliative care.[2]

Practitioners who provide palliative care include infectious disease specialists and geriatricians, but frequently they are oncologists. Most palliative care research is performed in the context of cancer treatment. Therefore, the approach to the management of malignant pain is relatively consistent, as is the promulgation of medical education on the topic, by virtue of the relative homogeneity of palliative care practitioners. In contrast, CNMP encompasses a diverse group of diagnoses and syndromes (neuropathic pain, fibromyalgia, failed back surgery syndrome, chronic abdominal or pelvic pain, migraines, etc.). Practitioners who manage CNMP are a diverse group of generalists and specialists in disparate fields (primary care, rheumatology, neurology, neurosurgery, orthopedics, gynecology, psychiatry, anesthesia, etc.). This diversity poses significant challenges to the development of unified goals in research and medical education regarding CNMP management.

Some of the early research in pain management involved cancer pain, so there are studies from which to derive best-practice guidelines. Evidence-based guidelines for management of malignant pain have been accepted and updated over the past two decades. In the absence of other evidence, CNMP management was initially guided by research involving patients with malignant pain. Due to the heterogeneity of CNMP diagnoses, though, unified guidelines are challenging, and a one-size-fits-all approach is impractical. Even narrowing the scope of possible guidelines to the issue of opioid analgesic use reveals significant controversy. Research on abuse liability in opioid therapy for pain treatment shows little consistency in patient populations or definitions of terms such as "abuse" and "addiction."[3] Much of the guidance in medical literature for practitioners treating CNMP is based more on expert opinion than empirical research.

Treatment of malignant pain is supported by a diagnosis of malignancy. With cancer, this is obtained through tissue diagnosis, and with AIDS it is done through specific serology and a well-defined constellation of infections and cancers. Patients with CNMP most often have pain as the only unifying factor. Many diagnoses are syndromes based on a set of criteria or clinical judgments and pattern recognition, e.g., Complex Regional Pain Syndrome. Definitive diagnosis is elusive without the benefit of tissue pathology or clear-cut biomarkers. Cancer may be rapidly progressive, and symptom escalation leads to aggressive evaluation, with tissue identification allowing confirmation of a diagnosis/prognosis. Malignant pain often worsens in direct response to tissue damage from tumor growth or treatment (radiation, chemotherapy). Because of this practitioners generally (and rightly) view pain reported by cancer patients as being primarily somatogenic, but they frequently regard pain reported by patients with CNMP, who lack adequate objective physical pathology, as psychogenic.[4] Complaints of pain from patients with CNMP are often considered out of proportion to findings from examinations or objective testing. Patients with CNMP may suffer for years before their pain is adequately managed. Maladaptive behaviors for dealing with chronic pain may develop over time while patients with CNMP try to convince practitioners of the

severity of their pain. Demands for opioids made by patients with CNMP may lead to frustration on the part of the practitioner and feelings that the patient is "malignant," even if the condition is not.

Another difference between the approaches to pain management taken with palliative care and CNMP is the time course of the treatment. Palliative care does not attempt to be curative, so pain management is undertaken with the understanding that therapy will be limited by the remaining life span of the patient, often less than 12 months. The concept is to keep the patient comfortable. The terminal nature of malignancy allows for increased acceptance of aggressive treatment. Management of CNMP may also be for the remaining life span of the patient, but this may be several decades. Initiation of long-term therapy is not undertaken lightly, and aggressiveness is often checked because negative outcomes may result in consequences the patient will have to endure for many years. The use of opioids for CNMP is regarded with caution, and the issue is debated by practitioners because of concern—whether justified or not—about the potential for misuse/abuse over years of treatment. However, only a small minority of patients with pain appears to be at high risk for developing addiction.[3]

Adequate treatment of chronic pain remains challenging, and even cancer pain is undertreated.[5] Aggressive management of pain with opioids is more accepted in palliative care, as the terminal nature of the diseases involved and the assumption of a relatively short treatment time minimizes concern about addiction. Definitive tissue diagnoses mitigate fears of malingering for secondary gain. Unfortunately, patients with CNMP are more likely to be viewed with suspicion by practitioners. Concerns about secondary gain include malingering to avoid employment, investment in the "sick" role to fulfill unmet dependency needs, and access to opioids that may lead to abuse or diversion. Some patients deriving secondary gains from their CNMP condition or its treatment do intentionally deceive practitioners so they can continue to benefit, and practitioners treating CNMP should be vigilant for possible secondary-gain seeking in patients, but definitive determination of patient motives can be a challenge. Approaching patients with suspicion for secondary gain is not a natural extension of the healing arts or helping attitude of many practitioners and usually causes discomfort and concern. Maladaptive behaviors, comorbid psychiatric conditions, and pseudoaddiction all contribute to drug-seeking behavior, but they are not the same as intentional malingering. This complexity and uncertainty about patient motives play large roles in feeding the frustration experienced by practitioners who are dealing with patients with CNMP.

Suspicion regarding secondary gain may lead to an adversarial relationship with patients suffering from CNMP, instead of a patient-physician relationship based on healing or helping. Adversarial feelings may be intensified by medication contracts that stipulate conditions for refills and require urine samples for drug testing. These are appropriate, and often necessary, tools for monitoring, but they may add to feelings of mistrust, doubting of patient motives, or patients' feeling their clinicians are trying to "catch them in the act." This adversarial relationship often revolves around opioids. Escalating demands for opioids, along with maladaptive behaviors, complex comorbid psychiatric conditions, and the lack of a clear etiology for the pain, may lead some practitioners to view patients with CNMP as being "malignant" themselves. The adversarial nature of the relationship between practitioner and patient with CNMP is not usually seen in the context of palliative care. Practitioners of palliative care will partner with the patient to fight against the cancer and the pain it causes. The cancer, not the patient's behavior, is malignant. This provides solidarity in the patient-physician relationship and reaffirms the helpful nature of the practitioner. This solidarity is often not present when CNMP is the focus of treatment.

It is important to recognize these different approaches to the management of pain, especially regarding the use of opioid analgesics, between palliative care and treatment of CNMP. This can help prevent the frustration felt by both practitioners and patients that arises from attempting to use a one-size-fits-all approach in different populations. Incorporating a clear understanding of this difference into medical education about pain management will assist trainees in diverse disciplines as they attempt to reconcile disparate approaches when working with different patient populations. Practitioners who focus on either palliative care or CNMP management can learn from both approaches to opioid use, since malignancy survivors may develop CNMP from complications of the malignancy or its treatment, and patients with CNMP may develop cancer or other conditions that should not be overlooked (i.e., attributed to CNMP until too late). Pain management research may benefit from more formal differentiation that utilizes more homogeneous populations and clear delineations when assessing outcomes of interventions, especially involving opioids.

In summary, the use of opioids in palliative care is often more liberal due to definitive diagnoses and the terminal nature of malignant pain. Practitioners who manage CNMP are from diverse subspecialties with varied educational backgrounds regarding chronic pain management. They are managing patients who often have maladaptive behaviors and complex comorbid psychiatric conditions stemming from years of poorly controlled pain without a clear etiology. In addition, long-term concerns about medication abuse and fewer

evidence-based management guidelines contribute to a more adversarial relationship with patients regarding opioid analgesics. Acknowledging and learning from differences in approach can lead to improvements in research and better pain management. With such changes, only the diagnosis will be considered malignant and not the patient, due to a better understanding of the behavior of patients with CNMP that now so often results in practitioner frustration.

Michael Weaver, MD, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia.

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The Fourth Circuit Court of Appeals' decision in *United States v. Hurwitz:* An important victory for pain management professionals and those living with pain

Jennifer Bolen, JD

INTRODUCTION

The federal court system has a way of leveling the playing field between the government and defendants, and it often does so in ways that benefit nondefendant stakeholders whose interests are affected by the cases processed by the system.[1] On August 22, 2006, the United States Court of Appeals for the Fourth Circuit,[2] at Alexandria, Virginia, leveled the playing field between the government and defendant William Eliot Hurwitz, MD, and in doing so opened the door for pain management professionals to reclaim their right to establish generally accepted standards of care and to grow a body of experts who are willing to monitor the application of these standards, in both civil and criminal cases, by refusing to allow medical practice to be dictated merely by arbitrary numbers and combinations of drugs and by providing accurate and complete testimony in the courtroom. The future of pain management in the courtroom rests, in part, on the shoulders of this body of experts and their willingness to stand up to the government[3] and its so-called experts, who jeopardize the interests of both pain management professionals and the patients they serve by giving testimony that falls short of expert standards.[4] These experts will also have to navigate the final policy statement on dispensing controlled substances to treat pain, recently released by the Drug Enforcement Administration (DEA).[5] You can read a short summary of the recently released DEA materials in Table 1.

HURWITZ

General case background

In December 2004, after a lengthy trial, a federal jury convicted Hurwitz of one count of drug trafficking conspiracy (21 USC § 846), one count of drug trafficking resulting in death, two counts of drug trafficking resulting in serious bodily injury, and 46 counts of drug trafficking (21 USC § 841(a)(1)). The jury acquitted Hurwitz of six counts of drug trafficking, one count of engaging in a continuing criminal enterprise, and two counts of healthcare fraud. The jury failed to reach a decision on the remaining drug trafficking counts. The trial court sentenced Hurwitz to 25 years' imprisonment.

Hurwitz appealed his conviction, arguing that the trial court improperly admitted evidence recovered in a search of his office and incorrectly instructed the jury on the law by failing to give the jury an instruction on "good faith" relating to the drug trafficking charges.[6]

The Fourth Circuit Court of Appeals' decision: General explanation

The Fourth Circuit affirmed (agreed with) the trial court's decision on the search warrant issue, meaning the Fourth Circuit found the law supported the trial court's decision to admit the search warrant as evidence at trial. But the Fourth Circuit disagreed with the trial court's decision on the jury instruction issue, so it vacated[7] Hurwitz's conviction and remanded the case back to the district court for a new trial.

The Fourth Circuit based its decision in *Hurwitz* on a legal issue rather than on the facts of the case. The Fourth Circuit framed the deciding legal issue as follows:

> [W]hether the trial court committed "reversible error" when it refused Dr. Hurwitz's request to give the jury an instruction on the subject of whether Dr. Hurwitz acted in "good faith"—that is according to generally accepted standards of care—as applied to the jury's examination of the facts relating to each of the drug trafficking charges against him.

The Fourth Circuit held that the trial court did indeed make a legal mistake by refusing to give the jury an instruction on good faith and based its decision to reverse Dr. Hurwitz's conviction and remand the case for a new trial on this point of law. The Fourth Circuit *did not consider*

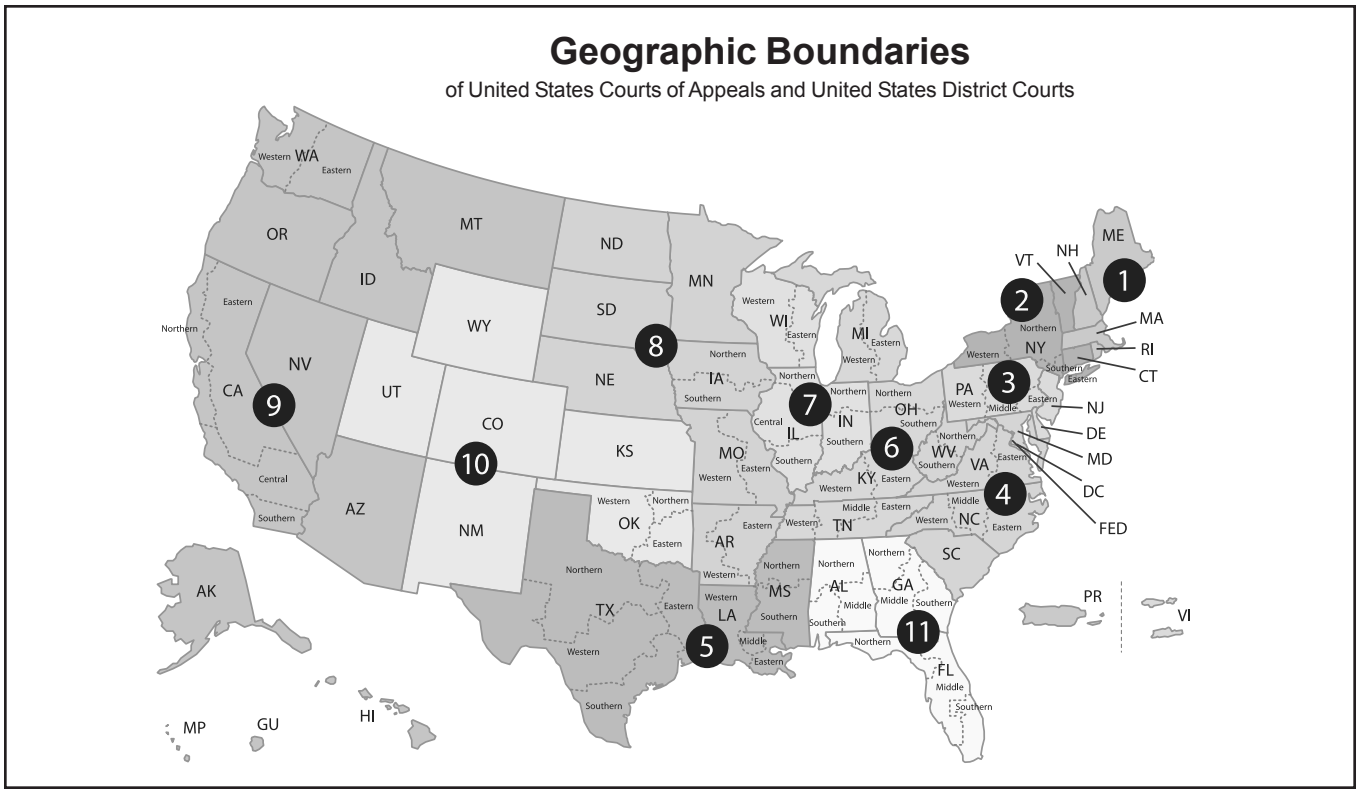

Figure 1. United States court districts.

whether the evidence against Dr. Hurwitz was sufficient as a matter of law.[8]

The Fourth Circuit's opinion in *Hurwitz* presents an opportunity for the pain management community to regain some ground and focus on the importance of accurate expert testimony. I believe the *Hurwitz* opinion may also help the pain management community direct the government's attention to other stakeholders, like healthcare plans,[9] who share responsibility for minimizing the potential for abuse and diversion of controlled substances while still ensuring that these medications remain available for people who have a legitimate medical need for them.

ELEMENTS OF A SECTION 841 OFFENSE

Federal law permits doctors who are "registered" by the Attorney General to write prescriptions for or to otherwise dispense controlled substances as long as they comply with the requirements of their registration.[10] The Code of Federal Regulations contains regulations addressing "the conditions under which registrants are authorized to dispense controlled substances." For example, 21 CFR § 1306.04(a) (2006) provides that a prescription for a controlled substance is effective only if it is **"issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice."** This regulation further provides that **"an order purporting to be a prescription issued *not* in the usual course of professional treatment or in legitimate and authorized research *is not a valid prescription* within the meaning and intent of [the Controlled Substances Act] and the person knowingly . . . issuing [such a purported prescription] shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances."[11]**

Against this background, then, the government can bring a federal criminal case against a physician for "drug trafficking" under Title 21, United States Code, Section 841(a)(1), which makes it unlawful for "any person knowingly or intentionally . . . to . . . distribute, or dispense, or possess with intent to . . . distribute, or dispense, a controlled substance."[12] To convict a physician of a drug trafficking crime under Section 841(a)(1), the government must prove each of the elements listed on the left side of Table 2 *beyond a reasonable doubt.*

Hurwitz argued that the trial court's failure to give an instruction on good faith deprived him of the ability to argue against the intent, or *mens rea,* element of a Section 841(a)(1) offense, which asserts that the defendant acted "knowingly and intentionally." Thus, the right side of Table 2 shows the application of the Section 841 elements to Hurwitz's arguments on appeal and demonstrates how important the good faith jury instruction is to negating (or potentially negating) the government's argument that

Table 1. Publications released by the DEA on September 6, 2006	
Item released	**Key concepts**
Updated DEA Practitioners Manual (*www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual090506.pdf*)	This is an update from the DEA's 1990 Practitioner's Manual. It contains a short summary of key registrant obligations under the Controlled Substances Act; good reference material.
Final Policy Statement on Dispensing Controlled Substances for the Treatment of Pain (*www.deadiversion.usdoj.gov/fed_regs/notices/2006/fr09062.htm*)	This is the DEA's final statement on two earlier items, the Interim Policy Statement (issued November 2004) and the Clarification Statement (issued August 2005). It is also a compromise for the published and retracted document known as *Prescription Pain Medications: Frequently Asked Questions and Answers*. This is a **MUST READ**.
Notice of Proposed Rule-Making on the Use of Multiple Schedule II Prescriptions (*www.deadiversion.usdoj.gov/fed_regs/rules/2006/fr0906.htm*)	Concerns the so-called "Do Not Fill" prescriptions. The DEA has decided that the use of multiple Schedule II prescriptions, under certain circumstances, is proper and may help a physician minimize the potential for abuse and diversion. This rule is *only* proposed and will become final after the public comment period and other legal notification periods take place.
Cases Against Doctors (*www.deadiversion.usdoj.gov/crim_admin_actions/index.html*)	The DEA has summarized both administrative and criminal actions against physicians over the past few years. This reference contains illustrative examples of cases where the DEA used its investigative authority to pursue a physician because of his/her prescribing activity.
Note from the author: All pain management professionals should obtain, print, and review these items and keep them in a "Pain Law Compliance" notebook. If you need help putting your notebook together for your specific state, call Jennifer Bolen at 865-755-2369, or e-mail her at *jbolen@painlawmentor.com*.	

Hurwitz acted knowingly or intentionally. The harm done by the trial court's failure to give the good faith instruction is obvious: if the jury should have been instructed to consider whether Hurwitz acted in good faith, then one or more of the jurors may have believed that he acted in good faith instead of knowingly or intentionally and thus may have voted differently on the Section 841 charges.[13] Since the trial court never gave the *Hurwitz* jury this opportunity, the Fourth Circuit held that such a failure constituted legal error which could only be cured by reversing the conviction and sending the case back for another trial.[14] The Fourth Circuit's decision means even more to the pain management community as a whole.

The Fourth Circuit made the following additional observations about the application of the good faith standard to drug trafficking charges against physicians:

> 1. "[A] doctor's good faith generally is relevant to a jury's determination of whether the doctor acted outside the bounds of medical practice or with a legitimate medical purpose when prescribing narcotics."[6]
>
> 2. Referring to *United States v. Moore*, 423 US 122 (1975), a doctor could not be convicted if he merely made "'an honest effort' to prescribe . . . in compliance with an accepted standard of medical practice."[16]
>
> 3. "When resolving the ultimate question in a Section 841 prosecution against a doctor—whether the doctor acted without a legitimate medical purpose or beyond the bounds of accepted medical practice—some latitude must be given to doctors trying to determine the current boundaries of acceptable medical practice."
>
> 4. Courts have consistently concluded that it is proper to instruct juries that a doctor should not be held criminally liable *if the doctor acted in good faith when treating his patients*, citing cases from the Second, Fifth, Sixth, and Ninth Circuits.[17]

SUBJECTIVE VERSUS OBJECTIVE GOOD FAITH STANDARDS

The Fourth Circuit held that the trial court erred by concluding that good faith is not relevant when a registered physician is charged with violating Section 841 and stated that an objective good faith standard applies in the prosecution of Section 841 drug trafficking cases against physicians. The Fourth Circuit carefully distinguished and rejected the use of a subjective good faith standard (as

Table 2. Elements of a Section 841 offense[15]	
	Application to Hurwitz's case
The defendant	Hurwitz
Knowingly and intentionally	This is where the jury instruction was key
Distributed or dispensed	Includes writing prescriptions
A controlled substance	Various proven at trial in various schedules
In a manner that demonstrates his actions were not for legitimate medical purposes in the usual course of professional practice[12] OR	This is where the expert witness and factual testimony are key to the retrial
In a manner that was beyond the bounds of medical practice[12]	This is where the expert witness and factual testimony are key to the retrial

requested by Hurwitz), stating that the phrase "professional practice" refers to "generally accepted medical practice," and "a practitioner is not free deliberately to disregard prevailing standards of treatment . . . ."[18] In this regard, the Fourth Circuit reasoned that "to permit a practitioner to substitute his or her views of what is good medical practice for standards generally recognized and accepted in the United States would be to weaken the enforcement of our drug laws in a critical area."[19]

APPLICABILITY OF THE GOOD FAITH ISSUE TO EXPERT TESTIMONY

Much of *Hurwitz* involved a "battle of the experts," and many medical professionals have commented on the substance of the expert testimony and the negative impact (intended or not) of the government medical expert's testimony on the pain management community as a whole.[20] Fortunately, the Fourth Circuit's opinion in *Hurwitz* softens the potential harm of that testimony and offers an opportunity for medical experts to correctly address these issues in the future, at the retrial and certainly in future cases where the government medical expert opts to take the same position or is available for cross-examination.

The Fourth Circuit's decision in *Hurwitz* opens the door for the pain management community and Hurwitz's trial team to go back and prepare to completely discredit the government medical expert's claim concerning the existence and nature of a daily ceiling dose of opioids and to revisit incredibly important medical issues such as treating pain in addicts (or those with a history of addiction or who exhibit aberrant drug-related behaviors) and the concepts of physical dependence and tolerance.

Table 3. Importance of the good faith instruction		
District court action at trial	**Hurwitz's objections**	**Appellate court's position**
The district court refused to issue Hurwitz's good faith instruction.	Hurwitz believed the court should have given the good faith instruction he drafted.	Hurwitz's instruction WAS NOT PROPERLY WORDED, and thus the district court rightfully rejected the instruction.
The district court refused to give any good faith instruction relating to the drug trafficking charges.	Hurwitz believed the court should have given some form of a good faith instruction relating to the drug trafficking charges.	The court agrees with Hurwitz and believes the district court confused the rejection of Hurwitz's improperly worded good faith instruction with its decision not to issue any good faith instruction to the jury related to the drug trafficking charges. This constituted reversible error because a reasonable juror could have found that Hurwitz's actions were in good faith. Thus, the appellate court decided to vacate (or take away) Hurwitz's conviction and remand (send back) the case to the district court for a new trial.

Those who contributed to the "friends of the court" briefs in the *Hurwitz* case are largely responsible for focusing the Fourth Circuit on the good faith standard's importance to the pain management community as a whole. The Fourth Circuit has done its job, and now it is up to the leaders in the pain management community to consider its accepted standards of care and what they mean to prescribers and patients alike, so that good faith remains a strong shield against any government attempt (through its agents or hired experts) to dictate how much of what drug it thinks I or any other patient who lives with chronic pain should take or what our physicians can prescribe to us.

Jennifer Bolen, JD, The J. Bolen Group, LLC, Knoxville, Tennessee.

NOTES AND REFERENCES

1. Several groups or stakeholders filed *amicus curiae* ("friends of the court") briefs with the Fourth Circuit. The American Academy of Pain Medicine filed such a brief in an effort to set forth the interests of its members. I believe this brief, and others, had a large impact on the Fourth Circuit's decision in this case and certainly helped the appellate court understand the larger interests at stake. This is significant because of the nature of the expert witness testimony during the *Hurwitz* trial and its potential impact on the pain management community as a whole.
2. Federal appellate courts are referred to by circuit number. For example, the Fourth Circuit Court of Appeals covers multiple states, and the federal district courts within each of those states feed into the Fourth Circuit according to federal law and the rules of appellate procedure. By example, the State of Virginia has two federal districts—Eastern and Western—and a defendant's appeal of a jury trial conviction in either of those districts goes to the Fourth Circuit Court of Appeals. The basic order of the federal criminal court system is 1) district court (trial), 2) court of appeals (appeal), and 3) US Supreme Court (assuming there is a prerequisite for Supreme Court jurisdiction). If you want more information on the specifics of the federal court system, see www.uscourts.gov.
3. The government is not the only source of problem expert testimony in this area. There are many examples of civil cases against pharmaceutical companies and physicians brought by plaintiffs' attorneys whereby medical experts support lawsuits founded on "you got me addicted" or "you caused my daughter/son to overdose and die" allegations. Any party or expert putting forward allegations that lack the support of generally accepted standards of care jeopardizes the pain management community.
4. This may also be stated as expert testimony that fails to recognize the lack of literature on a specific issue when the issue has not been studied or has only recently been identified or that fails to recognize the many approaches to pain management and the varied state laws and regulations on the use of controlled substances to treat pain.
5. Released September 6, 2006, and available at *www.deadiversion.usdoj.gov* or through links set up on my Web site at *www.legalsideofpain.com*.
6. *Hurwitz*, 2006 US App. LEXIS 21425 (August 22, 2006).
7. When a sentence is *vacated*, it means that it is set aside. However, in this case this is a temporary situation, because the Fourth Circuit also sent the case back to the district court for a new trial with instructions that the trial judge follow the law regarding the use of the proper jury instructions. The government is very likely to retry this case, unless Hurwitz can convince the government that it will have big problems during the retrial with expert testimony, the concept of good faith, and the pain management community's current accepted standards of care on the use of high-dose opioid therapy. The government can use its old charges against Hurwitz in the second trial, or it can use a "superseding indictment" and proceed against Hurwitz in a slightly different manner. The government's decision will likely be based on how it views its expert testimony at this point, and given all the potential points of attack that this expert or one like him will face, the government's decision will be more difficult the second time around, especially now that it must operate under the law that it knew existed from the very beginning: the objective good faith standard.
8. The Fourth Circuit acknowledged that the more challenging issue is the government's claim that the trial evidence so "overwhelmingly demonstrated that Hurwitz was acting well beyond the bounds of accepted medical practice that the jury could not reasonably have found that he acted in good faith." In rejecting the government's claim, the Fourth Circuit said that "while the government's evidence [in *Hurwitz*] was powerful and strongly indicative of a doctor acting outside the bounds of accepted medical practice, we cannot say that no reasonable juror could have concluded that Hurwitz's conduct fell within an objectively-defined good-faith standard." Significantly, the Fourth Circuit pointed out that Hurwitz presented expert testimony showing that it was proper to use opioids when treating addicts who suffered from pain, that Hurwitz's high-dose opioid therapy was a medically appropriate way to treat *intractable pain*, and that the quantities of opioids he prescribed were appropriate. "Even as to the patients whose dosages appeared extraordinarily high, such as the patient who was prescribed over 500,000 pills during the course of his treatment, the record contains expert testimony showing that Hurwitz's treatment and the quantities of opioids prescribed was medically proper." The Fourth Circuit cited other evidence at trial supporting Hurwitz's position on the good faith jury instruction, including Hurwitz's testimony about his own practice, his use of medical history questionnaires, discussions with other physicians outside his practice about accepted procedures, and Hurwitz's reliance on information obtained at professional medical conferences.
The Fourth Circuit believed the trial court effectively deprived the *Hurwitz* jury of the opportunity to consider Hurwitz's defense. Although it recognized that the government's evidence against Hurwitz "was strong," the Fourth Circuit said it could not "conclude that the district court's error in removing the good faith from the jury's consideration was harmless." Thus, it concluded that good faith is relevant to Section 841 charges against a registered physician and that the trial court erred by incorrectly instructing the jury that Hurwitz's good faith was relevant only to the healthcare fraud charges. On remand, the Fourth Circuit specifically told the district court to include a good faith instruction using an objective standard (if requested by Hurwitz and if supported by the evidence presented at retrial).
9. Health plan providers may be one of the largest stakeholder groups and continue to make decisions that, in many ways, impede physicians' ability to both comply with the laws and regulations on controlled substance prescribing and care for patients according to generally accepted standards of care in the pain management community, especially regarding the long-term use of controlled substances to treat pain alone or in

special patient populations.
10. See 21 USC § 822(b).
11. 21 CFR 1306.04(a)(2006).
12. 21 USC 841(a)(1).
13. The same argument would apply to the Section 846 charge of conspiracy because the elements are essentially the same.
14. At trial, the district court did give a good faith instruction to the jury on the two healthcare fraud charges against Hurwitz and told the jury that "it could not convict Dr. Hurwitz if he 'acted in good faith in dispensing any of the prescriptions alleged to constitute the crime of healthcare fraud.'" However, the trial court also told the jury that "good faith applies only" to the healthcare fraud counts, and "not only declined to give a good-faith instruction with regard to the drug counts, but also informed the jury that it *could not* consider good faith when deciding whether to convict Hurwitz of drug trafficking under Section 841." The Fourth Circuit held that the trial court's actions further supported its decision to reverse the case because of legal error.
15. *United States v. Singh*, 54 F.3d 1182, 1187 (4th Cir. 1995); see also *Alerre*, 430 F.3d at 689-690; *United States v. Daniel*, 3 F.3d 775, 778 (4th Cir. 1993); *United States v. Tran Trong Cuong*, 18 F.3d 1132, 1141 (4th Cir. 1994). Note: according to the *Hurwitz* court, the issue of whether the defendant's actions were for legitimate medical purposes or were beyond the bounds of medical practice is not an essential element of a § 841 charge against a doctor (see *United States v. Steele*, 147 F.3d 1316, 1318 [11th Cir. 1998] [en banc]; *United States v. Polan*, 970 F.2d 1280, 1282 [3rd Cir. 1992]; *United States v. Seelig*, 622 F.2d 207, 211-212 [6th Cir. 1980]).
16. *Moore*, 423 US at 142 n.20.
17. Here are the cases cited by the Fourth Circuit in *Hurwitz: Alerre*, 430 F.3d at 692 (noting that "the jury was correctly instructed on the applicable legal principles," and that the jury was instructed that the defendant-doctors "could not be convicted if they had dispensed the controlled substances at issue 'in good faith'"); *United States v. Hughes*, 895 F.2d 1135, 1141-1142 (6th Cir. 1990) (citing *Moore's* standard that physicians can not be convicted if they "dispens[e] controlled substances in the course of professional practice" and explaining that "[b]ecause Dudley was a licensed physician, the jury could not find him guilty of distributing controlled substances, as long as he acted in 'good faith'"); *United States v. Vamos*, 797 F.2d 1146, 1151 (2nd Cir. 1986) ("[T]he doctor must act in the good faith belief that his distribution of the controlled substance is for a legitimate medical purpose and in accordance with the usual course of generally accepted medical practice"); *United States v. Hayes*, 794 F.2d 1348, 1351-1352 (9th Cir. 1986) (finding no error in the charge that required the jury to determine that the physician acted other than in good faith and defined good faith as "an honest effort to prescribe for a patient's condition in accordance with the standard of medical practice generally recognized and accepted in the country"); *United States v. Norris*, 780 F.2d 1207, 1209 n.2 (5th Cir. 1986) (finding proper the district court's instruction to the jury that "[a] controlled substance is prescribed by a physician in the usual course of a professional practice, and, therefore, lawfully, if the substance is prescribed by him in good faith, medically treating a patient in accordance with a standard of medical practice generally recognized and accepted in the United States"); *United States v. Carroll*, 518 F.2d 187, 189 (6th Cir. 1975) (reversing conviction because the trial court "did not advise [the jury] that physicians are exempt from the provisions of the drug abuse statute when they dispense or prescribe controlled substances in good faith to patients in the regular course of professional practice").
18. *Hurwitz*, 2006 US App. LEXIS 21425 (August 22, 2006), quoting *Vamos*, 797 F.2d at 1151, 1153; see also *United States v. Williams*, 445 F.3d 1302, 1309 (11th Cir. 2006) ("Williams's proposed instruction fails to introduce any objective standard by which a physician's prescribing behavior can be judged. Under Williams's proposed instruction, if it is a physician's subjective belief that he is meeting a patient's medical needs by prescribing that patient a controlled substance, then that physician cannot be convicted of violating the Controlled Substances Act even if he acts outside all accepted standards of medical practice. Thus, the proposed instruction is contrary to *Moore*."); *Norris*, 780 F.2d at 1209 (rejecting defendant's claim "that a standard medical practice may be based on an entirely subjective standard" because "[o]ne person's treatment methods do not alone constitute a medical practice"); 3 Leonard B. Sand et al., *Modern Federal Jury Instructions*, Instruction 56-19, comment (2003) ("Every court to examine the issue has held that the objective standard that the doctor acted in accordance with what he *reasonably* believed to be proper medical practice should apply.").
19. See references in the note above. This argument can easily be applied to government experts who substitute their own views of what is good medical practice for standards generally recognized and accepted in the United States, which would weaken pain management; see note 20 below and related text.
20. Specifically, the government hired Michael Ashburn, MD, as its medical expert. Ashburn testified that it was his expert opinion that the daily ceiling dose of opioids is 195 mg morphine equivalent and that physicians are limited by law to prescribing a 30-day supply of any Schedule II controlled substance. Medical experts testifying on Dr. Hurwitz's behalf and those who wrote the trial judge during the sentencing phase of Hurwitz's case took a strong stance against Ashburn's position, stating that it did not accurately reflect generally accepted standards of care among pain professionals. My purpose in pointing this out is not to "pick on" Dr. Ashburn but to illustrate the damage that can be done when one testifies without doing so according to generally accepted standards of care or the good faith standard discussed by the Fourth Circuit in the *Hurwitz* opinion. A careful reading of Dr. Ashburn's testimony before the jury reveals he sometimes used a subjective standard of care in pain management or even a specific rule of law applicable to physicians in Utah (where Dr. Ashburn practiced) but **not** in Virginia (where Dr. Hurwitz practiced), referring to the 30-day limit on a Schedule II controlled substance prescription. This is significant because testimony like this has the ability to mislead a jury into thinking that such a limit applies nationwide (whether a daily or monthly dosage limit). The DEA has recently stated that every patient's case is different, and state laws on this issue vary. Better yet, the DEA has acknowledged—and the *Hurwitz* prosecutors should have known—that the federal law does not have a monthly dosage quantity limit when it comes to Schedule II medications. Because of the Fourth Circuit's decision, the pain management community is in a better position to stand up to government medical experts who take positions contrary to generally accepted standards of care in their field and to set the record straight so that in future cases their prescribing rights are not jeopardized.

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Methadone for cancer-related neuropathic pain: A review of the literature

Rosemarie Mannino, MD
Patrick Coyne, MSN, APRN
Craig Swainey, MD
Lea Ann Hansen, PharmD
Laurie Lyckholm, MD

ABSTRACT

Neuropathic pain is commonly seen in cancer patients, either as a direct result of the malignancy or as a consequence of the treatment rendered. In recent years, methadone has been utilized in the treatment of neuropathic pain because of its additional mechanism of action as an NMDA-receptor antagonist. In this paper we discuss the etiology of neuropathic pain in cancer patients, unique properties of methadone, and prior studies on methadone in this patient population. While methadone has been established as a cheap and effective agent in treating cancer pain, specific studies are needed comparing methadone to other opioids in the management of cancer-related neuropathic pain.

Key words: neuropathic pain, NMDA receptors, methadone, morphine

INTRODUCTION

Pain and symptom management are an integral part of cancer management.[1,2] Neuropathic pain is commonly seen in cancer as a result of either the treatment or the cancer itself. Because of its mechanism of action, methadone is thought by many pain and palliative medicine specialists to be more effective than other opioids in the treatment of neuropathic pain. No specific agent has been identified as the preferred or clearly superior treatment of neuropathic pain, but morphine remains the gold standard for the treatment of cancer pain. A first-line agent should be identified in order to standardize care, and methadone may be a candidate for this distinction. In this article, the causes of neuropathic pain in cancer are reviewed, as well as the literature regarding the use of methadone for neuropathic pain in cancer patients.

NEUROPATHIC PAIN IN CANCER

Clinical presentation

Persons with cancer often experience several different types of pain simultaneously, making neuropathic pain difficult to distinguish from somatic and visceral pain. Various malignant processes—for example, vertebral invasion with nerve compression—may present as both somatic and neuropathic pain.

Neuropathic pain can be defined as pain related to abnormal somatosensory processing in either the peripheral or central nervous system.[3] It may come to exist independently of any initial injury or damage, resulting in a state of persistent pain,[4] and it can occur at any time during the person's life. In an international survey of 1,095 consecutive cancer patients with severe pain, 40 percent reported a neuropathic component.[5]

Descriptions of neuropathic pain include burning, electric shock, tingling, pricking, itching, cold, aching, numbness, tenderness, pulling, tugging, penetrating, punishing, miserable, and nagging, and the sensations can be associated with neurologic deficits.[6,7] Patients with neuropathic pain may complain of spontaneous and/or evoked pain. Spontaneous pain, due to sudden, unprovoked firing of axons or dorsal horn neurons, can present as paroxysmal lancinating pain, as constant burning pain, or as a cramping or aching sensation. Evoked pain, caused by damage or alterations to peripheral and central sensory neurons, can present as hyperalgesia (lowered threshold to painful stimuli), allodynia (pain from normally innocuous stimuli, such as light touch), and hyperpathia (increased pain from a normally painful stimulus).[4] It can be elusive and resistant to many types of analgesics, making it a challenge to treat.[8,9]

Causes

The etiology of neuropathic pain in cancer patients can be a direct result of the malignant disease (compression of a nerve or nerve plexus) or a consequence of treatments such as radiation, surgery, and/or chemotherapy.[10,11] Radiation-induced plexopathies are most often described as occurring in the brachial or lumbosacral plexus. They include three distinct clinical syndromes: reversible or transient plexopathy; classic delayed, progressive radiation injury with fibrosis; and acute ischemic plexopathy. Transient brachial plexopathy occurs during or within a few months of finishing radiation treatment; it results when an external beam's field has included the brachial plexus, and it usually resolves with time. Most often this occurs in women with early breast cancer who are receiving radiation after conservative surgical treatment. Symptoms include numbness in the thumb and first finger of the affected side and weakness in the shoulder and biceps muscles.[12]

The pathogenesis of radiation-induced plexopathy is unknown and symptoms may resolve spontaneously within weeks or months. Late delayed brachial plexopathy occurs months to years following axillary or supraclavicular radiation. Observation-based evidence suggests that damage stems primarily from vasculitis resulting in sclerotic occlusion of small supplying vessels, or demyelination and fibrosis within and surrounding nerves in the radiation field. Paresthesias, hypesthesias, weakness, and impaired reflexes may occur.[12]

Chronic post-thoracotomy pain syndrome occurs in 44 to 67 percent of patients after thoracotomy, most commonly from recurrent or persistent tumor in the distribution of the thoracotomy. It is defined as pain persisting along the thoracotomy scar longer than two months postoperatively. It usually involves moderate or severe pain in the distribution of one or more intercostal nerves, and the duration of pain appears to be longer in patients with malignancy. The most severe pain in the syndrome, occurring in approximately 3 percent of patients, appears to be due to intercostal neuralgia. The exact mechanism is unclear.[13]

Postmastectomy pain syndrome (PMPS) is a chronic pain condition that was first reported in the 1970s. It is typically neuropathic in nature and can occur following surgery on the breast. PMPS is described as a dull, burning, and aching sensation in the anterior chest, arm, and axilla, exacerbated by movement of the shoulder girdle. The etiology of PMPS is unclear, but theories have been postulated implicating dissection of the intercostobrachial nerve, intraoperative damage to axillary nerve pathways, and/or pain caused by neuroma.[14]

Phantom pain originates from a missing body part (such as a limb or breast) and may exacerbate already disabling conditions, especially in patients with cancer. Phantom limb pain is reported to occur in as many as 66 percent of patients within the first six months after amputation. In 5 to 10 percent of patients the pain is severe, persistent, and often resistant to conventional therapy with drugs.[15] Phantom breast pain after mastectomy, which appears to be related to preexisting preoperative pain, can occur in 15 to 30 percent of patients.[16] There is postulation that transmission of noxious afferent input to the spinal cord from a peripheral injury causes a central neural sensitization, amplifying subsequent input.[17,18]

Chemotherapy-induced peripheral neuropathy has been a significant dose-limiting toxicity, as detailed in a 1999 review by Windebank.[19] In general, there is a predisposition to neuropathy in patients with prior nerve damage from conditions such as diabetes, heavy alcohol use, or inherited neuropathy.[20] Classes of agents causing neuropathy include platinum-containing compounds (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), and the vinca alkaloids (vincristine and vinblastine).[16]

With cisplatin, DNA synthesis is impaired as a result of platinum binding to DNA, thereby producing inter- and intrastrand crosslinks.[21] The neurotoxicity of cisplatin and oxaliplatin manifests as pure sensory involvement, is related to cumulative dosing, and can progress for weeks despite discontinuation of the drug.[22] Cisplatin is postulated to cause neuronal apoptosis by an unknown mechanism. Oxaliplatin appears to interfere with neural excitability and axonal ion conductance, resulting in neurotoxicity.[21]

The taxanes and vinca alkaloids interfere with microtubule-based axonal transport, thereby causing axonal injury that leads mainly to sensory loss. Paresthesias of the hands and feet are frequently the initial manifestation of neuropathy from these compounds. Unfortunately, these paresthesias can interfere with activities of daily living such as buttoning one's shirt or using a car's gas and brake pedals. The neuropathies associated with these agents tend to resolve in the months following their discontinuation, though not in all cases. Chemotherapy-induced central neurotoxicity may also be caused by methotrexate, cytarabine, and ifosfamide. Acute aseptic meningitis and delayed neurotoxicity including cognitive impairment, aphasia, progressive dementia, and hemiparesis have been described. Risk factors include higher doses of the agents, frequent administration, and radiation preceding methotrexate dosing.[21]

MANAGING NEUROPATHIC PAIN

Opioids

Opioids are considered a cornerstone in the management of neuropathic pain.[22] Two studies by Watson and colleagues[23,24] addressed this issue in randomized, double-blinded trials using controlled-release oxycodone.

One trial enlisted patients with postherpetic neuralgia, and the subsequent trial involved patients with painful diabetic neuropathy. Both trials concluded that controlled-release oxycodone is effective in treating neuropathic pain and improving quality of life. The latter study produced a 67.5 percent decrease in VAS pain scores from baseline to the last week of treatment, as compared to 28 percent in the active placebo group treated with benztropine.

Similarly, a multicenter, double-blind, randomized control trial of 159 patients using controlled-release oxycodone in patients with diabetic neuropathy also concluded that the opioid was effective. Of note, 44 of the patients withdrew from the study: 11 for inadequate pain control in the placebo group; one for the same reason in the oxycodone group; and 11 due to adverse events (nausea, constipation, dizziness, headache), seven of whom were in the oxycodone group. Seventeen patients were excluded due to protocol violations.[25]

Nonopioid agents

Nonopioid agents are often used to manage neuropathic pain in a palliative care context, either alone or in conjunction with opioids, and they exert their effects through a variety of mechanisms. Antidepressants frequently prescribed include tricyclic antidepressants (nortriptyline, amitriptyline), selective serotonin reuptake inhibitors (paroxetine, fluoxetine), and selective serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine). They are postulated to provide pain relief by preventing the reuptake of biogenic amines, such as norepinephrine and serotonin, and by affecting agonist activity on α-2 adrenoceptors.[9] Analgesic effect is thought to be related to enhancement of descending inhibitory pathways in the central nervous system.[4] Recently, a Cochrane review of 50 randomized trials concluded that tricyclic antidepressants are effective in treating neuropathic pain, but there is limited evidence to demonstrate the effectiveness of the selective serotonin reuptake inhibitors.[26]

Anticonvulsants such as gabapentin, pregabalin, lamotrigine, levetiracetam, and oxacarbazepine are thought to produce analgesia through modulation of central sensitization by inhibiting calcium flux through N-type channels.[4] Ketamine, a dissociative anesthetic, and dextromethorphan, a cough suppressant, modulate central sensitization by effects on N-methyl-D-aspartate (NMDA) receptors.[9]

Lidocaine, a local anesthetic, can modulate peripheral sensitization by reversibly blocking and inactivating sodium channels[4] and may be used topically or parenterally.[27] Capsaicin modulates peripheral sensitization by depleting Substance P, in effect destroying a subset of small primary afferent fibers.[4,28]

Table 1. Proposed methadone-to-morphine conversion ratios

Model	Conversion ratio of morphine to methadone
Edmonton[38,40]	10:1 to 11:1
Ripamonti[41]	4:1 if morphine 30 to 90 mg/d 6:1 if morphine 90 to 300 mg/d 8:1 if morphine > 300 mg/d
Soares[32]	5:1 if morphine < 100 mg/d 10:1 if morphine 100 to 300 mg/d 12:1 if morphine > 300 mg/d
United Kingdom model[37]	10:1 if morphine < 300 mg/d If morphine > 300 mg/d then 30 mg methadone

Many of these nonopioid agents have considerable side effects; antidepressants can cause anticholinergic side effects, and anticonvulsants can cause somnolence, dizziness, and blood and electrolyte abnormalities. Despite their side-effect profiles, these agents are considered to be first-line adjuvant analgesics for cancer-related neuropathic pain.[3]

METHADONE

Properties

Overactivation of NMDA receptors, a subtype of glutaminergic receptor, appears to be a common denominator in neuropathic pain.[29,30] In addition to arbitrating typical inflammatory and ischemic pain through its affinity for δ and μ receptors in the central nervous system,[31] methadone also noncompetitively inhibits the NMDA receptor, hence, purportedly, its effectiveness in ameliorating neuropathic pain.[32,33]

While the NMDA-receptor-antagonist property of methadone makes it appealing as an agent in treating neuropathic pain, issues such as equianalgesic dosing are difficult to standardize and are a subject of debate in the literature. Recommendations have varied in regard to the morphine-to-methadone ratio's conversion from 4:1 to 14:1.[30,32,34-41] (See Table 1 for an example of some conversion ratios.) Some of the uncertainty can be explained by wide interpatient variability and bioavailability. The role of the NMDA receptor is also a factor in the changing ratio as the methadone dosage increases.[42] Although authors differ on the exact equianalgesic dose, most agree that dosing varies according to dose range.[34,39,43] Our experience with the Ripamonti protocol has been favorable.

Methadone has characteristics similar to those of other opioids, including side effects of nausea, constipation,

Table 2. Substantiated pharmacokinetic interactions between methadone and other commonly used agents[42,45]

Drug	Effect on methadone	Effect of methadone on drug	Onset of effect	Mechanism interaction
Didanosine	none	↓ plasma conc 60 percent	rapid	↓ bioavailability
Efavirenz	↓ plasma conc	none	delayed	3A4 inhibition
Fluconazole	↑ plasma conc 35 percent	none	unknown	3A4 inhibition
Fluvoxamine	↑ plasma conc	none	delayed	3A4 inhibition
Nelfinavir	↓ plasma conc 50 percent	none	delayed	3A4 inhibition
Nevirapine	↓ plasma conc 50 percent	none	delayed	3A4 inhibition
Phenytoin	↓ plasma conc 50 percent	none	delayed	3A4 inhibition
Rifampin	↓ plasma conc 33 to 55 percent	none	delayed	3A4 inhibition
Risperidone	↓ plasma conc	none	rapid	unknown
Ritonavir	↓ plasma conc 36 percent	none	delayed	3A4 inhibition
St. John's Wort	↓ plasma conc 50 percent	none	delayed	3A4 inhibition
Voriconazole	↑ plasma conc 35 percent	none	unknown	3A4 inhibition
Zidovudine	none	↑ plasma conc 40 to 100 percent	delayed	unknown

headache, somnolence, euphoria, and respiratory depression.[44] One property unique to methadone among the opioids is its variable half-life, estimated to be between 8.5 and 47 hours, which may result in respiratory depression if the drug is titrated up too rapidly.[42] It may take three to 10 days to reach a steady state.

Major drug interactions are mostly secondary to the induction of CYP3A4-mediated methadone metabolism, and possibly protein-binding displacement. Problems with these drugs mainly occur when one of them is introduced while methadone is already at a stable dose. Communication between providers is essential. The CYP206 pathway is another that may be influenced by genetic differences.[42,44] Table 2 lists important drug interactions.

Another unique methadone property is its potential to cause QTc-interval prolongation, especially in high doses. This may be partially due to variation in its metabolism. There are several published reports of Torsades de Pointes occurring during methadone treatment.[30,45-47]

Some authors suggest that no dose of methadone may be considered completely safe and that routine electrocardiograms should be considered, both initially and at various points during treatment.[45,46] Although there is no consensus about EKG monitoring in the literature, it is prudent to be aware of the potential for QTc prolongation and to weigh risks and benefits and minimize other risk factors, such as electrolyte imbalance and drug interactions, that could increase circulating methadone levels.[30,45,46]

Table 3 summarizes pros and cons of methadone as compared to other opioids.

Is methadone effective in the treatment of neuropathic pain?

In a retrospective review of 50 consecutive patients with unrelieved nonmalignant neuropathic pain treated with oral methadone after being on various other agents (90 percent of whom were on chronic opioids), 26

Table 3. Pros and cons of methadone use[42,44,45]		
Feature	**Pro**	**Con**
Efficacy in cancer pain	Comparable to other opioids, with probable additional activity against neuropathic pain	
Neuropathic pain specific	Yes; NMDA receptor activity	
Onset of action	30 to 60 minutes[1]	
Elimination half-life	Long	Long and variable
Oral bioavailability	Excellent (can be variable)	
Active metabolites	Few, less potential for myoclonus	
Metabolism		3A4 causes interactions with other drugs[3]
Distribution	Lipophilic	
Excretion	Feces	
Routes of administration	Oral, IV, SQ, intraspinal, rectal	
Variety of formulations	Multiple: liquid, tablet, parenteral	
Titration		Slower than most other opioids; steady state at three to 10 days
Side effects compared to other opioids	Less potential for myoclonus	
Cardiac effects		Prolonged QT, reported cases of Torsades de Pointes[2]
Equianalgesic dose calculations		No consensus; varies with dose range
Social stigma		Used in heroin addiction treatment, could be negative
Cost	Inexpensive	

reported some relief with oral methadone after 13.9 months of follow-up. The mean maximal opioid dose prior to switching to methadone was 384 ± 64.6 mg/d (expressed as oral morphine equivalents). Twenty-four patients reported failure on the methadone, either due to intolerable side effects of nausea and vomiting (11), drowsiness (six), and constipation (two), or failure to respond to incremental dosing of the methadone (four).[5,48]

Another study that supports methadone's effectiveness in managing neuropathic pain is a double-blinded, randomized, controlled crossover trial for nonmalignant neuropathic pain involving 18 patients with a diverse range of chronic neuropathic pain syndromes. As compared with placebo, methadone resulted in statistically significant improvements in patient ratings of maximum pain intensity, average pain intensity, and pain relief. The analgesic effects extended over 48 hours. Interpatient analysis showed that the analgesic effects were not restricted to any particular type of neuropathic pain. Patient compliance was high throughout the trial. This was the first double-blind, randomized, controlled trial to demonstrate that methadone has an analgesic effect.[35]

Gagnon[49] reported a study of 18 cancer and noncancer patients with neuropathic pain who received relatively low doses (median stable dose of 15 mg/d) of methadone. Mechanical allodynia and paroxysmal pain were assessed clinically. Mean pretreatment pain scores of 7.7 ± 1.5 cm dropped significantly to 1.4 ± 1.7 cm on a stable dose of methadone ($p < 0.0001$). Nine of 13 patients (70 percent) experienced complete resolution of mechanical allodynia, and all eight patients with shooting pain reported a complete response.

Another report describing 13 patients on methadone for neuropathic pain refractory to other opioids suggested that methadone was effective. Nine of the patients reported that methadone relieved their pain by 43 percent on average, improved quality of life by 47 percent, and improved sleep by 30 percent, as compared to before initiation of methadone.[50] The same authors published a case report of a 50-year-old burn victim with chronic neuropathic pain refractory to morphine, amitriptylline, and gabapentin. The patient was started on oral methadone, leading to a reduction in his neuropathic pain score from an 8 to a 4.5 on average. After 10 months on methadone, his pain score remained stable. The conclusion of this case report and others was that controlled studies are needed to better define the benefit of methadone in neuropathic pain.[51]

Is methadone superior to other opioids for treating neuropathic pain?

No human studies have been reported comparing methadone to other opioids for neuropathic pain, but two preclinical animal studies examining this question have been reported. One study examined development of tolerance to chronically administered methadone and morphine in a rat model of neuropathic pain after ischemic nerve injury. In drug-naïve neuropathic rats, systemically administered morphine or methadone similarly and dose-dependently alleviated mechanical allodynia. Tolerance to the antihyperalgesic effect of equally effective doses of morphine or methadone developed; however, the rate of tolerance development was significantly slower for methadone in comparison to morphine. Chronic morphine treatment for 14 days induced almost complete loss of the antiallodynic effect of morphine, whereas methadone still had partial effect after 21 days of chronic treatment. Partial cross-tolerance was observed between morphine and methadone. It is suggested that the delayed development of tolerance to methadone in neuropathic rats may be related to the higher intrinsic activity of methadone compared to morphine, as well as the NMDA-receptor-blocking property of methadone. The latter may also contribute to preservation of μ-opioid antinociception following chronic methadone treatment.[52]

Morphine, methadone, and codeine were examined in rat models of peripheral and central neuropathic pain. In the spared nerve injury and chronic constriction injury models of peripheral neuropathic pain, both morphine and methadone attenuated mechanical allodynia, mechanical hyperalgesia, and cold allodynia, but codeine alleviated mechanical hypersensitivity only minimally, if at all. When administered to rats with spinal cord injury, morphine and methadone robustly attenuated mechanical and cold allodynia for at least two hours following injection ($p < 0.05$). Codeine also attenuated mechanical and cold allodynia in this model for at least three hours after injection. Interestingly, the therapeutic window (based on antiallodynia vs. ataxia) obtained for codeine was vastly superior to that obtained with morphine or methadone.[53]

Is methadone superior to other opioids in the treatment of cancer pain?

NMDA-receptor activation appears to have influence in neuropathic pain as well as inflammatory and ischemic pain. The use of an opioid such as methadone, which inhibits NMDA, may improve pain control by also attenuating development to tolerance. Another theoretical advantage the addition of NMDA antagonism may confer is incomplete cross-tolerance with the potential to control pain that is no longer responsive to μ-receptor-only agonists.[33]

The 2004 Cochrane review of methadone for cancer pain looked at eight randomized, controlled trials of methadone versus active placebo (using widely varying agents). Unfortunately, the active placebo drugs, starting doses, titration regimens, and pain scales were markedly dissimilar and thus difficult to compare. However, the reviewers concluded that overall, methadone was comparable to morphine in both analgesic-effect and side-effect profiles. The Cochrane reviewers also concluded that there was not enough trial evidence to support the proposal that methadone has a particular role in treating malignant neuropathic pain.[10]

In 2004, a randomized, double-blind study of 103 patients with cancer pain of various etiologies was conducted, in which the patients were randomly assigned to receive either oral methadone or morphine. The rates of patient-reported pain improvement and global benefit were nearly identical.[54] No further comparative studies have been performed since that time.

Is methadone superior to other opioids in treating cancer-related neuropathic pain?

Given that methadone is not only an opioid agonist but an inhibitor of the NMDA receptor, it has been postulated that methadone may be especially useful in palliating cancer-related neuropathic pain.[48] Several small studies point to the effectiveness of methadone in the treatment of both neuropathic pain and cancer pain. But is methadone a superior analgesic for *cancer-related* neuropathic pain? There are no reported studies to answer this question, but methadone is clearly becoming more popular as an important opioid in many clinical situations. Cleary,[36] in a bulletin of the American Academy of Hospice and Palliative Medicine, reflected on the growing use of methadone, especially in the pain and palliative care communities, as a "renaissance."

CONCLUSION

Methadone has many appealing qualities: it is inexpensive, highly lipophilic, and bioavailable, allowing for oral (in tablet and solution), rectal, intravenous, subcutaneous, epidural, and intrathecal routes of administration.[30,33,34] Unlike other long-acting opioid formulations, it can be divided. It is currently the only long-acting opioid in liquid form. It has no active metabolites, dramatically decreasing the potential for myoclonus.[33] Although variable pharmacokinetics and somewhat complex conversions present a challenge, it has shown tremendous promise for the treatment of cancer-related neuropathic pain.

Overcoming the stigma associated with methadone's use in heroin addiction presents a second challenge, and it is imperative that healthcare providers be educated about this potentially important and effective agent in the management of such a difficult, compelling, and significant clinical problem as cancer pain.

Further comparative studies are needed to establish the efficacy of this important analgesic. For example, a double-blinded, randomized, crossover trial comparing morphine to methadone could be performed in cancer patients with chemotherapy-induced neuropathic pain syndromes. Pain relief, side-effect profiles, necessity of breakthrough medications, and costs of the treatment arms could be examined.

Rosemarie Mannino, MD, Fellow, Division of Hematology/Oncology and Palliative Medicine, Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia.
Patrick Coyne, MSN, APRN, Clinical Director, Thomas Palliative Care Services, Massey Cancer Center, Virginia Commonwealth University Health Systems, Richmond, Virginia.
Craig Swainey, MD, Fellow, Division of Hematology/Oncology and Palliative Medicine, Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia.
Lea Ann Hansen, PharmD, Associate Professor, Virginia Commonwealth University School of Pharmacy, Richmond, Virginia.
Laurie Lyckholm, MD, Associate Professor, Hematology/Oncology and Palliative Medicine, Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, Virginia.

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CORRECTION

Two typographical errors appeared in "The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release sulfate capsules (AVINZA®) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin®) for the treatment of chronic, moderate to severe low back pain" (Rauck et al. 2006; 2(3): 155-156). Line 8 of paragraph 4 on p. 157 should read "scores consistently ≤ 4," not "scores consistently = 4." In Table 4 on p. 164, the incidence of nausea associated with O-ER in the AST population should be 54 percent, not 564 percent. The Journal apologizes for these errors.

ORIGINAL ARTICLE

Significant pain reduction in chronic pain patients after detoxification from high-dose opioids

Michael J. Baron, MD, MPH
Paul W. McDonald, PhD

ABSTRACT

Opioid tolerance is a well-established phenomenon that often occurs in patients taking opioids for the treatment of chronic pain. Typically, doctors need to periodically elevate patients' opioid doses in an attempt to manage their underlying pain conditions, resulting in escalating opioid levels with only moderate to negligible improvement in pain relief. Recently, opioid-induced hyperalgesia has been recognized as a potential form of central sensitization in which a patient's pain level increases in parallel with elevation of his or her opioid dose. Here, we report a retrospective study of patients undergoing detoxification from high-dose opioids prescribed to treat an underlying chronic pain condition which had not resolved in the year prior. All patients were converted to ibuprofen to manage pain, with a subgroup treated with buprenorphine during detoxification. Self-reports for pain scores were taken at first evaluation, follow-up visits, and termination. Twenty-one of 23 patients reported a significant decrease in pain after detoxification, suggesting that high-dose opioids may contribute to pain sensitization via opioid-induced hyperalgesia, decreasing patient pain threshold and potentially masking resolution of the preexisting pain condition.

Key words: opioid, tolerance, hyperalgesia, sensitization, detoxification, buprenorphine

INTRODUCTION

Opioid treatment is typically implemented in patients suffering from chronic pain who have not responded well to non-narcotic options, and it may also be used to supplement non-narcotic therapies. One concern with opioid treatment is the development of tolerance, which is often reported in patients maintained on opioids over a prolonged period. This results in the need for increased doses of opioids in order to achieve a level of pain alleviation comparable to that initially achieved.[1-4] As drug doses increase, opioid-induced side effects become problematic, as does the potential for physical dependence and opioid abuse.[5] Opioid use can also lead to hyperalgesia, or increased pain sensitivity, leading to the abnormal perception of pain (allodynia).[6] Recently, reports have been made on mechanisms that contribute to both tolerance and hyperalgesia.

Binding of endogenous opiates such as [D-Ala(2),N-MePhe(4),Gly-ol(5)]-enkephalin (DAMGO) to the μ opioid receptor activates G-protein-coupled signaling and receptor internalization. Signaling is terminated upon receptor phosphorylation and β-arrestin binding. Once β-arrestins bind, the receptor internalizes and β-arrestin is removed, allowing the receptor to be returned to the plasma membrane for another round of signaling.[7,8] Tolerance results from excessive stimulation of these pathways leading to receptor desensitization and an uncoupling from G protein signaling cascades.[9-14] Different agonists have been reported to have differential effects on this pathway. For example, morphine disrupts internalization of the receptor entirely.[8,15-17] Other clinically used opioids (oxycodone, fentanyl, and methadone) alter signaling by uncoupling the receptor from downstream effectors such as cyclic adenosine monophosphate.[18,19] Clinically, these molecular mechanisms contribute to the development of tolerance, requiring increased opioid concentrations to maintain signaling.[15,20] While tolerance is one unfortunate side effect of chronic opioid treatment, hyperalgesia is another and may contribute to pain elevation during prolonged opioid use.

Hyperalgesia is a result of biological adaptations that change pain threshold and increase perceived pain and which may contribute clinically to tolerance.[21,22] Hyperalgesia was initially demonstrated in rats when the μ receptor antagonist naloxone was administered after tolerance had been established. This administration led to a decrease in latency to tail flick compared to baseline, revealing an opioid-induced hyperalgesia that could be blocked using the NMDA antagonist MK801, implicating NMDA receptor activation in sensitization.[23]

Recently, a descending pathway from the rostral ventromedial medulla (RVM), an example of a "top-down" pain facilitation pathway, was discovered. Studies have revealed neuroplasticity in the RVM pathway as a result of prolonged opioid use, resulting in an increase in pain facilitation.[24,25] Lidocaine injections into the RVM reversed opioid-induced hyperalgesia, even after sensitivity had been established, revealing the importance of RVM signaling in maintenance of pain facilitation.[22] Mechanisms of opioid-induced tolerance and hyperalgesia are clearly systematic, involving not only cellular but also circuit-level adaptations and resulting in clinical manifestations of allodynia and opioid dependence. While hyperalgesia typically manifests itself as an abnormal increase in pain not usually associated with the preexisting condition, it is likely that the same mechanisms that cause hyperalgesia decrease pain thresholds globally, resulting in increased pain.

Once these mechanisms are in place, cessation of opioids or inhibition of receptor signaling results in withdrawal symptoms.[9] It is this withdrawal that signifies physical dependence upon the opioids and typically requires another opioid, such as buprenorphine, for treatment during rehabilitation.[26] It is possible that the same mechanisms that create these conditions might reset after opioid abstinence or rehabilitation, reducing overall pain. Here, we present a cohort of patients being rehabilitated from high-dose opioids who reported lower overall pain scores after detoxification, suggesting that central sensitization, hyperalgesia, and tolerance may contribute to long-term chronic pain, and that cessation of opioids may alleviate pain after rehabilitation.

MATERIALS AND METHODS

Patient cohort

Twenty-three patients were evaluated, and 16 were then admitted to the Psychiatric Hospital at Vanderbilt upon referral from their primary pain physician specifically for opioid detoxification. Admission to the hospital for detoxification was based on patient preference, coexisting disease, the proximity of the patient's house to the medical center, resources at home, and social support. This was a voluntary elective procedure and was done because the patient and/or the referring pain doctor felt that the patient was not getting any benefit from his or her current high dose of opioids. No patient presented here was referred for diversion, overuse, abuse, or addiction to opioid medications. The patients were on a variety of opioids, including extended-release (ER) oxycodone (n = 5), fentanyl (n = 6), hydrocodone (n = 2), methadone (n = 2), and morphine (n = 8), for a preexisting pain condition that had not resolved within the previous year. Due to the retrospective nature of this study, approval from the institutional review board was not required, but informed consent was given by all patients documented in this study. This cohort represents 23 sequential patients specifically treated for opioid detoxification following decreased analgesic efficacy between March 2004 and May 2006.

Procedures and measures

Upon evaluation and prior to detoxification, patients were asked to evaluate their existing pain using an 11-point pain scale (0 to 10) known as the Numerical Rating Scale (NRS). The value recorded was used as the predetoxification value. At the proper time the buprenorphine group received sublingual buprenorphine, with a loading dose of 4 mg every half hour for the first three doses followed by 4 mg TID. All patients were allowed to take ibuprofen 200 mg as needed (up to six doses per day) during detoxification to manage pain and withdrawal symptoms. Patients were weaned off of buprenorphine over a maximal period of 180 days (Table 1). All patients were then reevaluated for pain using the NRS. There was no mean difference in age between the ibuprofen-only and ibuprofen-buprenorphine groups (data not shown), nor was there a difference in age between sexes. There was, however, a significant difference between the number of men versus women in the study (16 men, seven women).

Statistical analysis

Data are presented as the mean ± SEM with 95 percent confidence interval. Comparisons were made using either a Student's t-test (paired, two-way) or a one-way ANOVA. All data were analyzed using Prism 4.0 for Mac (GraphPad Software Inc., San Diego).

RESULTS

Upon admission to the detoxification program, patients were asked to quantify their pain using an 11-point NRS ranging from 0 to 10. They were then reassessed after detoxification and reevaluated using the NRS. Individual pain reports were graphed and displayed a general decrease in individual pain reports for each patient (Figure 1). All but two patients (Patients 5 and 22, Table 1) showed a marked decrease in reported pain following opioid rehabilitation, with 21 of the 23 patients showing significant pain reduction using paired, two-tailed Student's t-test ($p < 0.001$). Regardless of detoxification regimen, when grouped all patients displayed an overall reduction in reported pain (8.0 predetoxification versus 3.3 post, Student's two-tailed, paired t-test, $p < 0.001$) after opioid detoxification (Figure 2).

To assess whether buprenorphine made a greater contribution to the reduction of patients' pain scores, patients

Table 1: Patient data									
Patient	**Age**	**Sex**	**Diagnosis**	**Pain meds (pre)**	**Pre-detox pain**	**Post-detox pain**	**Inpa-tient?**	**Bupre-norphine adjunct therapy?***	**Bupre-nor-phine taper**
1	48	F	Fibromyalgia	480 mg/d oxycodone (ER)	6	1	No	No	0
2	34	M	Degenerative disk disease	1200 mg/d oxycodone (ER)	10	6	No	No	0
3	38	M	Herniated cervical disk	160 mg/d morphine	8	3	Yes	No	0
4	46	M	Lumbar disk disease	400 mg/d morphine	8	3	Yes	No	0
5	45	M	Degenerative disk disease	125 μg/hr fentanyl	7	6	Yes	No	0
6	44	M	Burst lumbar vertebrae	720 mg/d oxycodone (ER)	10	3	Yes	Yes	60 days
7	66	M	Fibromyalgia	60 mg/d methadone	8	3	Yes	Yes	50 days
8	36	M	Degenerative disk disease	200 mg/d morphine	6	3	No	Yes	30 days
9	55	M	Degenerative disk disease	200 μg/hr fentanyl	8	4	Yes	Yes	180 days
10	62	F	Spinal stenosis	150 mg/d hydrocodone	10	4	No	Yes	45 days
11	35	F	Degenerative disk disease	120 mg/d morphine	10	4	Yes	Yes	14 days
12	50	M	Rotator cuff	320 mg/d oxycodone (ER)	9	2	No	Yes	90 days
13	56	M	Post-laminectomy syndrome	240 mg/d oxycodone (ER)	5	1	Yes	Yes	90 days
14	66	F	Vertebral fracture	45 mg/d hydrocodone	7	3	Yes	Yes	120 days
15	44	M	Degenerative disk disease	260 mg/d methadone	7	3	Yes	Yes	150 days
16	42	M	Ruptured disk	120 mg/d morphine	7	4	Yes	Yes	45 days
17	54	F	Degenerative disk disease	75 μg/hr fentanyl	8	4	Yes	No	0
18	56	F	Degenerative disk disease	400 μg/hr fentanyl	8	2	Yes	Yes	90 days
19	53	M	Degenerative disk disease	50 μg/hr fentanyl	8	4	No	Yes	30 days
20	69	M	Degenerative disk disease	400 mg/d morphine	8	4	Yes	Yes	120 days
21	61	M	Peripheral neuropathy	160 mg/d morphine	9	3	No	Yes	120 days
22	56	F	Failed Back Syndrome	100 μg/hr fentanyl and 150 mg/d meperidine	10	7	Yes	No	0
23	51	M	Neuropathy induced by chemotherapy	580 mg/d morphine	7	0	Yes	Yes	120 days

*IB group was allowed 200 mg PRN; Bup group was given buprenorphine 12 mg/d and ibuprofen 200 mg PRN.

were sorted according to their detoxification medication (ibuprofen alone [IB] and ibuprofen with buprenorphine [Bup]). Both groups reported a significant decrease in pain after rehabilitation (one-way ANOVA, $p < 0.001$), with the IB group reporting a 47.44 percent decrease in pain and the Bup group reporting a 62.99 percent decrease. This translated on average to a final pain report of 4.2 for the IB group and of 2.9 for the Bup group (Figure 3). There was no significant difference between the two groups' pain reports at time of admission (7.2 for IB versus 8.25 for Bup). Despite the apparent difference between the Bup and IB groups' final pain score reports, the final levels of pain relief achieved were not significantly different (one-way ANOVA).

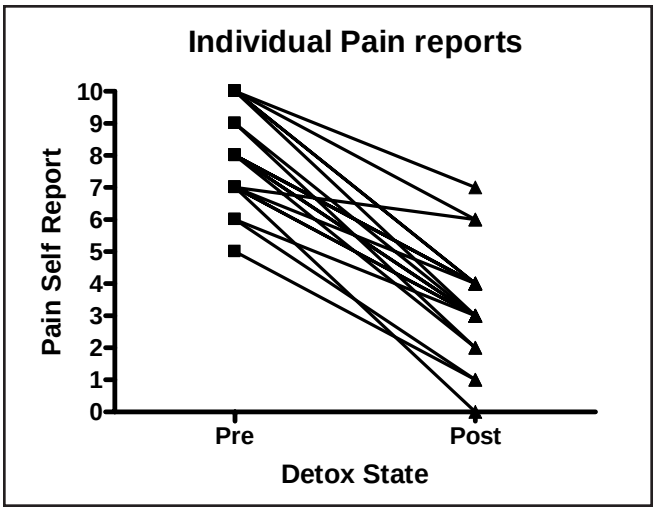

Figure 1: Changes in pain scores reported by individuals. NRS scores for all 23 patients represented in this study (patients having the same score are represented by a single symbol). Individual patients are charted using their pre- and post-detoxification NRS scores; lines connect individual scores to show overall pain-change trends. Only two patients reported insignificant pain relief after detoxification (changing from scores of 7 to 6 and 10 to 7, respectively).

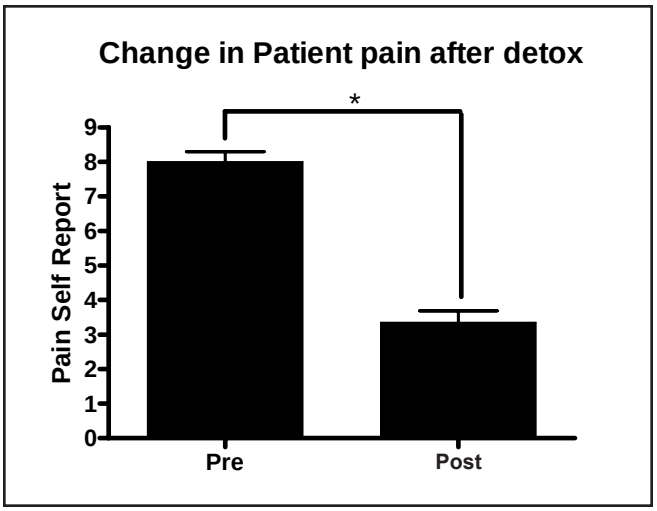

Figure 2. Patient pain reduction after opioid detoxification. *All patients were grouped and their pre- and post-pain reports were compared using the NRS. Patients' mean pain scores prerehabilitation were 8.00 ± 0.30 (N = 23) compared to a post-treatment report of 3.35 ± 0.33 (N = 23). Significance was calculated using a paired Student's two-tailed t-test ($p < 0.001$).

DISCUSSION

We have reported a retrospective study of patients taking high-dose opioids who experienced a significant decrease in their overall pain condition after opioid detoxification. All patients in this study were referred by their primary pain physicians for opioid detoxification. All patients had been receiving a substantial dose of opioids before referral and complained of significant chronic pain. Each patient reported a desire to stop opioid treatment, ruling out psychological dependence as a reason for referral. No patient was included in this retrospective cohort if he or she displayed addiction pathology such as overuse, multiple providers, running out of medications early, "dirty" urine drug screens, or a history of addiction. Physical dependence was noted in all patients in terms of withdrawal symptoms during detoxification, with some rebound pain reported in the Bup group that calls for further examination. Opioid detoxification was completed when the patient no longer displayed acute and/or chronic withdrawal symptoms or had been weaned off of buprenorphine, with all but two patients reporting a significant decrease in pain upon discharge.

We are not the first to report reduction in pain after discontinuation of opiates. Sjogren et al.[27] reported four individual cases of cancer patients who developed hyperalgesia while on morphine. In each of the four cases presented, hyperalgesia resolved after either morphine withdrawal or opioid substitution. While classical hyperalgesia was not examined or reported by any of the patients in our cohort, our data are consistent with reversal of pain upon opioid substitution or cessation.

Our current report directly contradicts an earlier report by Cowan et al.[28] in which patient pain reports were significantly elevated after opioid cessation. In the Cowan study, patients were initially sustained on a lower dose of opiates, with the majority using a 30 mg equivalent dose of morphine before cessation. In addition, none of the patients in the study displayed symptoms of tolerance or withdrawal upon cessation of treatment. Our sample represents a potentially different subset of patients, all of whom exhibited symptoms of both tolerance and physical dependence. This implies that patients who display tolerance to opioid treatment may be more susceptible to underlying pain facilitation pathways. A genetic difference has been noted in various strains of rats during laboratory testing. In a study performed by Hoffman et al.,[29] inbred rats were assayed for morphine-induced tolerance and hyperalgesia, and it was noted that the strain that initially displayed the least amount of antinociceptive effect displayed the highest rate of tolerance acquisition, indicating that tolerance may be linked to rapid requirements for dose increase. While all strains displayed withdrawal symptoms upon naloxone administration, the animals were not assayed for opioid-induced hyperalgesia.

In the current study, patients treated with the partial μ agonist buprenorphine reported both rebound pain and withdrawal symptoms during initial rehabilitation. This is consistent with reports of hyperalgesia revealed by naloxone treatment seen in the literature, and it reveals that these patients had developed physical tolerance to opioids.[23] While buprenorphine is not an

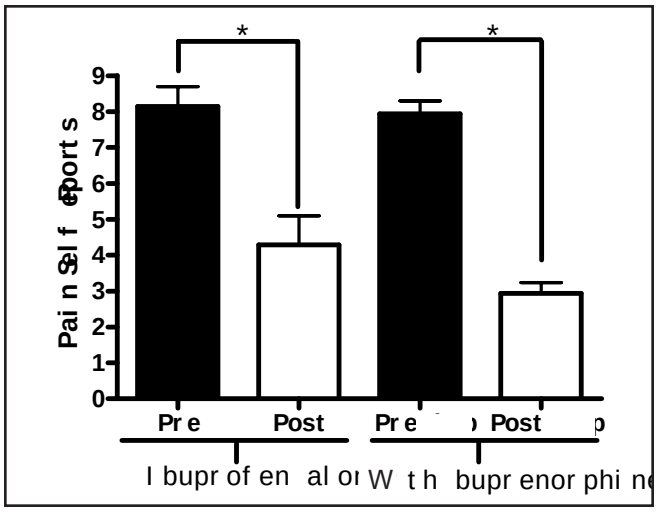

Figure 3: Effect of buprenorphine or ibuprofen during detoxification. *To examine whether buprenorphine or ibuprofen might be responsible for the amount of pain relief reported, patient data were binned according to detoxification regimen. Both the buprenorphine and ibuprofen groups showed significant reduction in pain reports after rehabilitation (two-way ANOVA, $p < 0.001$). The levels of predetoxification pain and pain relief reported between the two groups were not significantly different.

antagonist per se, the effect of a partial agonist is to reduce signaling (both basal and stimulated) to a submaximal level.[30] The use of buprenorphine in these patients would mean a severe blunting of the established opioid pathways, resulting in partial antagonism. The fact that buprenorphine treatment resulted in transient rebound pain in these patients leads us to believe that pain facilitation pathways were potentiated in this population.

To investigate the effect of buprenorphine coadministration during detoxification, we binned the patient data so that those detoxified using buprenorphine were compared to those detoxified on ibuprofen alone. Buprenorphine treatment for opioid therapy is used to decrease withdrawal effects seen with opioid cessation. Because buprenorphine acts as a partial agonist at the μ opioid receptor, we were interested to see if there would be a difference in reported pain in the group that used buprenorphine during rehabilitation. Interestingly, while there was a trend toward decreased final pain levels in the Bup group, this difference did not reach a significant level.

A similar phenomenon is reported elsewhere in the pain literature. Patients who take daily over-the-counter pain medications for headaches can become "dependent" and develop "rebound" headaches once the medication has been metabolized or excreted.[31] The typical treatment for analgesic-induced rebound headache is withdrawal of the offending medication. Our data are consistent with a similar mechanism of medication-induced pain facilitation, which may or may not involve similar molecular pathways or neurocircuitry.

This report represents an initial finding of pain reduction in a small cohort of patients following opioid rehabilitation and warrants further examination in a larger-scale study. This cohort may also represent an interesting subpopulation of patients who are more susceptible to both opioid tolerance and sensitization than other populations previously reported, as several other studies investigating long-term use of opioids for chronic pain have seen no significant tolerance or development of hyperalgesia in their subjects.[28,32]

There is little information in the literature regarding reversal of pain reports following long-term opioid rehabilitation in human subjects. Here, we propose that the mechanisms of both tolerance and sensitization may combine to increase underlying pain conditions, leading to an increase in subjective pain which can be alleviated by opioid detoxification.

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Michael J. Baron, MD, MPH, Psychiatry, Vanderbilt University, Nashville, Tennessee.
Paul W. McDonald, PhD, Neuroscience, Booz Allen Hamilton, McLean, Virginia.

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ORIGINAL ARTICLE

Prescription opioid abuse among drug-involved street-based sex workers

Hilary L. Surratt, PhD
James A. Inciardi, PhD
Steven P. Kurtz, PhD

ABSTRACT

National population surveys and individual studies over the past decade have documented the escalating abuse of a variety of prescription medications, particularly prescription opioids. Although surveillance data provide important information for estimating the prevalence of prescription opioid abuse in the general population, studies documenting the patterns of prescription drug abuse among chronic street-drug-using populations are extremely rare. This paper examines the abuse of prescription opioids among drug-involved street-based sex workers in Miami, Florida. The data for this study were drawn from an ongoing HIV intervention trial initiated in 2001, designed to test the relative effectiveness of two alternative HIV prevention protocols for this population. Participants in the study were recruited through traditional targeted sampling strategies, and complete data are available on 588 street-based sex workers. In terms of prescription drug abuse, 12.2 percent of the sample reported using at least one opioid analgesic in the past 90 days without having a legitimate prescription. Logistic regression analyses were conducted to examine the associations between prescription opioid abuse and its predictors. In the multivariate model, factors positively associated with prescription opioid abuse included: Caucasian race (OR = 2.53; 95 percent CI 1.30 to 4.91), current powder cocaine use (OR = 2.28; 95 percent CI 1.28 to 4.08), current heroin use (OR = 2.08; 95 percent CI 1.10 to 3.92), 90-day physical abuse/victimization (OR = 2.07; 95 percent CI 1.18 to 3.61), and shorter sex-work involvement (OR = 1.98; 95 percent CI 1.13 to 3.48). In contrast, daily crack smoking was negatively associated with prescription opioid abuse (OR = 0.61; 95 percent CI 0.33 to 1.10). This study provides some of the first empirical evidence to indicate that prescription opioid abuse is emerging in a heretofore unstudied community of marginalized drug-using sex workers. In addition, data on this population's mechanisms of access to prescription opioids clearly suggest that there is an active black market for these drugs. These findings warrant intensive study to determine the relative contribution of each mechanism of diversion to the illicit market.

Key words: opioids, substance abuse, diversion, sex workers

INTRODUCTION

National population surveys and individual studies over the past decade have documented the escalating abuse of a variety of prescription medications.[1-4] By the close of the 1990s, data gathered through the Drug Abuse Warning Network (DAWN), the National Institute on Drug Abuse's Community Epidemiology Work Group, the Monitoring the Future surveys, and the National Survey on Drug Use and Health (NSDUH) clearly indicated that rates of prescription drug abuse were rising, particularly with regard to prescription opioids. The 2004 NSDUH found that the numbers of new abusers of prescription pain relievers (primarily products containing codeine, hydrocodone, and oxycodone) increased from 600,000 in 1990 to over 2.4 million in 2004, marking it as the drug category with the largest number of new users in 2004.[5] In addition, reports from DAWN indicate that abuse-related emergency department visits involving opioid analgesics increased by 153 percent between 1995 and 2002,[4] and similar increases are reflected in drug abuse treatment admissions data.[6]

Adolescent and young adult populations appear particularly prone to abusing prescription opioids.[7,8] In fact, the 2004 NSDUH documented significant increases in the lifetime and past-month abuse of prescription pain relievers among persons ages 18 to 25, and among this cohort past-year abuse of opioid analgesics ranked second, after marijuana use, in overall prevalence. The increased popularity of particular types of prescription drugs among this group was also apparent. Specifically, between 2003 and 2004 statistically significant increases occurred in the

use of Vicodin, Lortab, Lorcet, and other hydrocodone products, as well as with OxyContin, Percodan, Percocet, Tylox, and other oxycodone products.[5]

Although these surveillance data provide important information for estimating the prevalence of prescription opioid abuse in the general population, much less is known regarding the scope of such abuse in hard-to-reach populations. Available surveillance data suggest that illicit drug use and prescription drug abuse are increasingly overlapping phenomena, yet studies documenting the patterns of prescription drug abuse among chronic street-drug-using populations are extremely rare. Nevertheless, two recent studies of methadone maintenance clients indicate widespread abuse of prescription opioids, benzodiazepines, and barbiturates among long-term drug users.[9,10] Similarly, a recent study of chronic drug users in Hartford, Connecticut, has documented the increasing incursion of prescription drugs into the street drug culture, finding that 21.5 percent of inner-city illicit drug users had abused opioid analgesics in the past month.[11]

Within this context, this paper examines the abuse of prescription opioids among drug-involved street-based sex workers in Miami, Florida. It has been well documented that sex trading is significantly associated with illicit drug use, and that many female sex workers are heavy users of cocaine, crack, or heroin.[12-20] In contrast, no studies of prescription drug abuse among sex workers are apparent in the literature. As a result, the prevalence and predictors of prescription opioid abuse in this highly marginalized population are unknown at present; yet this information is urgently needed in order to document the scope of prescription drug abuse in hard-to-reach communities. Increasing awareness of the extent to which patterns of opioid abuse in street-based populations mirror trends in the general population, or represent divergent trajectories of abuse, can inform the development of appropriate outreach, prevention, and treatment initiatives by research and practitioner audiences.

METHODS

The data for this study were drawn from an ongoing HIV intervention trial, initiated in 2001, designed to test the relative effectiveness of two alternative HIV prevention protocols for drug-involved street-based female sex workers in Miami, Florida. Testing for HIV and hepatitis A, B, and C is provided on a voluntary basis in both intervention conditions, and the full intervention protocols have been described elsewhere.[21]

Eligible participants are defined as women ages 18 to 50 who have a) traded sex for money or drugs at least three times in the past 30 days, and b) used heroin and/or cocaine three or more times a week in the past 30 days. Participants in the study are located for recruitment through traditional targeted sampling strategies, which are especially useful for studying hard-to-reach populations.[22] Targeted sampling is a purposeful, systematic method by which specified populations within geographical districts are identified and detailed plans are designed to recruit adequate numbers of cases within each of the target areas. Several elements are necessary for this approach, including the systematic mapping of the geographical areas in which the target population is clustered, the examination of official "indicator data" (such as police arrest reports), information from professional and indigenous key informants, and direct observations of various neighborhoods for signs of sexual solicitation. Similar strategies have been used successfully in recent years in studies of injection and other out-of-treatment drug users.[23-25]

A unique aspect of the project's sampling plan is the use of active sex workers as client recruiters. The effectiveness of indigenous client recruiters in drug abuse research has been well documented.[26-30] Because active sex workers carry out the recruitment of study participants, and because of their membership in the target population, they know of many locations on and off the primary "strolls" (places where sex workers solicit clients) where potential participants can be found. In addition, sex worker recruiters are more likely to have familiarity with drug user networks, drug "copping areas," and markets; they typically approach potential clients with culturally appropriate language, dress, and methods, and their "insider status" helps to build the trust and confidence necessary for successful outreach and recruitment.

Client recruiters make contact with potential participants in various street locations to explain the nature and procedures of the study. Those meeting project eligibility requirements are scheduled for appointments at the project intervention center, just north of downtown Miami, where they are screened and interviewed by project staff members. The interview process takes approximately 90 minutes to complete. Participation in all phases of the project is voluntary, and the project protocols for the protection of clients against research risks were reviewed and approved by the University of Delaware's Institutional Review Board.

Interviews were conducted using a standardized data collection instrument based primarily on the National Institute on Drug Abuse Risk Behavior Assessment[31-33] and the Georgia State University Prostitution Inventory.[34] The instrument captures demographic information, health status, abuse and victimization history, and treatment history, as well as lifetime and current measures of illicit drug use and sexual risk behaviors. Key questions regarding the abuse of selected prescription opioids in the past 90 days (OxyContin and other oxycodone products, morphine, fentanyl, hydrocodone, hydromorphone,

buprenorphine, and tramadol) were also developed and included in the interview schedule.

Complete data are available on 588 street sex workers, who are the focus of this analysis. Descriptive statistics were compiled on baseline demographic characteristics as well as on the drug use patterns and sexual behaviors of the participants. Bivariate and multivariate logistic regression analyses were then conducted to examine the associations between prescription opioid abuse and its potential predictors. The independent variables entered into the model included: age; race/ethnicity; homelessness; level of education; past-month injection drug use; past-month use of crack, heroin, and/or powder cocaine; 90-day victimization history; HIV status; history of sexually transmitted infections; length of sex-work involvement; number of sexual partners in the past 30 days; having an injection-drug-using sexual partner in the past month; and unprotected sexual activity in the past month. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) v. 13.0 for Windows.

RESULTS

The participants ranged from 18 to 50 years of age, with a mean of 36.2 years. In terms of race/ethnicity, the majority (65.5 percent) were African American, followed by equal proportions of Latinas (16.2 percent) and Caucasians (16.3 percent). More than half of the sample (55.5 percent) failed to complete high school, and nearly 40 percent reported being homeless at the time of interview.

The sex-work careers of the participants were lengthy, with nearly 80 percent involved in the sex trade for five or more years. The sample reported an average of 20.9 sexual partners in the past month, and 8.9 percent reported at least one current sexual partner who was an injection drug user. Unprotected sexual activity in the past month was common, reported by 55.1 percent of the participants. HIV prevalence among the sample was elevated, at 20.7 percent, and nearly half (49.9 percent) reported histories of other sexually transmitted infections.

The drug-use histories of the participants were also quite extensive. The participants were typically multiple-drug users, and reports of past-month activity indicated that alcohol and crack-cocaine were the substances most widely used (80.4 percent and 68.2 percent, respectively), followed by marijuana (62.7 percent), powder cocaine (50.0 percent), and heroin (16.3 percent). Although smoking and snorting were the most common routes of administration, nearly 11 percent had injected drugs in the month prior to the interview. In terms of prescription drug abuse, 12.2 percent of the sample reported using at least one opioid analgesic in the past 90 days without having a legitimate prescription. OxyContin and other oxycodone products were the most frequently abused opioids, having been mentioned by 5.3 percent and 8.0 percent of the sample, respectively. These female sex workers reported obtaining prescription opioids through a variety of mechanisms; 30.6 percent reported acquisition through street buys, 65.3 percent from friends, 12.1 percent from clients and other sex workers, 4.2 percent from "script doctors," 2.8 percent from relatives, and 1.4 percent from theft. None of the women reported accessing prescription opioids through prescription thefts, prescription forgery, doctor shopping, or the Internet.

Table 1 displays the results of bivariate and multivariate logistic models predicting sex workers' prescription opioid abuse in the past three months. In the bivariate models, the factors positively associated with prescription opioid abuse included younger age (OR = 1.78; 95 percent CI 1.05 to 3.01), Caucasian race (OR = 2.85; 95 percent CI 1.64 to 4.96), higher educational attainment (high school: OR = 1.91; 95 percent CI 1.07 to 3.39; more than high school: OR = 2.64; 95 percent CI 1.39 to 4.97), current powder cocaine use (OR = 1.91; 95 percent CI 1.15 to 3.19), current heroin use (OR = 2.85; 95 percent CI 1.64 to 4.96), current injection drug use (OR = 2.85; 95 percent CI 1.52 to 5.36), current injection-drug-using sexual partner (OR = 3.22; 95 percent CI 1.70 to 6.11), 90-day physical abuse/victimization (OR = 2.40; 95 percent CI 1.43 to 4.02), 90-day sexual abuse/victimization (OR = 2.09; 95 percent CI 1.19 to 3.69), and shorter sex-work involvement (OR = 2.36; 95 percent CI 1.38 to 4.02). Factors negatively associated with prescription opioid abuse included daily crack smoking (OR = 0.57; 95 percent CI 0.33 to 0.98). When all of the independent predictors were included in a multivariate model, several remained significant: Caucasian race (OR = 2.53; 95 percent CI 1.30 to 4.91), current powder cocaine use (OR = 2.28; 95 percent CI 1.28 to 4.08), current heroin use (OR = 2.08; 95 percent CI 1.10 to 3.92), 90-day physical abuse/victimization (OR = 2.07; 95 percent CI 1.18 to 3.61), and shorter sex-work involvement (OR = 1.98; 95 percent CI 1.13 to 3.48). Despite marginal significance, daily crack smoking was also retained in the final multivariate model (OR = 0.61; 95 percent CI 0.33 to 1.10).

DISCUSSION

Recent research has indicated that the abuse of prescription opioids is a widespread and growing problem in the general population,[2,35-37] and this study has documented that the phenomenon is also apparent in street-based populations of illicit drug users. This study provides some of the first empirical evidence to indicate that prescription opioid abuse has penetrated a street-based community of marginalized drug-using sex workers.

Table 1. Predictors of prescription opioid abuse in logistic regression models among 588 female sex workers in Miami, Florida

	Regression coefficient	Odds ratio	95 percent CI	Significance level
Bivariate predictors[a]				
Age[b]	0.574	1.775	(1.05, 3.01)	0.033
Race/ethnicity[c]	1.047	2.848	(1.64, 4.96)	0.000
Level of education[d]				
High school	0.645	1.907	(1.07, 3.39)	0.028
More than high school	0.969	2.635	(1.39, 4.97)	0.003
Daily crack use[e]	-0.559	0.572	(0.334, 0.979)	0.042
Current cocaine use[e]	0.648	1.912	(1.15, 3.19)	0.013
Current heroin use[e]	1.047	2.848	(1.64, 4.96)	0.000
Current injection drug use[e]	1.048	2.851	(1.52, 5.36)	0.001
Current IDU sexual partner[e]	1.171	3.224	(1.70, 6.11)	0.000
Length of sex work[f]	0.857	2.357	(1.38, 4.02)	0.002
Physical abuse/victimization[e]	0.875	2.399	(1.43, 4.02)	0.001
Sexual abuse/victimization[e]	0.738	2.091	(1.19, 3.69)	0.011
Multivariate predictors				
Race/ethnicity	0.926	2.525	(1.30, 4.91)	0.006
Daily crack use	-0.501	0.606	(0.334, 1.10)	0.100
Current cocaine use	0.826	2.284	(1.28, 4.08)	0.005
Current heroin use	0.731	2.077	(1.10, 3.92)	0.024
Length of sex work	0.684	1.981	(1.13, 3.48)	0.017
Physical abuse/victimization	0.725	2.065	(1.18, 3.61)	0.011

[a]Nonsignificant predictors included income, homelessness, current alcohol use, current marijuana use, number of current sexual partners, unprotected sexual activity, STI history, and HIV serostatus; [b]Under age 30 vs. 30 or older; reference category is "30+"; [c]White vs. all other; reference category is "other"; [d]Reference category is "less than high school"; [e]Reference category is "no"; [f]Less than five years vs. five or more years; reference category is "5+ years."

As Gilson and colleagues[2] have observed, it is essential to understand the reasons for this growing abuse, as well as the unique patterns of abuse in specific populations, in order to develop targeted and appropriate responses to this public health problem. In this regard, we identified significant statistical associations between a variety of demographic and behavioral factors and prescription opioid abuse. The present study documented an elevated prevalence of opioid abuse among White sex workers, finding them more than twice as likely as women of other races/ethnic backgrounds to report such abuse in the past three months. These data are supported by previous research documenting higher rates of prescription drug abuse among Whites in a variety of populations, including college students, substance abuse treatment clients, illicit drug users, and the general population.[3,11,38-40] Similarly, the data indicated that a shorter sex-work career (less than five years) is associated with a higher likelihood of prescription opioid abuse. This finding is most probably a function of the younger age of these sex workers, given that 54 percent of those with less than five years' history of prostitution were under age 30, compared to just 17 percent of those with histories of five or more years. Younger age groups have consistently reported higher rates of prescription drug abuse in a variety of studies.[3,5]

Several patterns of illicit drug use were also found to be associated with prescription opioid abuse in this sample. Specifically, current users of heroin and powder cocaine were more likely to abuse prescription opioids than nonusers, while daily crack-cocaine users were less likely to report such abuse. For the most part, these findings resonate with previous studies that have identified heroin and other illicit drug use to be risk factors for prescription opioid abuse.[3,39,40] In this regard, opioids have been posited to function as "substitutes" when heroin is unavailable or of poor quality. We suggest that crack users' lower levels of prescription opioid abuse may be related to the relatively high street price of opioid drugs,[41] particularly OxyContin, and crack users' economic deprivation relative to other drug users.[42,43]

A somewhat surprising finding was the association between physical victimization and the abuse of prescription opioids. Specifically, female sex workers who reported having been physically assaulted in the past 90 days were twice as likely as nonvictims to report abusing prescription opioids in the same time period. Because rates of victimization in drug-involved street-based sex worker populations are elevated, and access to legitimate medical care and other health services is fraught with barriers,[21,44,45] we speculate that the illicit use of prescription opioids documented here may represent attempts at self-medication by these marginalized women. This contention is supported by study data indicating that victimized women were no more likely than nonvictims to receive medical treatment from legitimate providers (e.g., physicians, emergency rooms). Given such, it appears likely that legitimate needs for prescription pain medication arose from incidents of assault, but their acquisition through licit channels was hampered by the population's general lack of medical insurance and routine care providers and by appearance factors that would make legitimate physicians reluctant to prescribe pain medications. In this regard, Grzybowski[46] suggests that inner-city street markets in which individuals obtain prescription medications through illicit sales are common.

An interesting finding in our survey data relates to how the prescription opioids being abused by this population were obtained. While the DEA has contended that "illegal acts by physicians and pharmacists are the primary sources of diverted pharmaceuticals available on the illicit market,"[47] only 4.2 percent of the women in this study indicated so-called "script doctors" as their source of prescription opioids. By contrast, 30.6 percent obtained opioid medications through street buys, 65.3 percent from friends, 12.1 percent from clients and other sex workers, 2.8 percent from relatives, and 1.4 percent from theft; of course, one can not rule out illegal prescriptions as the initial source for these obtained opioids. Since this is a primarily indigent population, with almost 40 percent reporting being homeless at the time of interview, it is not surprising that none reported the Internet as a source of prescription drugs. Moreover, none reported prescription thefts, forgery, or "doctor shopping" (visiting numerous physicians to obtain multiple prescriptions). Although a variety of studies among pain patients and the general population have suggested that "doctor shopping" is a major mechanism of prescription opioid diversion,[2,48,49] this does not appear to be the case among this marginalized population of street drug users. These data raise important questions about the nature and scope of prescription drug diversion. Given that almost one-third of the women in this sample purchased their prescription opioids through street buys, it is important to understand how these drugs are reaching the street, yet data on this topic are virtually unavailable. Furthermore, since nearly two-thirds of the women obtained the drugs from friends, one wonders what mechanisms of access to prescription opioids are available to their friends and associates. These data clearly suggest that there is an active black market in prescription opioids, as well as growing rates of abuse among street populations, warranting intensive study to determine the relative contribution of each mechanism of diversion to the illicit market.

Limitations

Although the data presented in this paper make a compelling case that the abuse and diversion of prescription opioids among street-based sex workers is an emerging problem, the findings should be interpreted within the context of

the study's limitations. First, the methods and procedures utilized to locate and recruit these hard-to-reach participants did not produce a random sample. Recruitment was localized, since drug-using sex workers are concentrated in certain neighborhoods and geographical districts in the Miami area. Because of this, a targeted sampling plan was constructed that would best reflect what was typical of the larger population of sex workers. Such strategies have been used successfully in previous studies of marginalized populations of injection and other out-of-treatment drug users.[23-25] Although not random, this targeted sampling plan produced a generally representative sample of drug-involved sex workers in Miami's inner-city neighborhoods. Nevertheless, this sampling methodology may have influenced the findings of the study.

Also, unique features of the Miami community may have impacted our findings on prescription opioid abuse. Although scientific research specifically designed to document the nature and extent of prescription drug abuse and diversion in South Florida has not yet been conducted, government reports suggest that the area is saturated with prescription drugs.[50,51] Consequently, the high level of illicit pharmaceutical activity in the Miami area may weaken our ability to generalize the findings reported here to other populations and other locales. Nevertheless, the female sex workers described in this paper are similar to chronically drug-involved women in other urban communities,[52-55] and the findings of this study represent a potentially significant first step in understanding the incursion of prescription opioids into marginalized communities.

The finding that prescription opioid abuse and diversion is emerging among street-based populations suggests a number of implications for the field. First, further study is warranted to examine precisely which prescription opioids are reaching the streets, through what mechanisms and in what quantities. Second, studies are needed to determine how and why these drugs are being abused by street-based populations (e.g., for their euphorigenic properties, for the self-treatment of pain, or for some additional reasons). Third, given that self-medication would appear to be the motivation for at least some part of the prescription opioid abuse that is occurring, issues related to healthcare access and the under-treatment of pain must be examined in relation to marginalized populations.

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Hilary L. Surratt, PhD, Center for Drug and Alcohol Studies, University of Delaware, Coral Gables, Florida.
James A. Inciardi, PhD, Center for Drug and Alcohol Studies, University of Delaware, Coral Gables, Florida.
Steven P. Kurtz, PhD, Center for Drug and Alcohol Studies, University of Delaware, Coral Gables, Florida.

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ORIGINAL ARTICLE

Interpleural bupivacaine and intravenous oxycodone for pain treatment after thoracotomy in children

Hannu Kokki, MD, PhD
Merja Laisalmi, MD
Kari Vanamo, MD, PhD

ABSTRACT

Introduction: *The results of studies exploring the efficacy of interpleural analgesia in children post-thoracotomy have frequently been inconclusive. In this pilot study, we have evaluated the efficacy and safety of interpleural bupivacaine and intravenous (IV) oxycodone in pain treatment after thoracotomy in 10 generally healthy children, aged 10 months to 12 years, with patent ductus arteriosus who underwent thoracotomy.*

Methods: *After surgery, all 10 children were given ibuprofen 10 mg/kg rectally every six hours. The first dose of interpleural bupivacaine (2 mg/kg) was given with epinephrine at the end of surgery, and thereafter plain bupivacaine (1 mg/kg) was given every two hours if the pain score was 4 or higher on an 11-point numeric rating scale (0 = no pain, 10 = worst possible pain). For rescue analgesia, children were provided oxycodone 0.1 mg/kg IV if pain was not relieved sufficiently with ibuprofen and bupivacaine. Vital signs, pain scores, and all adverse effects were monitored continuously for 24 hours.*

Results: *All 10 children needed both interpleural bupivacaine and IV oxycodone. The number of bupivacaine doses ranged between three and 10 (mean = 6.1, SD = 2.3), and the number of oxycodone doses ranged between one and 12 (mean = 6.0, SD = 3.6). No cases of low respiratory rate or low peripheral oxygen saturation or any serious adverse events were recorded.*

Conclusion: *Scheduled nonopioid analgesic (ibuprofen) with interpleural bupivacaine did not provide sufficient analgesia for post-thoracotomy pain in young children. IV oxycodone was found to be an effective and safe opioid supplement to the pain regimen.*

Key words: oxycodone, intravenous, bupivacaine, interpleural, ibuprofen, rectal, thoracotomy, pain, child

INTRODUCTION

Patients undergoing thoracotomy experience significant postoperative pain. Studies in adults indicate that severe early postoperative pain predicts long-term pain after thoracotomy.[1-3] This may also be the case in children, and therefore effective pain management is essential not only to avoid unnecessary suffering immediately after surgery but also in order to prevent chronic pain.

Several methods may be used to prevent and treat established pain after thoracotomy, but no ideal method has been developed.[3] Regional anesthesia techniques are commonly used for the treatment of severe postoperative pain. Reiestad and Stromskag[4] described the technique of interpleural analgesia in adults in 1986, and two years later McIlvaine and co-workers[5] used this technique in children undergoing thoracotomy. Reiestad and Stromskag[4] used bolus injections of bupivacaine-epinephrine, while McIlvaine and co-workers[5] used a continuous infusion. Their preliminary results with this technique were encouraging, but in some later trials the technique has not performed sufficiently well.[6]

Oxycodone is the most commonly used analgesic for the management of moderate and severe postoperative pain in adults in Finland,[7] and a potent pain-relieving effect has also been confirmed in children.[8] Oxycodone induces the same adverse effects that occur commonly with any opioid, but it does not release histamine, and it may cause less nausea, vomiting, and sedation and fewer excitatory central nervous system effects than morphine.[9,10] In our institution, we have used oxycodone for postoperative pain management in children for the last two decades, and our experiences have been promising.[11,12] However, we are unaware of any published data about how repeated doses of oxycodone perform in young children undergoing thoracic surgery.

In order to improve pain treatment and to gather necessary background information in the target population, we designed this clinical trial to evaluate the efficacy and safety of intravenous (IV) oxycodone in adjunct to scheduled ibuprofen, a traditional nonsteroidal anti-inflammatory analgesic (NSAID), and interpleural bupivacaine, a long-acting local anesthetic, in children undergoing thoracotomy. Post-thoracotomy pain consists of incisional pain and pleural pain originating from the indwelling chest tube.[3] Local anesthesia in combination with a topical anesthetic applied directly to the pleura is expected to reduce post-thoracotomy pain. NSAIDs may be sufficient to

treat incisional pain if pleural pain is not present. For these reasons, it was hypothesized that interpleural bupivacaine in conjunction with an NSAID would provide sufficient analgesia to obviate the need for opioids.

METHODS

This study was approved by our ethics committee, and it was conducted in accordance with the latest revision of the Declaration of Helsinki. All parents and any children thought to be able to understand it were given information about the pain treatment protocol, and parents provided consent. Ten generally healthy children, aged 10 months to 12 years, scheduled for thoracotomy due to persistent patent ductus arteriosus were enrolled in the study. All the children were included after it was shown that they had no contraindications for the use of NSAIDs, opioids, or amide-type local anesthetics in their medical and surgical histories or in a physical examination (e.g., allergy to the drugs used, asthma, renal or hepatic diseases, snoring or sleep apnea).

All patients were premedicated with oral flunitrazepam 0.03 mg/kg 60 minutes before induction. A standardized general anesthesia, with IV induction with thiopental 5 mg/kg, fentanyl 10 μg/kg, and atracurium 0.5 mg/kg and maintenance with isoflurane and nitrous oxide in oxygen, was used in all children. The ligation of ductus arteriosus was performed from a left thoracotomy. At the end of surgery, before chest closure, the surgeon inserted a 20-gauge epidural catheter into the posterior interpleural space along the paravertebral column. A thoracostomy tube was positioned more anteriorly and attached to a 5 to 10 cm H_2O suction tube.

After surgery, the children were transferred to the postanesthesia care unit for continuous follow-up of vital signs and pain. The children were administered oxygen until they were able to keep their hemoglobin oxygen saturation (SpO_2), as measured by pulse oximetry, at 94 percent or higher when breathing room air. During the 24-hour study period, the following parameters were recorded on a follow-up chart every hour: systolic and diastolic blood pressure, pulse rate, respiratory rate, SpO_2, body temperature, and worst pain on an 11-point Maunuksela pain scale (0 = no pain, 10 = worst possible pain). The Maunuksela pain score is a validated observer assessment tool based on facial expression, vocalization, movement or rigidity of the limbs and body, response to handling, irritability, and measured cardiorespiratory variables.[13] All adverse effects were recorded. Prospective assessments defined desaturation as an SpO_2 of 90 or less; low respiratory rate was defined as fewer than 12 breaths/min in children older than seven years and fewer than 15 breaths/min in children younger than seven. Vomiting was defined as either retching or the forceful expulsion of liquid gastric contents, and nausea as an unpleasant sensation in the stomach, usually accompanied by the urge to vomit. Pruritus and urinary retention were recorded as present or not.

For prevention of postoperative pain, the children were given rectal ibuprofen 10 mg/kg (Burana, Orion-Pharma, Espoo, Finland), and bupivacaine (5 mg/ml at a dose of 2 mg/kg) with epinephrine (5 μg/ml) (Marcain-Adrenaline, AstraZeneca, Södertälje, Sweden) was introduced into the interpleural catheter at the end of surgery. The ibuprofen dose was repeated every six hours. If the child was in pain (observed pain score of 4 or higher on a 0 to 10 scale), bupivacaine 2.5 mg/ml (Marcain, AstraZeneca, Södertälje, Sweden), at a dose of 1 mg/kg, was given through the interpleural catheter. The thoracostomy tube was clamped for 10 to 15 minutes after bupivacaine administration. Interpleural bupivacaine was allowed to be given every two hours. If the pain was not diminished by bupivacaine within 15 minutes, IV oxycodone hydrochloride 0.1 mg/kg (Oxanest, Leiras, Turku, Finland) was provided every 15 minutes for rescue analgesia until the pain had diminished to "slight" (pain score of 3 or less). All doses and administration times for bupivacaine and oxycodone were recorded on the patients' follow-up sheets.

All patients were observed for 24 hours in the postoperative care unit. Following this, the interpleural catheters were removed and the patients were treated in a pediatric surgical ward. On the ward, the patients were provided ibuprofen 10 mg/kg every six hours, and IV oxycodone 0.1 mg/kg was allowed if the pain score was 4 or higher.

The sample size of 10 children was considered sufficient for this pilot study, as the study's aim was to provide necessary background information to see whether pain treatment with interpleural bupivacaine and ibuprofen would provide sufficient analgesia in this patient population. Because no control group was enrolled, no statistical tests were used. The results are presented as number of cases, minimum and maximum, and mean, with standard deviations as appropriate.

RESULTS

Patient characteristics and main outcome data are summarized in Table 1.

All children needed rescue analgesic in addition to the baseline analgesics (rectal ibuprofen and interpleural bupivacaine). The number of rescue oxycodone doses ranged between one and 12 (mean = 6.0, SD = 3.6) doses. The multimodal pain treatment with ibuprofen, interpleural bupivacaine, and IV oxycodone was deemed to have performed sufficiently because the mean pain scores were low in all 10 children.

The time to first dose of oxycodone after surgery ranged between 50 minutes and 21 hours (mean = 7.1,

Table 1. Patients' characteristics and outcome data

Patient number	Gender	Age (months)	Weight (kg)	Height (cm)	Pain scores (0 to 10)*	Number of bupivacaine doses	Number of oxycodone doses	Lowest respiratory rate	Lowest SpO_2	Adverse reactions
1	Female	10	9	70	0 – 5 1.3 [1.7]	8	1	20	95	No
2	Male	13	8	76	0 – 4 0.7 [1.3]	7	12	14	94	Apnea (15 sec)
3	Female	38	13	95	0 – 5 1.2 [1.6]	8	5	19	91	Vomiting
4	Male	153	43	159	0 – 5 1.2 [1.6]	7	8	12	93	Nausea
5	Female	68	20	114	0 – 8 1.9 [2.2]	6	7	20	95	No
6	Male	41	12	89	Not available	3	3	24	92	No
7	Male	11	7	69	0 – 6 2.4 [2.2]	10	11	28	94	No
8	Female	13	11	78	0 – 4 0.4 [1.3]	3	4	24	97	No
9	Female	29	12	89	0 – 3 1.3 [1.3]	4	6	23	94	No
10	Female	27	12	92	0 – 4 1.2 [1.7]	5	3	24	96	Urinary retention
Mean (SD) min-max		40 (44) 10 – 153	15 (11) 7 – 43	93 (27) 69 – 159	1.3 (0.6) 0 – 8	6.1 (2.3) 3 – 10	6.0 (3.6) 1 – 12	20.8 (4.9) 12 – 28	94 (1.8) 91 – 97	

Bupivacaine was administered interpleurally at a dose of 1 mg/kg, and oxycodone hydrochloride IV at a dose of 0.1 mg/kg.
* Data are minimum-maximum and mean [SD] of 24-hourly recording.

SD = 6.2 hours). On most occasions (49 out of 60 administrations) a single 0.1 mg/kg dose of IV oxycodone provided sufficient pain relief for at least an hour. In nine children, the duration of the analgesic action of oxycodone doses ranged between 0.5 and 10 (mean = 2.7, SD = 2.1) hours. Patient 3 was an exception; she required three doses of oxycodone within 30 minutes at three hours after surgery, and two doses within 15 minutes at 17 hours, before her pain was diminished to "mild" (pain score < 3).

The pain treatment in this patient population was judged to be safe because no serious adverse events were recorded. Four nonserious adverse reactions were recorded. One child, a 13-month-old boy, developed brief apnea (duration of 15 seconds) two minutes after his tenth oxycodone injection (total dose of 1 mg/kg in 12 hours). His SpO_2 was 96 percent before and 94 percent immediately after the incident. His respiratory rate was 23 breaths/min before the incident, 14 breaths/min after the tenth oxycodone dose, and 15 to 20 breaths/min during the rest of the observation period. One three-year-old girl vomited twice, and one 12-year-old boy developed nausea. One two-year-old girl was catheterized due to urinary retention.

CONCLUSION

In the present study, interpleural analgesia with bupivacaine did not perform sufficiently after thoracotomy, as evidenced by the fact that all children needed IV oxycodone to achieve appropriate pain relief. Our data are consistent with the increasing evidence seen in studies of adult populations that interpleural analgesia may not be effective for post-thoracotomy pain. Scheinin et al.[14]

and Silomon et al.,[15] among others, found no opioid-sparing effect with repeated interpleural injections of bupivacaine in adults.

In some trials in children, interpleural bupivacaine has performed sufficiently, and children have not required supplementary opioids for pain relief.[5,16-18] However, many children in these studies also received sedatives to provide additional anxiolysis. In the Semsroth et al.[18] study, eight out of 11 children were administered midazolam, and in the McIlvaine et al.[16] investigation most children received diazepam and chloral hydrate. In young children, it is often difficult to separate pain from anxiety. After thoracotomy there is pleural pain from the therapeutic thoracostomy tube and incisional pain that is associated with breathing. Some of the children in previous studies who were treated with sedatives may actually have had pain and perhaps should have been provided analgesic rather than sedatives. Moreover, it should be noted that several children in the Semsroth et al.[18] study had SpO_2 values below 90 percent, with some of them even below 80 percent, although the children did not receive any postoperative opioids. Therefore, it can be assumed that during the postoperative period close monitoring of children is necessary not only when opioids are used but also after administration of sedatives and anxiolytics.

Extremely high infusion rates of interpleural bupivacaine have been required to achieve satisfactory analgesia after thoracotomy in children. In the McIlvaine et al.[5,16] and Semsroth et al.[18] studies, the mean rate of bupivacaine infusion was higher than 1 mg/kg/hr, and in some patients it went up to 2.5 mg/kg/hr. These doses may be considered unsafe because high plasma levels of bupivacaine are known to be toxic to the cardiovascular and central nervous systems.[19] McIlvaine et al.[5,16] measured high bupivacaine concentrations (> 2 μg/ml) in 75 percent of the patients, and the highest plasma concentration determined was 7 μg/ml, which is well above the potential central nervous toxicity level of 2 to 4 μg/ml.[20] Although none of the children was reported to develop central nervous system toxicity, it should be noted that the hypnotic-sedative drugs given to most of the children increase the threshold for convulsions. Moreover, the symptoms of anxiety and early signs of local anesthetic toxicity may be difficult to separate. Therefore, the infusion rates of bupivacaine used in these trials[5,16-18] may not be considered safe. Although the presence of chest tubes may remove large quantities of local anesthetic from the pleural cavity, as previously recommended with infusion in other sites,[19] we advise not exceeding a bupivacaine infusion rate of 0.4 mg/kg/hr in any continuous infusion.

In the present trial, pain treatment with oxycodone performed well, and no serious adverse reactions were recorded. The mean duration of the analgesic action of oxycodone was 2.7 hours, which corresponds well to the drug's elimination half-life of two to three hours in children.[9,21] The duration of analgesic action is also similar to that reported by Olkkola et al.,[8] who worked with children who had undergone strabismus surgery. In children undergoing tonsillectomies, oxycodone needed during the first 24 hours after surgery averaged 5.1 doses,[22] and after open appendectomy children needed 5.2 doses,[23] compared to the six doses called for in the present trial. However, it should be noted that in the two studies mentioned above a dose of 0.05 mg/kg of IV oxycodone was used, compared to 0.1 mg/kg in the present study. Moreover, the interindividual variation in pain and need for analgesics is large, and therefore in acute pain treatment the opioid dose should be individually titrated against the pain to achieve the optimal clinical response.

In the present trial, oxycodone did not cause significant respiratory depression. However, when any opioids are administered to children, the respiratory effects should be borne in mind. Olkkola et al.[8] administered oxycodone 0.1 mg/kg IV in children after strabismus surgery and found a significant respiratory depressive effect in several patients. Their results may be explained by the fact that they gave oxycodone shortly after halothane anesthesia to sleeping children without known pain. It is known that low levels of halothane (0.1 to 0.2 minimum alveolar concentration) markedly depress the hypoxic respiratory response.[24] On the contrary, pain stimulates ventilation by an additive effect, and it does not alter the chemoreflex response depressed by opioids.[25]

In conclusion, pain after thoracotomy seems to be significant in children. Because severe acute pain is a significant factor predicting continuing pain after surgery[1,3] and negative behavioral changes after discharge,[26] it is obvious that pain treatment after thoracotomy needs to be effective. The performance of new analgesic techniques should be evaluated before they are adopted into clinical use. In the present trial, interpleural bupivacaine did not perform sufficiently. However, IV oxycodone performed well, and no serious adverse reactions were observed in this small patient population.

Hannu Kokki, MD, PhD, Department of Anaesthesiology and Intensive Care, Kuopio University Hospital; Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, Finland.
Merja Laisalmi, MD, Department of Anaesthesiology and Intensive Care, Kuopio University Hospital, Kuopio, Finland.
Kari Vanamo, MD, PhD, Department of Paediatric Surgery, Kuopio University Hospital, Kuopio, Finland.

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Ultra-low-dose opioid antagonists to enhance opioid analgesia

Paul Sloan, MD
Scott Hamann, PhD, MD

ABSTRACT

This article will review decades of science contributing to current interest in opioid excitatory pharmacology. A long history of clinical confusion provided the stimulus for recent, detailed in vivo and in vitro investigations of the neuropharmacologic mechanisms involved in analgesic and hyperalgesic actions of opioid agonists and antagonists. Following the discovery of central nervous system opioid excitatory-hyperalgesic processes in animals, detailed neuronal cell culture experiments established opioid receptor/G protein/adenylate cyclase neurobiochemical mechanisms for bimodal inhibitory versus excitatory actions of opioids. Once this novel model was available to explain the cellular mechanisms responsible for the duality of opioid actions, clinical translation of this technology began to emerge, with a primary focus on selective antagonism of opioid excitatory actions with concomitant low-dose opioid antagonists. Encouraging results from recent animal and clinical studies will be discussed as further evidence that therapeutic pain management may be improved through enhancement of opioid agonist analgesia by cotreatment with ultra-low-dose opioid antagonists that selectively attenuate opioid-mediated hyperalgesia.

Key words: chronic pain, opioid agonists, opioid antagonists, adjuvant analgesics, cancer pain, hyperalgesia, analgesia

INTRODUCTION

Opioid therapy is recommended and effective for most patients with moderate or severe cancer pain[1,2] and has been used in recent years for analgesia in patients with chronic nonmalignant pain. While opioids are often effective in the long-term treatment of chronic cancer and nonmalignant pain, they are not without side effects or other limitations.[3] Tolerance to opioid analgesia may occasionally limit such medications' usefulness in patient care. Patients treated with opioids for chronic pain may exhibit a paradoxical increase in sensitivity to pain, recently described as opioid-induced hyperalgesia.[4] It is well recognized that there is tremendous variability in individual patients' analgesic response to a given opioid,[5] which may be due in part to individual differences in terms of the balance of analgesic versus hyperalgesic actions of opioids.

In order to improve opioid analgesia in patients with chronic moderate to severe pain, clinicians use several strategies: 1) combining therapy with other analgesics such as nonsteroidal anti-inflammatories or NMDA receptor antagonists; 2) adding adjuvant analgesic agents such as tricyclic antidepressants, anticonvulsants, oral local anesthetics, or muscle relaxants; 3) rotating to a different opioid; 4) changing the route of opioid administration (for example, from oral to intravenous or spinal); 5) using surgical or anesthetic interventional techniques; or 6) adding nonpharmacological pain therapies such as physical therapy, massage therapy, biofeedback, and acupuncture.[3] All of the above strategies have their limitations, side effects, and contraindications[6-9]; thus, future pain management practice requires development and testing of novel pharmacological approaches to achieve optimal pain relief with minimal side effects for every patient. Selective antagonism of opioid excitatory-hyperalgesic actions with ultra-low-dose opioid antagonists may represent one such novel therapeutic approach and could enable clinical enhancement of opioid agonist analgesic efficacy.[10] Opioids are known to activate stereospecific opioid receptors on cell membranes in the central nervous system (CNS).[11] The exact mechanisms of action are not fully understood, but they are known to involve G protein–adenylate cyclase second-messenger systems. How opioid antagonists could possibly enhance the efficacy of opioid agonist analgesia is the subject of this review article.

The first description of the paradoxical analgesic effect of opioid antagonists dates back 60 years. This review begins with discussion of early human and animal observations and how they provided historical evidence for opioid excitatory actions that inspired the systematic and detailed in vivo and in vitro studies of the last two decades. Literature related to the discovery of opioid excitatory processes will be reviewed as a prelude to the presentation of evidence for our current understanding of the novel neuropharmacologic mechanisms of low-dose opioid antagonists responsible

Table 1. Analgesic potency of nalorphine compared with morphine for postoperative pain*		
Number of patients	**Drug and dose/70 kg**	**Percent pain relief**
19	Nalorphine 5 mg	28 percent
35	Nalorphine 10 mg	64 percent
35	Morphine 10 mg	74 percent
*Lasagna and Beecher; 1954. Published with permission of *ASPET*.		

for enhancement of opioid agonist analgesia. Finally, we will summarize the latest clinical evidence supporting use of low-dose opioid antagonists for the treatment of perioperative and chronic pain.

HISTORICAL EVIDENCE

Opioids have been used as analgesics for several millennia, their effects recognized long before opioid receptors were discovered in animals and humans in the early 1970s. While the concept of opioid agonists and antagonists, as related to "multiple opioid receptors,"[12] was not developed until the 1970s, researchers in the 1950s were investigating medications that could antagonize all or part of the effects of morphine. Dr. Harris Isbell, Director of the Public Health Service Addiction Research Center (Lexington, KY), was perhaps the first to suggest, in 1950, that the opioid antagonist nalorphine had analgesic properties in humans and could raise the pain threshold.[13] In the early 1950s, Lasagna and Beecher,[14] working at Massachusetts General Hospital, strove to investigate and develop a combination of opioid analgesic and opioid antagonist that would offer the analgesia of morphine without the undesirable side effects. During their landmark studies, the authors "accidentally" discovered that the opioid antagonist nalorphine was itself an analgesic agent.[15] In an elegant double-blind study of postoperative pain, Lasagna and Beecher[14] noted that while low doses of nalorphine produced analgesia comparable to placebo, higher doses produced significant postoperative pain relief (Table 1). Keats and Telford[16] repeated the Lasagna-Beecher study using a placebo control and found the postoperative analgesic potency of nalorphine to compare with that of 10 mg of morphine.

Studies on the analgesic effects of opioid antagonists were limited over the next 25 years and often gave conflicting results. In 1965, Lasagna[15] reported that among patients with postoperative pain, naloxone had a "strange biphasic quality," exerting the greatest analgesic effect at low doses and becoming antianalgesic at higher doses. McClane and Martin[17] (1967), using a dog model to evaluate opioid analgesics, found that nalorphine produced a partial opioid analgesic response and that naloxone was inactive. The authors suggested that opioid antagonists may have some agonistic actions different from, and possibly initiated at a different site than, those of morphine. This mechanism of opioid antagonist analgesic versus hyperalgesic actions still remains under debate.

The 1975 discovery of opioid receptors and endogenous opiates in the human brain led to renewed interest in opioid and opioid antagonist pharmacology. Levine and colleagues[18] (1978) reported that naloxone given to patients with dental pain resulted in significantly greater increases in pain intensity than placebo controls. In retrospect, the naloxone dose used in their study was rather high, and the results support Lasagna's earlier finding of a biphasic response to naloxone for postoperative pain. Levine et al.[19] later published a second study using a dental pain model and also observed this biphasic response to naloxone. That is, naloxone at low doses (0.4 and 2 mg) produced analgesia, while higher doses (7.5 and 10 mg) of naloxone produced the more expected hyperalgesia (Table 2).

The 1970s ended with animal experiments that were inconclusive as to the analgesic action of opioid antagonists. Intracerebral naloxone microinjected into the third ventricle, the medulla, and the periaqueductal gray of the midbrain of rats did not produce a consistent analgesic response.[20] Holaday and Belenky[21] found that low-dose naloxone resulted in analgesia in a rat experimental pain model, while higher naloxone doses produced hyperalgesia, consonant with the experiments of Levine et al.[19] The research of the most recent 25 years has benefited from improved cell culture and receptor pharmacology techniques, with much investigation of low-dose opioid antagonists as possible analgesic agents.

BASIC SCIENCE EVIDENCE

This discussion will first focus on the discovery of opioid excitatory processes and then summarize in vivo animal pain and pharmacology studies, which provided direction for subsequent in vitro electrophysiologic and biochemical investigations. Following that, more current preclinical research will be reviewed, with emphasis on understanding the mechanisms of the analgesia-enhancement effects of low-dose opioid antagonists and an eye toward clinical translations of these concepts that will improve chronic pain management. For the sake of this discussion, opioid antagonist enhancement of analgesia

Table 2. Analgesic dose response of naloxone on postoperative pain[19]	
Postoperative pain score (0 = no pain, 10 = worst pain imaginable)	**Naloxone dose (mg)**
4	0 (placebo)
2.2	0.4
1.8	2
7	7.5
6.8	10
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will be considered the primary therapeutic innovation and clinical goal. Other potential therapeutic benefits of low-dose opioid antagonists, including decreased opioid side effects, physical dependence, and tolerance, are important but are not our focus. Furthermore, to provide subject clarity the many terms used throughout earlier literature to describe enhanced nociception (i.e., excitation, hyperalgesia, pain enhancement, antianalgesia, pronociception, and allodynia) will be used interchangeably. It is understood that this approach varies from traditional descriptive terminology of pain and does not recognize important differences in nociceptive assays and experimental paradigms.

Discovery and pharmacologic characterization of opioid excitatory processes

While the analgesic actions of opioid agonists have been utilized clinically with confidence since antiquity and studied in detail for over a century, interest in opioid excitatory actions has lagged behind, as has clinical application. Animal and clinical reports that opioid antagonists produce both analgesia and hyperalgesia provided the most important "paradoxical" observations and have driven the considerable effort toward understanding the neuropharmacologic mechanisms of opioid excitatory actions.[15,19-25]

Four decades' worth of preclinical pharmacologic evidence for opioid excitatory actions indicates that systemic opioid agonists and antagonists produce either analgesia or hyperalgesia in several animal models of nociception. The earliest direct pharmacologic demonstration of opioid agonist excitatory actions resulted from experiments in the decerebrate and spinalized decerebrate dog.[26,27] Profound hyperalgesic actions of opioid agonists were demonstrated using changes in skin-twitch reflex following brainstem drug infusions as the experimental paradigm. Further, these studies provided evidence for CNS opioid excitatory processes, since naloxone produced independent analgesic effects and antagonized both the analgesic and hyperalgesic actions of opioid agonists. Both inhibitory and excitatory actions of opioids have been subsequently demonstrated following systemic, intrathecal, and brainstem injections in rodents.

The neuropharmacology of opioid excitatory actions is not fully understood, and description of the phenomena has varied considerably depending upon the experimental model and whether endogenous neuropeptides were studied in combination with exogenous drugs. The research efforts of many investigators have contributed to the current understanding of differential excitatory versus inhibitory actions of opioid agonists and antagonists. Several important neuropharmacologic models have been developed, including 1) brainstem opioid hyperalgesic processes,[26-31] 2) the dual-system hypothesis of pain perception involving a putative endogenous opioid system that is antagonistic to analgesia,[25,32-35] 3) an endogenous dynorphin "antianalgesia" system,[36-40] and 4) presynaptic autoinhibition of endogenous hyperalgesic opioid peptides.[41] Taken together, this diverse literature demonstrates that distinct excitatory versus inhibitory actions of opioid agonists occur at extremely low versus higher doses, respectively. Conversely, antiexcitatory versus anti-inhibitory actions of opioid antagonists occur at extremely low versus higher doses, respectively. The resultant biphasic dose-response curves (Figure 1) for opioid agonists and antagonists demonstrate the concept that opioid drugs elicit hybrid actions on nociception, which depends upon the dynamic balance of CNS excitatory versus inhibitory processes. Although the existence of opioid excitatory processes had been established during the 1980s, there was no model to explain mechanisms of opioid excitatory actions and no direction for future clinical translation of this knowledge.

Opioid antagonist enhancement of opioid agonist analgesia

In addition to the paradoxical analgesic effects of opioid

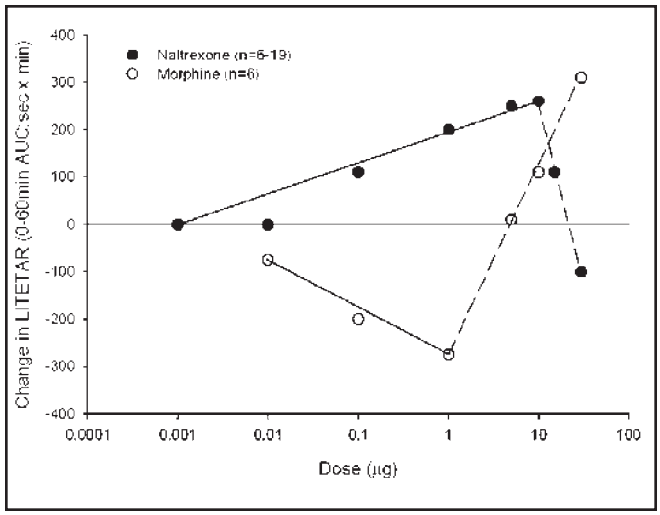

Figure 1. Bimodal hyperalgesic vs. analgesic effects of morphine and naltrexone microinjections into the brainstem of rodents. These data demonstrate the concept that opioid drugs elicit hybrid actions on nociception with resultant biphasic dose-response curves for the hyperalgesic (excitatory) vs. analgesic (inhibitory) actions of opioid agonists at extremely low vs. higher doses, respectively. Conversely, antiexcitatory (analgesic) vs. antiinhibitory (hyperalgesic) actions of opioid antagonists occur at extremely low vs. higher doses, respectively.

antagonists already discussed, several studies found paradoxical hyperalgesic effects of opioid agonists[4] when they were given chronically or acutely in low doses. Researchers also found that low-dose naloxone enhanced the analgesic actions of opioid agonists.[42-44] To take clinical advantage of this evolving knowledge required a succinct pharmacologic model consistent with established neurobiochemical mechanisms of opioid actions. During a decade-long series of experiments, Crain and Shen[45-66] (Albert Einstein College of Medicine in the Bronx) studied the effects of opioid agonist and antagonist cotreatment of nociceptive sensory neurons in vitro and in vivo in mice. This systematic research effort produced an innovative "bimodal opioid modulation" neurobiochemical model which provides a foundation for future therapeutic applications related to opioid excitatory pharmacology. Electrophysiologic studies of opioids on dorsal root ganglion (DRG) sensory neuron cultures demonstrated not only known opioid inhibitory (analgesic) actions mediated by Gi- and Go-coupled opioid receptors but also previously unrecognized excitatory actions mediated by Gs-coupled opioid receptors.[45,58-60,67] Detailed description of complex electrophysiologic experiments is beyond this review, and our discussion will focus on fundamental concepts that bring more clarity to potential clinical applications. A simplified diagram for the "bimodal modulation" model of opioid actions is presented in Figure 2; more detailed descriptions of this model are presented in research articles on the subject.[45-69]

Briefly, opioid agonists are proposed to act acutely via bimodal modulation of neuronal membrane calcium-versus-potassium conductance and resultant action potential duration (APD) of DRG sensory neurons.[45,55] This bimodal modulation of APD is influenced by activation of neuronal membrane opioid receptors that are coupled to interconvertible intracellular G protein–adenylate cyclase second-messenger systems. Because opioid receptors are abundantly distributed on the membranes of cell bodies as well as on the axonal terminals of immature nociceptive DRG neurons in culture, an opioid-induced decrease in the duration of the Ca^{2+}-dependent component of the DRG neuron APD will result in decreased presynaptic release of transmitters mediating afferent pain signals to the spinal cord. Conversely, an opioid-induced increase in the APD will increase presynaptic transmitter release, resulting in increased pain signals. Depending upon the dynamic state of the G protein system, modulation of the APD by opioid agonists may occur in either Gi- or Go-coupled inhibitory (analgesia) or Gs-coupled excitatory (hyperalgesia) modes. APD modulation by this dynamic system is further influenced by acute versus chronic opioid agonist exposure and relative affinities of opioids for the inhibitory versus excitatory forms of the opioid membrane receptor.[46,55,59] In the DRG electrophysiologic assay, low concentrations of bimodal opioid agonists have excitatory actions, high concentrations produce inhibitory effects, and intermediate concentrations result in hybrid/variable effects. Selective blockade of opioid agonist excitatory effects was demonstrated by cotreatment with picomolar concentrations of naloxone or naltrexone. This selective antagonism of opioid excitatory receptors resulted in attenuation of the excitatory action of opioid agonists and enhancement of their inhibitory (analgesic) potency.[48,57,64] These in vitro studies provided insight toward clinical translation of opioid excitatory pharmacology and future improvement in clinical efficacy and safety of opioid narcotics.

Subsequent behavioral tail-flick assays in mice by Crain and Shen[48,55-57,66] confirmed the analgesia-enhancement effects of low-dose opioid antagonists on opioid agonist analgesia. Other investigators have demonstrated enhancement of opioid agonist analgesic potency via low-dose opioid antagonists in animal studies, although the magnitude and character of the response are influenced somewhat by experimental variables (i.e., rodent species, gender, age, nociceptive assay, and dose).[70-79] Figure 3 presents an exemplary time-action curve for the morphine analgesia-enhancing effects of a low-dose opioid antagonist in a rodent model of nociceptive pain. More recent preclinical in vitro and in vivo laboratory studies are further refining our understanding of the neurobiochemical mechanisms of opioid excitatory pharmacology, as well as of the efficacy of low-dose opioid agonists and antagonists in models of neuropathic pain syndromes.[73-79]

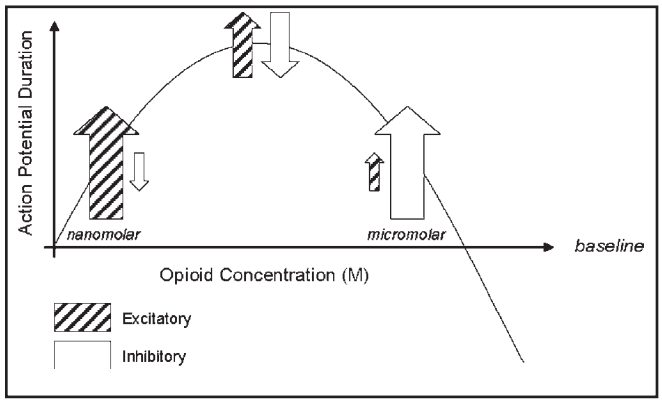

Figure 2. Bimodal modulation model of opioid agonist actions on membrane APD of DRG sensory neurons. Electrophysiologic studies of opioids on DRG sensory neuron cultures demonstrate both opioid inhibitory (analgesic) actions (mediated by Gi- and Go-coupled opioid receptors) and excitatory actions (mediated by Gs-coupled opioid receptors). Published with permission of *JPSM* and Elsevier.

CURRENT CLINICAL EVIDENCE

A handful of clinical studies and observations from the past 25 years have suggested that opioid antagonists may enhance opioid agonist analgesia. During clinical evaluation of the postoperative analgesic effects of buprenorphine, Schmidt and colleagues[42] treated patients exhibiting breakthrough postoperative pain with naloxone (80 to 400 µg), resulting in long-lasting pain relief (median duration of 22 hours). Levine and colleagues[43] examined the possible analgesic actions of naloxone using a human model of dental pain. In their earliest study, 90 patients with postoperative dental pain were given either 400 µg or 1,000 µg doses of naloxone in a double-blind manner. Compared with placebo controls, naloxone (400 and 1,000 µg) produced a significant decrease in pain intensity, suggesting an analgesic effect on naloxone's part. Subsequent clinical studies by this group examined the opioid-enhancing effect of naloxone for pentazocine and morphine in 105 patients, using the same double-blind postoperative dental pain model. The combination of 400 µg of naloxone with 60 mg pentazocine produced significantly greater analgesia than pentazocine or 15 mg of morphine alone, suggesting an opioid-enhancing effect of naloxone. The combination of 400 µg of naloxone with 8 mg of morphine, however, produced less analgesia than morphine administered alone. Although this apparent discrepancy between naloxone's analgesia-enhancement effects with pentazocine and morphine was not readily explained, the authors speculated that the analgesia-enhancing effect of naloxone was opioid specific.

Clinical interest in the possible enhancement of opioid analgesic effects by low-dose opioid antagonists has been stimulated by anecdotal case reports and encouraging

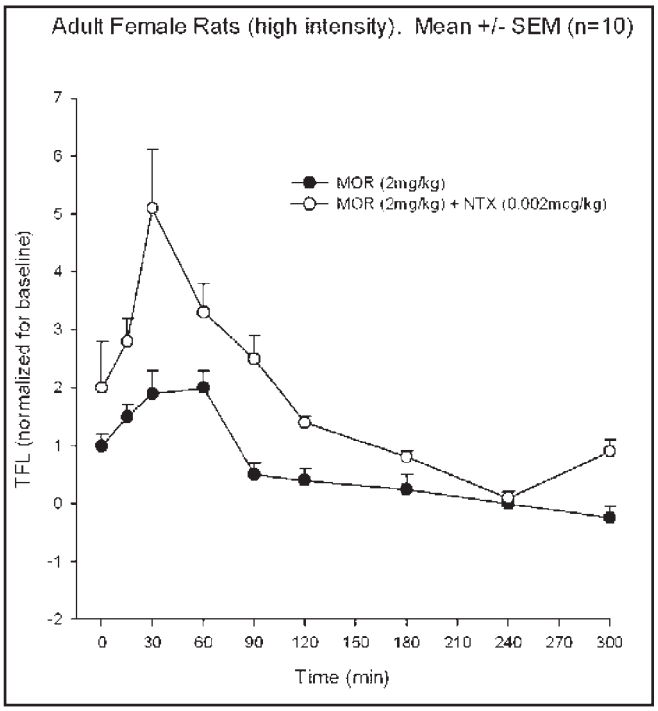

Figure 3. Exemplary time-action curves for the morphine-analgesia-enhancing effects of low-dose opioid antagonist in a rodent model of nociceptive pain. Behavioral tail-flick assays in mice and rats confirm the analgesia-enhancement effects of low-dose opioid antagonists on opioid agonist analgesia.

results from several clinical studies using different "analgesia efficacy versus side effects" paradigms.

Case reports

Cruciani et al.[10] published a case report demonstrating the analgesia-enhancing effect of the oral opioid antagonist naltrexone with methadone in a patient with chronic and resistant painful diabetic neuropathy. The addition of oral naltrexone 1 µg BID resulted in dramatic pain relief, accompanied by a 16 percent dose reduction of methadone.

Another case report describes a patient with chronic refractory pain who was treated with combined intrathecal morphine and low-dose opioid antagonist (naloxone).[80] After multiple treatment modalities failed to relieve severe post-laminectomy radicular pain, the patient remained in excruciating pain, with related depressive symptoms. The patient was treated with a combination of intrathecal morphine (2 mg) and low-dose naloxone (20 ng) to test the concept that selective antagonism of excitatory opioid receptor function at the level of the spinal cord may provide relief for this type of chronic neuropathic pain. Within 15 to 30 minutes, the patient reported onset of persistent pain relief, particularly over the most aggravated region of referred lower extremity pain (40 to 50 percent reduction in visual

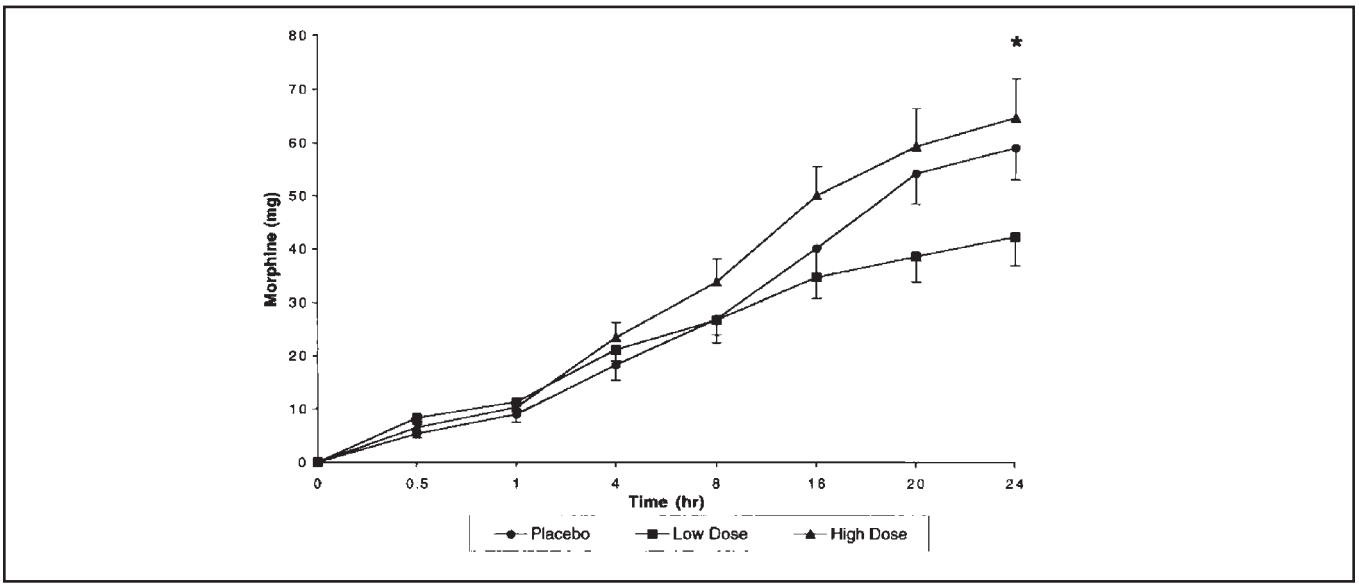

Figure 4. Mean (SEM) cumulative postoperative morphine dose vs. time. *p < 0.05 for both low-dose or high-dose naloxone regimens compared with placebo. Published with permission of *Anesthesiology*.

analogue score one hour after the dose). Following 48 hours of close clinical observation of repeated intrathecal trials, a continuous intrathecal infusion of morphine with ultra-low-dose naloxone was initiated, and acceptable pain control was maintained through this method. The enhanced analgesia (60 to 80 percent improvement by patient report) provided by small doses of intrathecal morphine and naloxone continued for several months.

Clinical studies

Perioperative pain. Low doses of opioid antagonists have enhanced, diminished, or had no effect on morphine analgesia in the perioperative setting, depending upon the drug administration regimen and pharmacokinetic characteristics of the studied antagonist. Gan and colleagues[81] studied the effects of naloxone when combined with patient-controlled analgesia (PCA) morphine for control of narcotic side effects and post-hysterectomy pain. Surgical patients received either a 0.25 µg/kg/h or 1 µg/kg/h dose of naloxone as a double-blind infusion for postoperative pain, allowing unlimited PCA morphine for pain relief and using a placebo control group. While the study objective was to reduce opioid-related side effects with the naloxone infusion, the authors discovered by serendipity that although all groups of patients had excellent pain relief, the cumulative (over 24 hours) PCA morphine doses were the lowest in the low-dose naloxone group (Figure 4). This opioid-sparing effect of naloxone suggested a morphine-analgesia-enhancing effect of naloxone, and the authors proposed that "the conventional understanding of naloxone acting as a direct postsynaptic opioid antagonist may be flawed."[81]

Joshi and colleagues[82] used a similar postoperative pain model to investigate the opioid-related side effects of a long-acting oral opioid antagonist, nalmefene. At the end of surgery, patients received either one of two doses of nalmefene or a saline placebo, and all patients had access to PCA morphine for postoperative pain relief. The study showed that although morphine consumption was similar in all groups, patients who received nalmefene had significantly lower pain scores during the 24-hour study period.

Sartain and colleagues[83] recently completed a double-blind study of postoperative pain using PCA morphine for pain relief, comparing morphine alone with morphine plus naloxone 13 µg given with each PCA bolus dose. They found no difference in pain relief or total 24-hour morphine dose between the two groups. Of note, this study differs from the previous work of Gan et al.[81] in that slightly higher doses of naloxone were given, and naloxone was given in boluses rather than as a continuous infusion. The authors concluded that if low-dose naloxone is to have opioid-enhancing effects, it should be given as an infusion or long-acting oral agent. Using a similar study design, Cepeda et al.[84] reported no clinical benefit, and an increase in morphine consumption, when naltrexone 13 µg was added to each PCA morphine bolus. In contrast to the single-gender and single-surgery study by Sartain et al.,[83] this study recruited male and female patients undergoing a variety of surgical procedures.

In a prospective, double-blind, randomized, placebo-controlled clinical trial of postoperative pain in children, continuous low-dose naloxone infusions were added to PCA morphine.[85] Low-dose naloxone infusions sustained morphine-induced analgesia, reducing the incidence and severity of opioid-induced side effects. The authors concluded that when PCA morphine is chosen for the treatment of postoperative pain, clinicians should consider starting a concomitant low-dose naloxone infusion.

Table 3. Effects of low-dose naloxone infusion on morphine MAC-reduction actions		
Naloxone dose (ng/kg/hr)	**MAC determination (n = number of crossovers per group)**	**Average DES (percent) (n = number of subjects per group)**
Placebo	6.93 ± 0.05 (n = 4)	6.20 ± 0.56 (n = 8)
0.15	4.60 ± 0.60 (n = 3)*	4.53 ± 0.34 (n = 8)
0.46	4.38 ± 0.05 (n = 6)*	4.45 ± 0.20 (n = 8)
4.60	4.54 ± 0.27 (n = 5)*	4.63 ± 0.32 (n = 8)
15.4	5.33 ± 0.88 (n = 3)*	5.28 ± 0.46 (n = 8)
*Significantly different from placebo (one-way ANOVA, p = 0.05); MAC = minimum alveolar concentration; DES = desflurane.		

When these PCA-morphine-based clinical studies are considered together, it appears that enhancement of opioid agonist analgesia may be most effective with sustained antagonism versus intermittent blockade of opioid excitatory actions. As seen in preclinical animal studies, several clinical variables may influence the effectiveness of introducing low-dose opioid antagonists to PCA morphine regimens. Importantly, these early postoperative pain studies consistently demonstrate that combining a low-dose opioid antagonist with morphine is safe and may be associated with diminished clinical side effects.

Surgical pain. Recently we completed a pilot study of the effects of low-dose naloxone infusions on the ability of morphine to decrease minimum alveolar concentration (MAC) of a potent volatile anesthetic, desflurane.[86] Patients undergoing abdominal hysterectomy were enrolled in a randomized, double-blind, placebo-controlled study of the effects of extremely low doses of naloxone on the MAC-reduction effects of morphine. Low doses of naloxone consistently enhanced the analgesic effects of morphine, as reflected in decreased MAC of desflurane (Table 3). There were no apparent signs of reduced morphine analgesia, toxicity, or hemodynamic compromise throughout three hours of general anesthesia and completion of the surgical procedures.

Chronic pain. The first large-scale, Phase II, double-blind, placebo-controlled study of low-dose oral naltrexone with oxycodone (Oxytrex) has recently been completed in patients with chronic osteoarthritis pain.[87] This multicenter study evaluated 243 patients randomized to receive placebo, oxycodone QID, Oxytrex (oxycodone plus 1 µg naltrexone) QID, or Oxytrex BID. The daily oxycodone dose was the same for all active treatment groups, although the Oxytrex BID group received only 2 µg/d, compared with 4 µg/d for the Oxytrex QID group. Oxytrex twice daily produced pain relief that was better than that provided by placebo or oxycodone QID (Table 4). No difference between groups was noticed with regard to adverse events or opioid-related side effects. The authors concluded that opioid enhancement by low-dose naltrexone may occur in humans, and longer-treatment trials are ongoing.

In a recently completed Phase III clinical study of patients with chronic low back pain, Oxytrex demonstrated equivalent pain reduction to oxycodone.[88] Patients titrated themselves to adequate analgesia or intolerable side effect. Importantly, Oxytrex maintained equivalent analgesic efficacy, although the doses of oxycodone combined with low-dose naltrexone were significantly lower than of the control oxycodone alone. Several large-scale clinical trials are under way and/or planned for future development of combined low-dose opioid antagonist and opioid agonist formulations.

A pilot clinical trial of combined intrathecal morphine and oral naltrexone in refractory chronic pain has been conducted.[89] Patients with chronic neuropathic pain and indwelling intrathecal drug delivery systems were enrolled in a randomized, double-blind, placebo-controlled study of the effects of extremely low doses of oral naltrexone on pain relief produced by intrathecal morphine. After baseline evaluations were performed using continued intrathecal morphine alone, patients were challenged twice daily, for seven days, with oral placebo or low-dose naltrexone during continued intrathecal morphine infusions. Oral naltrexone exhibited dose-dependent enhancement of intrathecal morphine analgesia that persisted for the entire week. No clinical evidence of decreased intrathecal morphine analgesia (i.e., antagonism) or of serious side effects were observed with the addition of oral naltrexone. Although consistent enhancement of pain relief was observed, the small number of refractory chronic patients studied precludes definitive conclusions about the efficacy of combining low-dose naltrexone with intrathecal morphine. Further studies using this unique clinical model are indicated, but they will be difficult to conduct in this complex patient population.

CONCLUSION

In summary, clinical evidence to support the use of low-dose opioid antagonists as analgesia-enhancing agents has been demonstrated in patients with surgical, postoperative, and chronic neuropathic pain. As in preclinical animal studies, the magnitude of response is

Table 4. Mean (SD) pain intensity scores (0 = no pain, 10 = worst pain imaginable) among patients with chronic osteoarthritis pain treated over three weeks[87]				
Week of treatment	**Placebo**	**Oxycodone QID**	**Oxytrex QID**	**Oxytrex BID**
Baseline	7.7 (1.3)	7.4 (1.3)	7.7 (1.4)	7.6 (1.4)
Week 3	6.1 (2.8)	5.6 (2.3)	5.7 (2.4)	4.5 (2.4)
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influenced by clinical trial variables, particularly opioid agonist and antagonist dosing regimens. Thus far, there has been no apparent enhanced risk of side effects when low-dose opioid antagonists are combined with clinical doses of opioid agonists or other anesthetics.

An evolving understanding of opioid excitatory pharmacology has been driven by decades of confusing clinical observations followed by focused in vivo and in vitro investigations of the neuropharmacologic mechanisms responsible for the apparent bimodal actions of opioid agonists and antagonists. Dose-dependent inhibitory-analgesic and excitatory-hyperalgesic actions of opioid agonists have been demonstrated in animal and neuronal cell culture experiments. The excitatory versus inhibitory actions of opioids involve dynamic neuronal G protein–adenylate cyclase intracellular biochemical signaling mechanisms. Enhancement of opioid agonist analgesia by low-dose opioid antagonists has been shown in several animal and clinical models of pain. Clinical translation of this novel pharmacology has been focused on enhancement of opioid agonist analgesia by ultra-low-dose opioid antagonists in the treatment of perioperative and chronic pain. Although the clinical paradigms differ, when viewed together the available literature strongly supports the concept that ultra-low-dose opioid antagonists can enhance the analgesic efficacy of opioid agonists. This exciting breakthrough in the therapeutic management of pain deserves further, detailed clinical and laboratory evaluation. While enhanced side effects of the combination of opioid agonists and low-dose opioid antagonists have not been reported, cautious clinical application is warranted while safety and efficacy profiles of combination drug formulations are documented in large, controlled clinical trials.

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Paul Sloan, MD, Professor, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky.
Scott Hamann, PhD, MD, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky.

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