Journal of Opioid Management™

A medical journal for proper and adequate use

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Official Journal of Opioid Management Society

CONTENTS

The manufacturers of Suboxone (buprenorphine) suggest "performing and reviewing appropriate urine drug screens, laboratory evaluations and [blood alcohol levels]" during both the induction and follow up treatment phases of patients to whom this medication is prescribed.

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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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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

EDITORIAL

Opioid safety

Robert E. Enck, MD

In this issue, Gupta and Weber concisely review the literature on the renal effects of opioids, both acute and chronic. Several fascinating facts emerge, such as the following:

- Opioid receptors similar to those found in the central nervous system are expressed in the kidney.
- In the animal model, morphine stimulates angiogenesis-dependent tumor growth and ischemic wound healing.
- The central opioid pathway is activated by dietary restriction, resulting in maximum sodium retention.
- Morphine induces a transient dose-dependent reduction in blood pressure and a subsequent decrease in urine output.
- Extrapolation of the chronic use of opioids can be tied in with the occurrence of heroin-induced nephropathy.
- Opioids are likely to have physiologic renal effects and could potentially contribute to the progression or treatment of chronic kidney disease.

Now, speaking as a clinician, the authors appear to stretch some of the animal data considerably to hypothesize human outcomes; however, this may not be all that bad if it stimulates more thought and research in this area. As a medical oncologist, I find the suggestion that opioids stimulate angiogenesis-dependent tumor growth both tantalizing and worrisome. At some time during the course of their clinical diseases, the vast majority of cancer patients are treated with some sort of opioid drug. If these theories surrounding angiogenesis are on the mark, maybe we are doing our patients more harm than good. Viewing this point differently, will blocking the opioid receptors in cancer patients improve their survival as an antiangiogenesis tactic?

Although all this speculation is academically stimulating, there remains the clinical issue of opioid use and impaired renal function. Of all the natural and synthetic opioids, morphine is the drug of choice and the standard for comparison for severe pain. Orally administered morphine is subject to the first-pass effect of liver metabolism, which causes a large reduction in its potency. Hepatic biotransformation modifies the opioid through dealkylation, glucuronidation, hydrolysis, and oxidation. Once converted to water-soluble forms, 90 percent is excreted in the urine. Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are the two major metabolites of morphine. Both of these metabolites depend on renal excretion for clearance. M6G is a more potent analgesic than morphine, whereas M3G is associated with hyperalgesia and neurotoxicity. It has been suggested that morphine doses be reduced in patients with severely impaired renal function, and that they be substantially reduced if creatinine clearance is less than 30 ml/min/1.73m^2. Furthermore, there appear to be some pharmacokinetic differences with morphine in different age groups, with reduced renal clearance and smaller volume distribution in older patients.

Ultimately, all good research leads us to ask questions, sometimes more than it answers. I hope the articles in this current issue of *Journal of Opioid Management* encourage you in your investigations.

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

CALENDAR

Opioid Management Society
Journal of Opioid Management
Opioid Education Program
Chicago: September 16-17, 2006
Philadelphia: October 7-8, 2006
Miami: October 28-29, 2006
Houston: November 11-12, 2006

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Palliative Care Leadership Center (PCLC) Training
Building Academic Palliative Care
August 21-23, 2006
Medical College of Wisconsin
Madison, Wisconsin

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Rose Hackbarth
Tel.: 414-805-4607
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Web site: *http://www.capc.org/pclc*

American Academy of Pain Management
17th Annual Clinical Meeting
Beyond Boundaries: Forging New Alliances in Pain Management
September 7-10, 2006
Walt Disney World Swan and Dolphin
Orlando, Florida

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International Association for the Study of Pain (IASP)
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5th Congress of the European Federation of IASP Chapters
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Istanbul Convention & Exhibition Centre (ICEC)
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16th International Congress on Care of the Terminally Ill
September 26-29, 2006
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November 2-4, 2006
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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
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Web site: *http://www.neuropathicpain.org*

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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Robert E. Enck, MD

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

FALL 2006

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ACCREDITATION

Medicine

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.

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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.

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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.

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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."
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"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 October 1, 2006.

2. Presenting author will be contacted by October 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.

Questions regarding abstracts or the submission process should be directed to OMS Conference Planning Committee, Attention: Martin Schumacher at *martin_schumacher@pnpco.com.*

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Getting Informed Consent and Agreement for Treatment right: A legal perspective on key obligations for practitioners who use controlled substances to treat chronic pain

Jennifer Bolen, JD

Medical practitioners who use controlled substances to treat pain must learn and demonstrate compliance with the ethical and medical obligations of Informed Consent and Agreement for Treatment. This article distinguishes the concept of Informed Consent from that of Agreement for Treatment (sometimes called a Narcotic or Opioid Contract[1]) and offers basic suggestions for demonstrating compliance with federal and state legal/regulatory materials related to these concepts. In this regard, this paper offers suggestions on how to:

1. determine your state's position on the matter;

2. distinguish Informed Consent elements from terms comprising an Agreement for Treatment and properly construct office forms based on the key distinctions between these concepts; and

3. perform a self-audit of your existing Informed Consent and Agreement for Treatment document (in whatever form) to determine whether changes are necessary to improve compliance with state legal/regulatory materials on the use of controlled substances to treat pain.

No amount of medical record documentation, let alone an Informed Consent document or an Agreement for Treatment, will prevent a lawsuit or licensing board investigation, but all documentation plays a role in how a jury or board reviewer perceives you and your practice. When you use well-drafted office forms and understand your legal/regulatory obligations related to prescribing controlled substances to treat pain, you will be in a better position to stay focused on quality medical care and preserve your patients' access to controlled substances. Remember, quality medical care starts with a commitment to professional interaction with your patients and is supported by the proper paperwork. Time invested in reviewing this article and following the suggestions set forth herein will help you better understand the concepts of Informed Consent and Agreement for Treatment and improve your compliance with state legal/regulatory materials on the use of controlled substances to treat pain.

WHAT IS YOUR STATE'S LEGAL/REGULATORY POSITION ON THE AGREEMENT FOR TREATMENT?

You need to know whether your state has a guideline or regulation on using controlled substances for the treatment of pain (or a similarly worded item). In fact, your state may have more than one of these, so be prepared to read all items related to the use of controlled substances in the treatment of chronic pain. Use a comprehensive legal/regulatory Web site[2] or your state board's Web site and search for items posted under headings like "laws and regulations," "guidelines," or "policies/position statements."

WHAT IS A GUIDELINE/POSITION STATEMENT?

It is easier to state what a guideline or a position statement is not. First, these items are not clinical standards of care or laws themselves; they generally do not have the force of law, meaning that your failure to follow them exactly is not likely to bring board reprisal so long as you have documented good-faith reason for your departure from them. Through guidelines or position statements, licensing boards usually attempt to define or explain the meaning of a state law or regulation/rule that governs medical practice in the state. Licensing boards usually do not intend for guidelines or position statements to be comprehensive or to exhaustively set out every standard that might apply in every circumstance. Moreover, the absence of a guideline or position statement, or the silence of such material on certain matters, should not be construed as the lack of an enforceable licensing board standard.

WHAT ARE REGULATIONS/RULES?

Most licensing boards have legal authority to make regulations or rules, and these items have the force of

law, meaning that your failure to follow them may result in your loss of license privileges and the imposition of monetary sanctions. Regulations and rules generally explain state laws and set conduct expectations, stating what the licensing board expects you to do or not do concerning specific aspects of medical practice. States often define the failure to follow a regulation or rule as "unprofessional conduct."

UNDERSTANDING YOUR STATE'S POSITION

Once you locate your state materials and determine what category these items fall into (guideline, regulation, or both), read them and look specifically for a section called "Informed Consent and Agreement for Treatment." Because many state prescribing guidelines or regulations are based wholly or in part on the Federation of State Medical Boards' *Model Policy for the Use of Controlled Substances for the Treatment of Pain*,[3] or an older version of this document known as the *Model Guideline for the Use of Controlled Substances for the Treatment of Pain*,[4] I have quoted the language from the "Informed Consent and Agreement for Treatment" section of the Federation's 2004 policy below. However, I have divided this language into three sections to help you follow my legal/regulatory perspective on it.

Informed Consent and Agreement for Treatment

Section One. The physician should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient, or with the patient's surrogate or guardian if the patient is without medical decision-making capacity.

Section Two. The patient should receive prescriptions from only one physician and one pharmacy whenever possible.

Section Three. If the patient is at high risk for medication abuse or has a history of substance abuse, the physician should consider the use of a written agreement between physician and patient outlining patient responsibilities, including:

- urine/serum medication-level screening when requested;
- awareness of the number and frequency of all prescription refills; and
- understanding of reasons for which drug therapy may be discontinued (e.g., violation of agreement).

To learn how to distinguish Informed Consent from Agreement for Treatment in your practice, use the *Model Policy's* language above and my discussion below, and note the subtle distinctions between the sentences in each section of the *Model Policy's* component on Informed Consent and Agreement for Treatment.

Section One underscores the ethical and medical obligation of Informed Consent and contains a legal/regulatory directive suggesting the physician *should* discuss the risks and benefits of using controlled substances with the patient.[5] Arnold et al.[6] discuss the ethical obligation of informed consent related to controlled substances. Pain practitioners should familiarize themselves with the Informed Consent process described by Arnold et al.[6] and others,[7,8] including myself, who have written on the subject.

Section One also implicates the legal/regulatory directive to prescribe controlled substances *for a legitimate medical purpose within the usual course of professional practice*,[9-11] and to minimize the potential for abuse and diversion of these substances.[10] Although these directives originate in federal law, most states adopt these standards and incorporate them into state controlled-substances acts and state medical-practice acts.

Look at Section One again; you will find the *Model Policy* and many state legal/regulatory materials suggest that the physician need only discuss "risks and benefits" of using controlled substances, seemingly suggesting that the Informed Consent ethical obligation stops there; it does not. The Arizona Board of Medical Examiners is one of the only states in the country to set out the ethical obligation of Informed Consent correctly, as reflected in its new *Guidelines for the Treatment of Chronic Pain*, issued Spring 2006 (discussed below).[12]

As I have previously stated,[8,13-15] and as Arnold et al.[6] correctly point out, there are two additional elements of a legal Informed Consent: 1) available treatment alternatives, if any; and 2) special issues concerning the use of controlled substances, like driving, pregnancy, lowered testosterone levels, etc.[16] The new Arizona guideline contains the element of available treatment alternatives, and one can argue that the element called "special issues" may be considered part of "risks" and/or "benefits." All of this is important because guidelines and regulations, and "go-by" Informed Consent and Agreement for Treatment documents that omit critical elements and language, put pain practitioners at a disadvantage, at the very least from a legal/regulatory perspective. This means there is potential for increased legal exposure. It also means there is greater potential for licensing board sanctions, but a licensing board might be hard pressed to argue that you messed up these concepts if the board has not stated them correctly to begin with. Thus, you should take care to distinguish between the concepts of Informed Consent and Agreement for Treatment and document them separately, or at the very least in separate sections of the same document, so you do not mingle concepts and terms and make it more confusing for your patients and those who might end up reviewing your documentation. Also, take

care to ensure your Informed Consent and Agreement for Treatment contain the proper elements and proper terminology, so your intent is clear—legal/regulatory compliance and quality medical care.[17,18]

Sections Two and Three do not implicate any ethical obligations per se, but these sections do relate to minimum licensing board expectations concerning the physician's duty to evaluate patients, establish a treatment plan, review the treatment plan, and make changes during patient follow-up based on whether the patient is meeting treatment plan goals and acting responsibly in terms of medication handling and usage. Further, these sections relate to a practitioner's obligation to minimize the potential for abuse and diversion of controlled substances.[10,11,19] In the introductory paragraphs to most state guidelines or regulations on the use of controlled substances for the treatment of pain, you will find this statement, or something like it:

> The Board is obligated under the laws of the State of _____ to protect the public health and safety. The Board recognizes that the use of [controlled substances/opioid analgesics] for other than legitimate medical purposes poses a threat to the individual and society and that the inappropriate prescribing of controlled substances, including opioid analgesics, may lead to drug diversion and abuse by individuals who seek them for other than legitimate medical use. Accordingly, *the Board expects that physicians incorporate safeguards into their practices to minimize the potential for the abuse and diversion of controlled substances.*[20]

Looking individually at the points in Section Two, one sees that it contains a suggestion to limit control of the patient's access to, or oversight authority for the patient's use of controlled substances for the treatment of pain to, one provider and one pharmacy. This certainly makes sense in theory, but in reality it is extremely difficult to enforce and monitor, especially if you live in a state that lacks a prescription drug monitoring database. I think this is a good practice or boundary for an Agreement for Treatment, and I think you should have this statement in yours. Remember, however, that it is up to the patient to select the pharmacy, and you should not tell him or her which pharmacy to pick. Likewise, if you are a specialist and the patient will be seeing you and continuing to see his/her primary care physician, you may consider using an Agreement for Treatment that involves you, the primary care physician, and the patient, and a clear statement as to which medical professional will be prescribing controlled substances to the patient. Fishman et al.[21] have discussed the concept of "trilateral agreements," and you should read their paper if you have not already done so.

Section Three seems to suggest that licensing boards want practitioners to address varying risk potentials in patient populations. This is significant, as such language arguably implies the practitioner has at least a medical obligation to do some form of risk analysis on his/her patients if he/she intends to prescribe them controlled substances to treat pain. If your state has this language in a regulation or rule instead of a guideline or position statement, then I would urge you to see this section as a mandate to perform some form of risk analysis; you probably do this anyway, but you may need to find a more formal way of demonstrating your efforts. By this, I mean you might want to use a tool like the 1) Drug Abuse Screening Test (DAST-20),[22] 2) Screener and Opioid Assessment for Patients in Pain (SOAPP®),[23] or 3) Opioid Risk Tool.[24] Once you assess the patient's risk level, then you can construct your treatment plan, risk monitoring, periodic review sessions, and necessary consultations/referrals accordingly.

Section Three clearly contains a suggestion that if the practitioner determines the patient is at high risk for medication abuse or has a history of substance abuse, then he/she should consider the use of a written agreement between the physician and patient outlining patient responsibilities, including:

- urine/serum medication-level screening when requested;
- being aware of the number and frequency of all prescription refills; and
- understanding the reasons for which drug therapy may be discontinued (e.g., violation of agreement).

This language is significant because states using this language appear to suggest that, at a minimum, the licensing board's interest is in the use of a written Agreement for Treatment for *high-risk* patients. Some states attach a sample agreement to the guideline or regulation, like Colorado.[25] If your state does not "mandate" the use of any particular form for the Agreement for Treatment, you might consider the value of a frank discussion with the patient about your office policies, treatment expectations, and the patient's responsibilities, concerning the use of controlled substances. Look the patient in the eye, engage him or her in a real conversation and set clear boundaries and explain consequences. Following this meeting with the patient, send him or her a letter memorializing the conversation and, if you want, obtain the patient's signature on the letter at his or her next visit. Much of this is a matter of style and your patient population plays an important factor in how you approach the use of an Agreement for Treatment. Nonetheless, do not forget how important it is to interact

with the patient—pieces of paper cannot do this like you can.Be careful to note whether your state "suggests" or "mandates" the use of a written Agreement for Treatment and whether it draws distinctions between patient risk levels. Finally, to my knowledge, the law does not prohibit a practitioner from using a written Agreement for Treatment with all patients, if that is what he/she desires to do.

INFORMED CONSENT IS NOT THE SAME AS AGREEMENT FOR TREATMENT

Informed Consent is not the same as Agreement for Treatment, and it is important for you to modify your existing paperwork if it inaccurately refers to Informed Consent as something the patient must agree to in order to obtain treatment from your office and/or omits key elements. The State of Arizona recently recognized the distinctions between Informed Consent and Agreement for Treatment in its new 2006 *Guideline for the Treatment of Chronic Pain*.[12] In doing so, Arizona separated the concepts of Informed Consent and Agreement for Treatment within the guideline and differentiated the directive language associated with each concept as demonstrated below, making Informed Consent mandatory and Agreement for Treatment discretionary based on the circumstances of the patient's case.

> **Informed Consent—**The physician **must** discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient, or with the patient's surrogate or guardian if the patient is without medical decision-making capacity. ***This discussion should include the risks of addiction/abuse, not alleviating all pain, and treatment alternatives including the effects of no treatment.***
>
> **Agreement for Treatment—**There are circumstances in which the use of a documented verbal or written agreement between physician and patient outlining patient responsibilities ***may be necessary*** for safe and responsible opioid prescribing. ***Such an agreement should include***:
>
> - urine/serum medication levels and baseline screening when requested;
> - number and frequency of all prescription refills;
> - reasons for which drug therapy may be discontinued (e.g., violation of agreement);
> - requirement that the patient receive all controlled substance prescriptions from one physician and one pharmacy whenever possible.[12]

RELATED CONCEPT OF "MEDICAL RECORDS"

No discussion about the Agreement for Treatment is complete without reference to the physician's obligation to keep accurate and complete medical records. Most licensing boards have a guideline or regulation addressing medical records—what they are, what is to be included, how they are to be kept and for how long, who owns them, and what fees may be charged for copying them. The Medical Records component of the *Model Policy* reads as follows:

> **Medical Records—**The physician **should** keep accurate and complete records to include:
>
> 1. the medical history and physical examination;
> 2. diagnostic, therapeutic and laboratory results;
> 3. evaluations and consultations;
> 4. treatment objectives;
> 5. **discussion of risks and benefits**;
> 6. **Informed Consent**;
> 7. treatments;
> 8. medications (including date, type, dosage, and quantity prescribed);
> 9. **instructions and agreements**; and
> 10. periodic reviews.
>
> Records should remain current, be maintained in an accessible manner, and be readily available for review.[3]

You need to know what your state says about the type of medical records you "should" or "must" keep related to your prescribing of controlled substances to treat pain. You also need to know to what extent your licensing board expects you to document the listed items. It is likely your board will apply a standard that would allow a similarly situated physician to "step into your shoes" and follow your treatment logic and plan based on your documentation (or a similarly stated standard).

PERFORMING A SELF-AUDIT OF YOUR AGREEMENT FOR TREATMENT

Now that you know a bit about the distinctions between Informed Consent and Agreement for Treatment, take the

next step and review your current form(s). Use the checklist (Appendix 1) at the end of this article to guide your review, and consider the following additional items:

What should you call your form?

Use language similar to the language used by your state's guideline or regulation. For example, if your state has a guideline called the *Guideline for the Use of Controlled Substances for the Treatment of Pain* and refers to an individual step as "Informed Consent and Agreement for Treatment," then consider calling your form "Informed Consent and Agreement for Treatment for the Use of Controlled Substances for the Treatment of Pain," and refer to "controlled substances" throughout instead of any specific drug. Inconsistencies between state terminology and your form and/or the use of multiple terms to refer to controlled substances (i.e., pain medications, opioids, narcotics, narcotic medications) can cause confusion and look sloppy when viewed on the "big screen." I will post a marked-up form on my Web site (*www.legalsideofpain.com*) for your reference with the on-line version of this article.

What drugs should the Agreement for Treatment cover?

Once again, I recommend you use language similar to the language used by your state's guideline or regulation. This answer applies both to Informed Consent and Agreement for Treatment forms. For example, if your state guideline is called the *Guideline for the Use of* ***Controlled Substances*** *for the Treatment of Pain*, use the phrase *controlled substances* both in the introduction and throughout the body of your form. Remember, as pain practitioners you prescribe more than opiates, and your ethical obligation on Informed Consent is not limited to opiates; it applies to all medications and treatments you recommend.[7,26] Similarly, you likely intend for any boundary-type document, like an Agreement for Treatment, to cover the patient's conduct relative to the entire treatment plan, including all drugs prescribed, not just the opiates. If you limit your forms to specific medications, you may be limiting your ability to take action with your patient or, as I usually phrase it, you may be "handcuffing" yourself in the sense of limiting your discretion, and this is not smart business or compliance. In your review of your state materials, you may notice that very few states follow this rule, and most state guidelines or regulations jump back and forth between "controlled substances" and "opioids" or other terms, thereby making it hard for you to understand just where your state will draw lines or apply them.

What kind of "introductory" language should you use in an Informed Consent versus an Agreement for Treatment?

This is a very important question, and I am going to demonstrate its answer by quoting language from a form I recently reviewed during a compliance audit. If your form contains the following introductory language and you intend that form to represent Informed Consent, you will need to change it for the reasons described below:

> I agree to the following conditions and I am aware that my failure to abide by any of these conditions will be considered a breach of the contract and, at the sole discretion of my physician, may result in the termination of our physician-patient relationship.

This introductory language is not appropriate for an Informed Consent form. Moreover, if you were going to use it for an Agreement for Treatment, you would need to make a few changes. The language is not appropriate for an Informed Consent because, as discussed above, Informed Consent is not about "conditions" or the "patient's failure to abide by conditions." Also, Informed Consent is not a contract; it is the practitioner's ethical obligation to discuss the risks and benefits of using the controlled substances recommended, along with an explanation of available treatment alternatives and special issues associated with the use of the recommended controlled substances.

The sample language above, minus the word "contract" and the reference to a "breach of contract," is better suited as a "consequences statement" in an Agreement for Treatment. For an example of an introductory statement to an Informed Consent form, see the example on my Web site associated with the on-line version of this article.

What "boundary terms" should an Agreement for Treatment contain?

Incorporate the suggestions from your state's guideline or regulation and then, if you want, add a few of your own to clearly establish your practice boundaries. Many have published on the general categories of boundary terms (Arnold et al.,[6] Fishman et al.,[27] and Heit[28]), and it is not necessary to repeat their statements here.

PATIENT PROTECTION AND PHYSICIAN COMPLIANCE

Physicians must find a professional way to protect their patients' legitimate access to controlled substances and demonstrate compliance with legal/regulatory materials. Development of practice policies that insist on patient responsibility will help accomplish these goals. Controlling human behavior is difficult at best. In accomplishing the tasks suggested in this paper, remember that it is not about having lots of paper to show your compliance. Instead, it is about having the right paper—the kind that demonstrates your knowledge of and compliance

with your ethical, medical, and legal obligations and your knowledge of and adherence to accepted current clinical standards of care, and that paper can take many forms and may be even more effective when, as in the case of an Agreement for Treatment, it is a letter sent to the patient after and confirming a frank discussion about behavioral expectations and patient responsibilities during treatment involving the use of controlled substances. Overall, we know that the Agreement for Treatment is only as effective (and thus efficient) as those who stand behind it. Physicians must train themselves and their staff to stand behind the spirit and letter of a well-drafted Agreement for Treatment. The document should incorporate key provisions from your state legal/regulatory materials and should also be drafted professionally and in a manner that is helpful to your patient population.

If you want to get a good opinion of your Informed Consent and Agreement for Treatment, put your form(s) into PDF format and then into a PowerPoint presentation, and then project their image onto an office wall. When you see your form(s) "up in lights" you will notice the little things that can make a big difference, and you will understand why it is important to make changes now—proactively—before some attorney gets a chance to use these items against you on a courtroom screen before a board panel or jury. Empirical evidence may make you feel better about how science looks at the process of Informed Consent or the use of an Agreement for Treatment. Informed Consent is required, and you will want to get this concept right in your practice so you do not contribute to the likelihood of a successful malpractice case (like a wrongful-death action) against you. On the other hand, your state legal/regulatory materials will decide whether you *must* or *should* use an Agreement for Treatment.

CONCLUSION

The legal perspective in this paper is a relatively small part of the matter when it comes to the physician-patient relationship and the prescribing of controlled substances to treat pain. It is vital that medical professionals not lose sight of the fact that a "relationship" requires interaction and that the processes of Informed Consent and Agreement for Treatment cannot and should not be replaced by pieces of paper. While the law may require the documentation of processes, medicine requires, and safe prescribing mandates, good solid communication with patients about the issues surrounding the use of controlled substances to treat pain and the responsibilities of both parties—the physician and the patient.

Physicians will continue to study the concepts of Informed Consent and Agreement for Treatment and the effectiveness of these items in medical practice. Remember, however, that your medical license and DEA registration number depend, in part, on a slightly different perspective of your responsibilities, especially when it comes to prescribing controlled substances. Consequently, there is and will continue to be a focus on physicians' responsibility to minimize the potential for abuse and diversion of controlled substances, and many legal/regulatory entities—federal and state—consider the process of Informed Consent and the use of and adherence to an Agreement for Treatment or similar boundary-setting arrangement as a solid demonstration of a physician's compliance with his/her legal obligations in this area.

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NOTES AND REFERENCES

1. The terms "Narcotic Contract" and "Opioid Contract" are not really appropriate in a legal/regulatory context, even though these terms may sound more official. Most state legal/regulatory materials on prescribing controlled substances for the treatment of pain refer to a written agreement between the physician and patient as an "Agreement for Treatment." Once you learn what your state says about the use of such a document, you should call it what your state calls it and use language similar to your state's language. However, if you live in a state that refers to the agreement as a contract, consult with your legal counsel or a legal expert on the matter to decide whether you increase your legal exposure by using the term "contract." The rationale for using your state's terminology (unless it says "contract") is obvious—you signal your knowledge of your state's materials and, hopefully, you demonstrate your compliance with the same by the manner in which you document and use your Agreement for Treatment. Once again, the exception to the term "contract" relates to the potential increase in legal exposure or obligations.
2. The University of Wisconsin's Pain & Policies Studies Group Web site contains an index of state materials and may be accessed at *www.medsch.wisc.edu/painpolicy/index.htm*. The Legal Side of Pain Web site contains a comprehensive set of quick reference materials for all states related to the use of controlled substances to treat pain and related ethical and professional obligations and may be accessed at www.legalsideofpain.com.
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16. Most states' legal/regulatory materials likewise overlook the last two elements of a legal Informed Consent. One exception is Arizona's relatively new *Guidelines for the Treatment of Chronic Pain*, adopted in early 2006. If you want your Informed Consent to help you minimize liability and risk potentials, then use all four elements and review this issue with qualified legal counsel.
17. See example Informed Consent and Agreement for Treatment located on www.legalsideofpain.com. The American Academy of Pain Medicine also splits the concepts of Informed Consent and Agreement for Treatment into separate forms, and readers can find samples on the Academy's website at *www.painmed.org*.
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29. Check your state law to make sure there is no requirement in pain management to implement "random" urine or serum drug testing. Usually, the randomness requirement is limited to employment or workplace drug testing, the nature of which is *very* different from that of urine drug testing in pain management.

APPENDIX 1. FROM *THE LEGAL SIDE OF PAIN®*—A BASIC CHECKLIST ON INFORMED CONSENT AND AGREEMENT FOR TREATMENT RELATED TO THE USE OF CONTROLLED SUBSTANCES TO TREAT PAIN

Does your state have a GUIDELINE or POSITION STATEMENT *OR* REGULATION or RULE *OR* BOTH related to the Use of Controlled Substances for the Treatment of Pain?

Write down the title of your state's document(s): _____

Does this document use the term "Controlled Substances" throughout? ___ Yes ____ No

What other terms does the document use to refer to controlled substances? _____

What term does your state use to refer to Informed Consent? _____

Does your state say you MUST or SHOULD perform Informed Consent? _____

What elements do you find in your state's Informed Consent language? (risks, benefits, etc.) _____

_____

Does your state say you MUST or SHOULD use a boundary document with patients when you prescribe controlled substances for the treatment of chronic and/or intractable pain? ___ Yes ___ No

What term does your state use to refer to such a boundary document? (Agreement for Treatment, Treatment Agreement, Opioid Contract, etc) _____

With whom does your state suggest you use such a boundary document? (Open discretion, all patients, high-risk patients, does not say) _____

If your state suggests you use a boundary document with *high-risk* patients, do you have a tool you regularly use to rank or otherwise decide whether a patient is *high risk?* If so, which one? (DAST-20, SOAPP®, ORT, other): _____ If not, select one to try.

Does your state suggest the use of any specific boundary terms (one physician and one pharmacy for controlled substances, urine drug testing, family conferences, etc.) in a boundary document? If so, list them here:

_____

Make sure you remove language that limits your discretion—change "you will be discharged" to "we *may* change your treatment plan or discharge you from our practice." Also, change "you may be subject to *random* urine drug tests" to "you agree to provide a urine sample *when requested.*" You always want to retain your discretion to request a test whenever you think it is appropriate to do so and you do not want to add an unnecessary legal burden to your medical practice—the inappropriate use of the terms "random" or "unannounced" may do just that.[29]

Make sure your introductory language is proper for both your Informed Consent form and your Agreement for Treatment document.

For both Informed Consent and Agreement for Treatment, make sure you obtain the patient's signature, give the patient a copy of the document, and keep the original in the patient's medical record.

Make sure you address patient behaviors that are contrary to the promises made to you by the patient.

Make sure you document your efforts.

CASE REPORT

Dexmedetomidine to treat opioid withdrawal in infants following prolonged sedation in the pediatric ICU

Joseph D. Tobias, MD

ABSTRACT

This retrospective study aims to report on the use of dexmedetomidine to treat opioid withdrawal following sedation during mechanical ventilation in a cohort of infants. Seven infants in the pediatric intensive care unit of a tertiary care center, ranging in age from three to 24 months (12.4 ± 8.2 months) and in weight from 4.6 to 15.4 kgs (9.9 ± 4.2 kgs), had received a continuous fentanyl infusion, supplemented with intermittent doses of midazolam for sedation, during mechanical ventilation. Withdrawal was documented by a Finnegan score ≥ 12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/hr, followed by an infusion of 0.5 μg/kg/hr.

Dexmedetomidine effectively controlled the signs and symptoms of withdrawal in the seven patients. Subsequent Finnegan scores were ≤ 7 at all times (median 4, range 1 to 7). Two patients required a repeat of the loading dose and an increase of the infusion to 0.7 μg/kg/hr. These two patients had received higher doses of fentanyl than the other five patients (8.5 ± 0.7 versus 4.6 ± 0.5 μg/kg/hr, $p < 0.0005$). No adverse hemodynamic or respiratory effects related to dexmedetomidine were noted.

This report involves the largest cohort of patients to receive dexmedetomidine in the treatment of withdrawal following opioid and benzodiazepine sedation during mechanical ventilation. We conclude that dexmedetomidine offers a viable option for such issues in the pediatric intensive care unit (PICU) setting.

Key words: dexmedetomidine, pediatric, opioid, opioid withdrawal

INTRODUCTION

Given the potential for long-term consequences of both physical and emotional pain, there is now an appropriately heightened awareness of the need to provide analgesia, sedation, and anxiolysis during acute illness, particularly in children. As a result of these concerns, benzodiazepines and opioids are often administered to provide sedation and analgesia in the pediatric intensive care unit (PICU) setting. With prolonged administration, tolerance and physical dependence may develop, and if these agents are abruptly discontinued withdrawal symptoms are likely to occur.[1] Options for the management of these problems include slowly tapering intravenous administration, conversion to subcutaneous administration, or switching to oral medications.[1,2] Although these strategies may prevent withdrawal, therapies are also needed for patients manifesting acute signs and symptoms of withdrawal.

The α_2-adrenergic agonist dexmedetomidine (Precedex®, Hospira, Lake Forest, IL) was first released for clinical use in December 1999. It is currently FDA approved for sedation of adults during mechanical ventilation for up to 24 hours. In addition to its use for sedation during mechanical ventilation, there are anecdotal reports regarding its use for the treatment of withdrawal in the ICU setting in both adult and pediatric patients.[3-6] We present our experience with the use of dexmedetomidine to treat opioid withdrawal following the prolonged administration of fentanyl for sedation of infants and children during mechanical ventilation.

METHODS

Review of these cases and presentation of these patients was approved by the Institutional Review Board of the University of Missouri. Patients were identified as having received dexmedetomidine for the treatment of opioid withdrawal. Demographic data included age, weight, and gender. Additional data included the duration of the fentanyl infusion, the maximum fentanyl-infusion rate, and Finnegan scores prior to and after the administration of dexmedetomidine. As part of our routine practice, patients who manifest withdrawal are assessed every four to six hours using the Finnegan scoring system to assess the severity of withdrawal and the response to therapy.[7,8] Demographic and other parametric data are presented as the mean ± SD, while nonparametric data (Finnegan scores) are presented as the

median and range. A nonpaired t-test was used to compare the maximum fentanyl-infusion rate in patients who required a repeat bolus dose of dexmedetomidine and an increase in the infusion rate to control withdrawal versus those who did not. A paired t-test was used to compare heart rate, systolic blood pressure (SBP), and respiratory rate before and after the administration of the dexmedetomidine bolus dose.

RESULTS

Seven patients were identified who had received dexmedetomidine to treat opioid withdrawal. The patients ranged in age from three to 24 months (12.4 ± 8.2 months) and in weight from 4.6 to 15.4 kgs (9.9 ± 4.2 kgs). The patients had received a continuous fentanyl infusion, supplemented with intermittent doses of midazolam for sedation, during mechanical ventilation for respiratory failure due either to a primary pulmonary infection or following surgery for congenital heart disease. The patients were breathing spontaneously, having undergone successful tracheal extubation 24 to 48 hours prior to starting dexmedetomidine. The duration of the fentanyl infusion and midazolam administration ranged from four to nine days (5.9 ± 1.7 days). The maximum fentanyl-infusion range was 4 to 9 μg/kg/hr (5.7 ± 1.9 μg/kg/hr). The fentanyl infusion was gradually decreased over 24 to 48 hours in three patients and discontinued without weaning in the other four patients. Supplemental midazolam administration varied from 0.21 to 0.54 mg/kg/day in divided doses (0.37 ± 0.12 mg/kg/day). All seven patients manifested signs and symptoms indicative of severe withdrawal, with a Finnegan score ≥ 12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/hr over five to 10 minutes, followed by an infusion of 0.5 μg/kg/hr. Two patients required a repeat of the loading dose and an increase of the infusion to 0.7 μg/kg/hr. These two patients had received higher doses of fentanyl than the other five patients (8.5 ± 0.7 versus 4.6 ± 0.5 μg/kg/hr, $p < 0.0005$). The signs and symptoms of withdrawal were effectively controlled by dexmedetomidine. Following dexmedetomidine, Finnegan scores were ≤ 7 at all times (median 4, range 1 to 7). No adverse hemodynamic or respiratory effects related to dexmedetomidine were noted. With the bolus dose of dexmedetomidine, the heart rate decreased from 158 ± 12 to 138 ± 9 beats/min, $p = 0.02$, and the respiratory rate decreased from 40 ± 8 to 33 ± 6 breaths/min, $p = 0.0004$. No statistically significant change in SBP was noted (91 ± 11 to 87 ± 9 mmHg). SBP decreased in five patients and increased in two patients following the dexmedetomidine loading dose. No patient manifested a heart rate or SBP below the fifth percentile for age during the use of dexmedetomidine. The dexmedetomidine infusion was decreased in increments of 0.1 μg/kg/hr every 12 to 24 hours. No rebound hypertension was seen with this weaning regimen.

DISCUSSION

Dexmedetomidine is an α_2-adrenergic agonist. Although both dexmedetomidine and clonidine possess specificity for the α_2 versus the α_1 receptor, the specificity is greater with dexmedetomidine (200:1 for clonidine versus 1600:1 for dexmedetomidine).

An additional difference is the shorter half-life of dexmedetomidine (two to three hours) when compared with clonidine (12 to 24 hours), allowing for its titration by continuous infusion and a more rapid reversal of its effects should problems arise. Previous clinical and animal studies have reported the successful use of clonidine to treat withdrawal from various agents, including opioids, cannabinoids, and ethanol.[9-16] Baumgartner and Rowen[9] randomly assigned 50 adults undergoing ethanol withdrawal to receive either transdermal clonidine or chlorodiazepoxide. Therapy was deemed effective with either treatment arm, as no patient developed seizures or progressed to delirium tremens. The group receiving clonidine had a better response to therapy (assessed using the Alcohol Withdrawal Assessment Scale), less anxiety (assessed using the Hamilton Anxiety Rating Scale), and improved control of heart rate and blood pressure. Dobrydnjov et al.[10] evaluated the efficacy of either intrathecal or oral clonidine to attenuate postoperative alcohol withdrawal syndrome in 45 alcohol-dependent patients. The patients had undergone transurethral resection of the prostate, performed using spinal anesthesia. The patients were randomized to receive preoperative oral diazepam, intrathecal clonidine, or oral clonidine. Either oral or intrathecal clonidine was superior to oral diazepam. Twelve patients in the diazepam group had symptoms of alcohol withdrawal, compared with two in the intrathecal-clonidine group and one in the oral-clonidine group. Additionally, two patients receiving diazepam went on to develop delirium tremens. Patients in the oral diazepam group also manifested greater hemodynamic instability, with tachycardia and elevated blood pressure developing 24 to 72 hours after surgery.

Animal data also support the potential role of dexmedetomidine to treat withdrawal phenomena. Riihioja et al.[17-20] demonstrated that dexmedetomidine effectively controls ethanol withdrawal behavior, manifesting as hyperactivity of the sympathetic nervous system, in laboratory animals. To date, though, the use of dexmedetomidine to treat substance withdrawal in the clinical arena remains anecdotal (Table 1).[3-6,21] Our current cohort of seven patients is the largest series to date regarding the use of dexmedetomidine to control withdrawal behavior in the ICU population. We postulated

Table 1. Anecdotal reports of dexmedetomidine to control withdrawal in the ICU

Author	Patient demographics	Dexmedetomidine dosing regimen
Maccioli GA[3]	The first patient was a 49-year-old woman with a history of alcohol and cocaine use who presented with severe agitation.	Dexmedetomidine was administered as a loading dose of 1 μg/kg over 20 minutes, followed by an infusion of 0.7 μg/kg/hr. The dexmedetomidine was continued for 36 hours and effectively controlled the patient's agitation and autonomic hyperactivity.
	The second patient was a 54-year-old man who was recovering from multiple-system organ failure and a six-week ICU course, during which time he had received large doses of opioids and benzodiazepines.	Dexmedetomidine, administered as a bolus of 1 μg/kg followed by an infusion of 0.7 μg/kg/hr, effectively controlled the withdrawal behavior. Dexmedetomidine was weaned over a seven-day period.
Multz AS[4]	Thirty-three-year-old with a history of multiple substance abuse (cocaine, ketamine, cannabinoids, and benzodiazepines) with septic shock and multiple-system organ failure, which required prolonged mechanical ventilation and sedation with benzodiazepines, propofol, and opioids. Withdrawal behavior (tachypnea, fever, tachycardia) developed despite propofol (50 μg/kg/min) and a fentanyl patch.	Dexmedetomidine was started at 0.7 μg/kg/hr without a loading dose. The use of dexmedetomidine allowed for the tapering and discontinuation of the other medications. The dexmedetomidine was continued for a total of five days and then was weaned over a 48-hour period.
Finkel JC, Elrefai A[5]	Eight-month-old infant with Hurler syndrome who had required prolonged sedation during mechanical ventilation. The patient had undergone tracheostomy, and the goal was to discontinue use of benzodiazepines and opioids. Using a Bispectral Index monitor, the authors titrated the dexmedetomidine infusion after the midazolam and fentanyl infusions were discontinued.	Dexmedetomidine in a dose of 0.2 to 0.7 μg/kg/hr for seven days and then tapered over a 24-hour period allowed for withdrawal of benzodiazepines and opioids.
Baddigam K et al.[6]	Seventeen-year-old with infected aortic valve. History of cannabinoid, tobacco, ethanol, and other substance abuse. Manifested withdrawal symptoms during postoperative period.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr, effectively controlled withdrawal behavior (diaphoresis, agitation, tachycardia, and hypertension).
	Four-month-old infant exhibiting withdrawal behavior after use of fentanyl for sedation during mechanical ventilation following repair of congenital heart disease.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr, effectively controlled the withdrawal behavior. Infusion weaned over 48 to 72 hours.
	Fifty-five-day-old infant exhibiting withdrawal behavior after the use of fentanyl for sedation during mechanical ventilation following palliation of congenital heart disease.	Dexmedetomidine, administered as a loading dose of 0.5 μg/kg followed by an infusion of 0.25 μg/hr, effectively controlled the withdrawal behavior.
Finkel et al.[21]	Two pediatric patients (six-month-old and seven-year-old) who exhibited withdrawal behavior related to the prolonged administration of opioids and benzodiazepines following cardiac transplantation.	Dexmedetomidine, administered as a loading dose of 1 μg/kg followed by an infusion of 0.8 to 1.0 μg/kg/hr, effectively controlled the withdrawal behavior. Dexmedetomidine infusions administered and then weaned for a total duration of use of eight and 16 days in the two patients, respectively.

that dexmedetomidine was a viable option in such patients for several reasons: 1) both animal studies and anecdotal clinical reports have demonstrated its efficacy in treating withdrawal; 2) when compared to clonidine, dexmedetomidine has a shorter half-life, thereby allowing for ease of titration when administered by continuous infusion and adjustments as needed to control withdrawal behavior; 3) there is increasing experience with the use of dexmedetomidine in various clinical scenarios in the pediatric population; 4) dexmedetomidine has been shown to have limited effects on respiratory function, which is helpful when trying to control withdrawal behavior in patients like those in the current series who have recently been extubated; and 5) dexmedetomidine effectively controls withdrawal behaviors regardless of the withdrawn agent in question. Although the majority of our patients' issues were likely related to opioids, they were all also receiving frequent intermittent doses of benzodiazepines. In such instances, it is clinically useful to have a single agent that can be used when withdrawal may be related to more than one drug or medication.

Dexmedetomidine can have deleterious effects on both hemodynamic and respiratory function. Using CO_2 response curves, Belleville et al.[22] reported a slope depression of the CO_2 response curve and a decrease in minute ventilation at an end-tidal concentration ($ETCO_2$) of 55 mmHg following a bolus dose of 2 μg/kg. Hemodynamic effects have included hypotension, hypertension, and bradycardia, which occur most commonly with the loading dose.[23-25] Although in most cases such problems have been clinically insignificant, given the potential impact on the critically ill ICU patient the use of dexmedetomidine mandates close monitoring of hemodynamic and respiratory function.

α_2-adrenergic agonists have been shown to be effective in the treatment of withdrawal from various substances, including cannabinoids, alcohol, benzodiazepines, and opioids. The current cohort of patients adds to the increasing number of patients reported on in the literature in whom dexmedetomidine has been used to successfully treat drug and medication withdrawal. Our dosing regimen included an initial bolus dose of 0.5 μg/kg followed by an infusion of 0.25 μg/kg/hr. Repeat of the bolus dose and an increase of the infusion were required in two patients who had received larger doses of fentanyl. In our cohort, the dexmedetomidine infusion was decreased in increments of 0.1 μg/kg/hr every 12 to 24 hours.

Drawbacks of the current study include the use of the Finnegan score for a non-neonatal population and the study's retrospective design. Due to the lack of other withdrawal scores, our practice has been to use the Finnegan score not necessarily to define the severity of withdrawal but, more importantly, to provide an easy checklist to identify withdrawal behaviors and, by repeated monitoring over time, to attempt to gauge the efficacy of therapeutic interventions. Although retrospective, we hope that these preliminary data will provide the impetus for the performance of prospective clinical trials. Ideally, such trials would acquire data that we were unable to obtain in our retrospective study, such as the specific withdrawal symptoms present in each individual and which symptoms were most improved by treatment. It would also be practical to explore whether variations in age or individual opioid/benzodiazepine doses had any impact on the treatment's effectiveness. Questions to be answered may include whether dexmedetomidine should be used to treat withdrawal once it occurs or whether it has a role as a prophylactic agent in high-risk patients. Although our cohort was sedated with a fentanyl infusion, all patients also received intermittent doses of midazolam for supplemental sedation; it would be helpful to determine the efficacy of dexmedetomidine in treating/preventing withdrawal in various pharmacologic regimens for sedation involving opioids, benzodiazepines, and barbiturates, and perhaps even propofol-based regimens. More information is also needed to determine the appropriate dosing regimens and effective weaning patterns.

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Capnography monitoring during opioid PCA administration

Rob Hutchison, PharmD

INTRODUCTION

Opioid administration by patient-controlled analgesia (PCA) apparatus in hospital settings is standard therapy during the acute postoperative period. Whether medication is taken intravenously (IV) or using the new method of transdermal iontophoretic PCA administration, some patients require very close monitoring for respiratory depression.[1] Currently, hospitals use pulse oximetry to spot-check respiratory status, but with the recent availability of capnography monitoring in general care units, an evaluation of this new respiratory assessment is warranted. The goal of this article is to describe the use of capnography during safe and effective administration of opioids by PCA in spontaneously breathing (nonventilated) patients.

RESPIRATORY DEPRESSION

Respiratory depression is a consistent effect of all opioids and is usually related to excessive doses in opioid-naïve individuals, but it may occur with therapeutic doses. Alveolar gas exchange is diminished by effects on respiratory rate, minute volume, and tidal exchange. The decreased responsiveness of brainstem respiratory neurons to carbon dioxide (CO_2) is dose related. With sufficient suppression of CO_2 responsiveness, hypoxia may be the only stimulus for respiration, initiated through chemoreceptors in the aortic arch and carotid body. In such instances, administration of supplemental oxygen and the subsequent maintenance of oxygen saturation may completely suppress the breathing reflex.

Although IV PCA is a well-accepted means of controlling postoperative pain, there are many logistical steps and processes that may lead to errors resulting in respiratory depression. A meta-analysis of 116 studies found the incidence of respiratory depression during acute opioid therapy to be 1.1 percent.[2] Historically, reported medication errors have been an underestimation of the true incidence rate of opioid-induced respiratory depression.[3] The errors related to IV PCA may include programming errors, patient and family tampering, and device malfunctions.[4,5] MEDMARX, a national, internet-accessible database that hospitals and healthcare systems use to track and trend adverse drug reactions and medication errors, reported that four of the top 10 medications resulting in harm or fatality are opioids.[6] The use of IV PCA is associated with a 3.5-fold greater risk of patient harm compared to other IV medications. The most common types of errors involving IV PCA pumps submitted to MEDMARX^{SM} were improper dose and/or quantity of analgesic, accounting for nearly 38.9 percent (1,873 out of 5,110) of all errors examined; other common errors included unauthorized drug(s) (18.4 percent), omission errors (17.6 percent), and prescribing errors (9.2 percent).[7]

Because adverse events can arise quickly and require immediate intervention, adequate patient monitoring is essential in minimizing patient harm. Reversing the effects of opioid overdose may require extensive medical intervention and naloxone administration, resulting in increased hospital stays.[2,8,9] A change in respiratory status is a primary assessment tool for determining potential adverse events during opioid administration. Assessment of sedation level, while a helpful indicator of a potential adverse event, does not provide sufficient information on respiratory status. Intermittent nurse assessments may stimulate an oversedated patient, leading to a falsely high level of consciousness and providing an inaccurate estimation of true respiratory status.[10]

Currently, pulse oximetry is used in most US hospitals on a continuous or intermittent "spot-check" basis to measure arterial oxygen saturation (SpO_2). However, case reports suggest that using pulse oximetry alone can lead to an inaccurate assessment of a patient's condition, especially when supplemental oxygen is being used.[11,12] These case reports show that even with a low respiratory rate, SpO_2 may be maintained, especially with supplemental oxygen, resulting in an erroneous assessment of respiratory status.[12]

CAPNOGRAPHY

The American Society of Anesthesiologists has described ventilation and oxygenation as separate but

related physiological processes, and the assessment of oxygenation by pulse oximetry is not a substitute for monitoring ventilatory function by capnography.[13]

Capnography measures end-tidal carbon dioxide ($EtCO_2$) and monitors quality of respiration, changes in respiratory rate, levels of exhaled CO_2, and apneic events. Capnographic monitoring may anticipate a patient's desaturation by warning of a decrease in respiratory rate and rise in $EtCO_2$. In a procedural sedation study of $EtCO_2$ monitoring, capnography captured 100 percent of incidences of respiratory distress, while pulse oximetry captured only 33 percent.[14] Case studies have shown that early detection of declining respiratory status, before a patient goes into respiratory depression, may prevent harmful adverse events and avert transfer to an intensive care unit.[12,15,16]

In the past, continuous capnography has been limited to critical care areas and monitored units because of the requirements for intubation and heavy, complex devices. Now, there are handheld devices and portable modular units that measure SpO_2 and $EtCO_2$ in spontaneously breathing patients in the general care nursing units. The $EtCO_2$ disposable nasal cannulas are used to sample the exhaled breath, as well as to administer supplemental oxygen.

CONCLUSION

Opioids are associated with high error rates, which may result in harmful events. The clinical application of capnography in spontaneously breathing patients receiving opioids by PCA and supplemental oxygen may reduce harmful events during opioid administration. Monitoring of respiratory status in patients receiving supplemental oxygen by pulse oximetry and/or manual count of respiratory rate may provide inaccurate assessments. The availability of lightweight, handheld capnography devices and small, modular capnography monitors for general care units warrants evaluation of such instruments' efficacy in clinical studies.

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ORIGINAL ARTICLE

Single-dose extended-release epidural morphine for pain after hip arthroplasty

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ABSTRACT

This randomized, double-blind study compared the safety and efficacy of a new single-dose extended-release epidural morphine (EREM) formulation for postoperative pain following hip arthroplasty. Patients were administered a single dose of EREM (10, 20, or 30 mg, n = 93) or a single epidural dose of placebo (n = 27) before surgery and general anesthesia. Following surgery, patients had access to fentanyl with the use of intravenous patient-controlled analgesia. Postoperative fentanyl use, time to first postoperative fentanyl use, pain intensity at rest and with activity, patient ratings of pain control, and adverse events were recorded. Compared with placebo-treated patients, single-dose EREM patients used less total supplemental fentanyl ($p \leq 0.049$), had a longer time to first fentanyl use ($p < 0.001$), and were less likely to use any supplemental fentanyl ($p \leq 0.042$). EREM-treated patients reported lower pain intensity for up to 48 hours postdose compared with placebo-treated patients. Single-dose EREM was effective for postoperative pain relief for up to 48 hours following hip arthroplasty, with a safety and tolerability profile consistent with that of other epidurally administered opioids.

Key words: single-dose extended-release epidural morphine, postoperative pain management, orthopedic surgery

INTRODUCTION

Major orthopedic surgery of the lower extremities is accompanied by significant postoperative pain, as well as increased risks of serious medical morbidities.[1-4] Effective postoperative pain management following orthopedic surgery often requires opioid analgesics.[5] The perioperative administration of opioid analgesics can reduce postsurgical pain,[6,7] ameliorate postoperative complications,[8] improve patient mobilization,[9] shorten hospitalization stays,[9-11] and reduce hospital costs.[11]

Because a single epidural injection of morphine typically relieves pain for 24 hours or less,[12,13] control of postoperative pain beyond 24 hours often requires continuous infusion through an indwelling epidural catheter. Following major orthopedic surgery of the lower extremities,[14] the placement and maintenance of indwelling epidural catheters in anticoagulated patients can lead to serious complications, such as the development of an epidural hematoma.[15,16] This is of particular concern because prophylactic anticoagulation therapy is prevalent among patients undergoing major orthopedic procedures, such as joint replacement.[15,16]

The need for effective, extended analgesia with epidural morphine, without the complications stemming from indwelling catheters, provided the basis for the development of extended-release epidural morphine (EREM; brand name DepoDur™, Endo Pharmaceuticals Inc., Chadds Ford, PA). EREM is a single-dose extended-release epidural formulation of morphine developed with the DepoFoam™ (SkyePharma, Inc., San Diego, CA) delivery system. Following epidural administration, single-dose EREM remains within the epidural space, gradually releasing morphine; this produces low, centrally localized systemic drug concentrations.[17,18] In preclinical studies, the DepoFoam delivery system allowed for a slow release of morphine following a single dose of EREM to provide significant antinociceptive activity for up to 3.4 days; significant plasma and cerebrospinal fluid morphine concentrations were maintained longer for EREM compared with conventional morphine sulfate.[19]

The characteristics of EREM suggest that it might provide extended periods of analgesia in humans following single epidural injection, thus reducing the need for indwelling epidural catheters. Previous studies have examined EREM for postoperative pain management following abdominal surgery,[20] elective cesarean section,[21] and hip arthroplasty[22] at dosages ranging from 5 to 30 mg. This study was designed to evaluate the safety and efficacy of

a single dose of EREM at three dosages (10, 20, and 30 mg) for the management of postoperative pain in patients undergoing hip arthroplasty and to characterize its effect on patient-controlled analgesia (PCA) use.

METHODS

Patients

Patients scheduled for hip arthroplasty (including primary total arthroplasty, hemiarthroplasty, or revisions of previous hip arthroplasty) under general anesthesia were enrolled at 16 clinical sites in the United States. Men or women 18 to 75 years of age, with weight > 45 kg and American Society of Anesthesiologists Physical Status 1, 2, or 3, were included. Women of childbearing age were required to have a negative pregnancy test before enrollment. Eligible patients were able to use a PCA device and agreed to remain in the hospital for a minimum of 72 hours following surgery. Patients with a documented allergy to study medications, hepatic or renal dysfunction, morbid obesity, or laboratory evidence of coagulopathy were excluded.

All eligible patients were required to provide written informed consent. The protocol and informed consent form were reviewed and approved by the Institutional Review Board for each study center. This study was performed in accordance with the principles established by the Declaration of Helsinki.

Study design

This phase II, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study evaluated single-dose EREM 10, 20, and 30 mg vs. placebo (DepoFoam without morphine sulfate, suspended in saline). The dosages of single-dose EREM were selected based on a previous Phase I dose-ranging study (SkyePharma Inc., Data on File, 2003). Patients were randomized in a 1:1:1:1 ratio to one of the four treatment arms; after a patient's eligibility was confirmed, the randomization envelope (provided by the study sponsor) containing the study medication was opened by an unblinded pharmacist. All study-site personnel involved in observing and reporting patient responses, including the anesthesiologist, remained blinded to the assigned treatment groups.

All study drugs were diluted to a volume of 5 mL with 0.9 percent normal saline. Using a standard loss-of-resistance technique, an epidural needle or catheter was inserted preoperatively into a lumbar vertebral interspace. If an epidural catheter was used, it was then advanced 3 to 4 cm into the epidural space. To rule out improper placement of the epidural needle or catheter, that is, inadvertent intravascular or intrathecal injection, a test dose (lidocaine [2 percent] with epinephrine [1:200,000]) was administered. Patients were observed for hypertensive and/or tachycardic response suggestive of an intravascular injection. In addition, patients were examined for motor weakness suggestive of an intrathecal injection of lidocaine. Fifteen minutes were allotted for patient observation between administration of the test dose and beginning of procedure. Immediately before general anesthesia and within 30 minutes of surgery, a single bolus of study drug was administered through the epidural needle or catheter, at the discretion of the anesthesiologist and/or study investigator, and then the epidural needle or catheter was removed.

Intraoperative general anesthesia was limited to intravenous (IV) etomidate, thiopental, or propofol for induction, fentanyl, midazolam, oxygen, isoflurane, and a muscle relaxant. Intraoperative fentanyl was limited to a maximum of 500 μg per patient, and bolus administration of fentanyl was prohibited near the end of surgery.

Analgesia

Following surgery and on first request for pain medication, patients were given an initial dose of IV fentanyl (25 μg); if necessary, the dose was repeated until analgesic stability was achieved. Subsequently, each patient was given IV fentanyl through a PCA device programmed to deliver 10 to 20 μg/dose, with a lockout time of six minutes. The dose could have been increased or supplemented with additional doses, or, if required, a basal rate could have been added to control pain. Opioids other than fentanyl and all other analgesic or anti-inflammatory agents were prohibited for the first 48 hours after study dose. Aspirin in a maximum dosage of 325 mg/24 hours or acetaminophen in a maximum dosage of 1000 mg/24 hours were permitted to inhibit platelet aggregation or for fever or headache, respectively. After 48 hours, alternate opioid therapies were permitted at the investigator's discretion. Naloxone was permitted for treatment of opioid-related adverse events (AEs).

Efficacy assessments

Total fentanyl use through 24 and 48 hours postdose, fentanyl consumption for each successive six-hour period throughout the first 48 hours following study medication dosing, time from study drug administration to first fentanyl use, and the proportion of patients who required no postoperative fentanyl were recorded. Pain intensity was assessed on first request for supplemental pain medication and at regular intervals postdose (two, three, four, six, eight, 10, 12, 18, 24, 30, 36, 48, and 72 hours) using both the 0- to 100-mm

Table 1. Patient demographics

Demographic	Placebo (n = 27)	Single-dose EREM			
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	p values
Sex					0.871*
Men	12 (44.4)	20 (57.1)	17 (53.1)	13 (50.0)	
Women	15 (55.6)	15 (42.9)	15 (46.9)	13 (50.0)	
Race					0.514*
White	22 (81.5)	25 (71.4)	27 (84.4)	22 (84.6)	
Black	5 (18.5)	8 (22.9)	3 (9.4)	3 (11.5)	
Hispanic	0	1 (2.9)	2 (6.3)	1 (3.8)	
Other	0	1 (2.9)	0	0	
Age (y), mean (SEM)	57.5 (2.69)	54.1 (2.01)	56.4 (2.59)	54.6 (2.67)	0.079†
≥ 65 y, n (percent)	11 (40.7)	8 (22.9)	11 (34.4)	8 (30.8)	0.381*
Weight (kg), mean (SEM)	78.6 (3.27)	79.6 (2.12)	81.6 (3.07)	82.6 (3.98)	0.604†
Height (cm), mean (SEM)	170.0 (1.75)	171.0 (1.58)	169.3 (1.90)	170.6 (1.78)	0.938†
ASA Class					
1	4 (14.8)	6 (17.1)	5 (15.6)	3 (11.5)	
2	21 (77.8)	22 (62.9)	18 (56.3)	19 (73.1)	
3	2 (7.4)	7 (20.0)	9 (28.1)	4 (15.4)	

ASA, American Society of Anesthesiologists; EREM, extended-release epidural morphine; SEM, standard error of the mean.
* p value based on Cochran-Mantel-Haenszel test for treatment mean row scores (stratified by study site). p value for race based on two categories (white, black); † p value based on treatment effect in a two-way analysis of variance with main effects treatment group and study site.

Visual Analog Scale (VAS; 0 = no pain and 100 = most severe pain possible) and a 4-point categorical scale (CAT; from 0 = none to 3 = severe). Pain intensity was assessed on both scales at rest and with activity; activity was defined as sitting up in bed at a 30° to 90° angle. Patients provided global ratings of their study medication (at 24, 48, and 72 hours) by responding to the question, "How would you rate the pain medication overall?" using a 5-point CAT (poor, fair, good, very good, or excellent). The time to any prescribed physical therapy, such as standing or walking, was recorded.

Safety

Objective safety measurements included vital signs and clinical laboratory results, and clinical assessments were performed by study personnel throughout 72 hours postdose. In general, classification and treatment of AEs were left to each investigator's judgment. When AEs were identified, standard definitions were provided for assigning an intensity (mild, moderate, and severe) and causality AEs. Guidelines stipulated that persistent hypoventilation was to be treated with naloxone, pruritus with appropriate non-narcotic

Table 2. Mean (SEM) total fentanyl use (μg) after study drug dose					
Time postdose	Placebo (n = 28*)	Single-dose EREM			
		10 mg (n = 34)	20 mg (n = 32)	30 mg (n = 26)	p values
					Overall treatment effect†‡
0 to 24 hours	1,548 (180)	599 (109)	396 (63)	361 (61)	< 0.001
24 to 48 hours	885 (129)	722 (150)	510 (115)	291 (113)	= 0.023
0 to 48 hours	2,433 (291)	1,321 (243)	905 (143)	652 (151)	< 0.001

EREM, extended-release epidural morphine; SEM, standard error of the mean; * One patient randomized to the placebo group received 10 mg EREM due to a pharmacy error and was analyzed as part of the placebo group for the primary endpoint; † Two-way analysis of variance in which main effects are treatment group and study site, all pairwise comparisons with placebo were significant ($p \leq 0.049$) with the exception of 10 and 20 mg EREM for the 24- to 48-hour interval; ‡ $p < 0.001$ for dose response based on Jonckheere-Terpstra test.

medication, and nausea and/or vomiting with non-narcotic antiemetics.

Physical examinations were performed, and blood pressure, heart rate, respiratory rate, hemoglobin oxygen saturation, and capnometry (end-tidal CO_2) were recorded at screening, predose, and/or postdose at regular intervals (at the first 30 minutes, hourly through the first 12 hours, and at 18, 24, 30, 36, 48, and 72 hours). Arterial blood gas measurements were taken if respiratory rate fell below eight breaths/minute, if oxygen saturation on 2 L/minute was continuously lower than 90 percent, or end-tidal CO_2 tension was > 50 mm Hg for two consecutive measurements. Female patients of childbearing potential received a pregnancy test at screening, and hematology, serum chemistry assessments, and urinalysis were performed at screening and 48 hours postdose. Electrocardiogram monitoring was performed predose, continuously throughout surgery, and at 0.5, one, 1.5, and two hours postdose.

Statistical methods

All patients who received any study drug were included in the safety and efficacy analyses. The study was designed to enroll 30 patients in each treatment group to detect a treatment difference of 410 μg in 24-hour fentanyl usage. For the primary endpoint, the sample size calculation was based on a 50 percent reduction in 24-hour fentanyl usage assuming a placebo mean of 820 μg fentanyl, using a standard deviation of 490 μg, $\alpha = 0.05$ (two-tailed) and 89 percent power.

Statistical tests were two-tailed except for dose-response analysis and were performed at a 0.05 significance level, except for total fentanyl use through 48 hours postdose, which was set at 0.049 based on a Bonferroni inequality procedure. Measures of analgesia based on fentanyl usage and pain intensity (VAS) used a two-way analysis of variance (ANOVA) with treatment group, study site, and treatment-group-by-study-site interaction included in the model; Dunnett's test was used to compare each dose of EREM with placebo if the overall ANOVA model was significant. The dose response for total fentanyl use through 48 hours postdose was tested using the Jonckheere-Terpstra test.[23] Analysis of covariance analyzed the effect of age or weight covariates on postoperative fentanyl use. Median time-to-event analyses for time to first postoperative opioid pain medication were calculated from the Kaplan-Meier product limit estimates, with p values being calculated using a log-rank test for equality. For CAT evaluations and overall medication ratings, the Cochran-Mantel-Haenszel test was used to compare treatment effects.

Safety data were summarized using descriptive statistics when appropriate. The incidence of AEs among treatment groups was compared using the Fisher exact or chi-square test.

RESULTS

Patient characteristics

A total of 126 patients were randomized to receive study drug. One hundred twenty patients were administered single-dose EREM 10, 20, or 30 mg or placebo (n = 35, n = 32, n = 26, and n = 27, respectively) (Table 1). Six patients were not included in the safety and efficacy analysis owing to ineligibility and noncompliance. None received any doses of study drugs.

Patient demographics and baseline characteristics were similar (Table 1). The major indication for surgery was degenerative hip disease (89 percent, 107/120 patients), and

Table 3. Time to first fentanyl use					
Time	Placebo (n = 27)	Single-dose EREM			p values*
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	
Median time (h) between study drug and first postoperative fentanyl use	3.2	13.5	24.8	16.1	< 0.001
95 percent CI for median	(2.5, 3.8)	(4.1, 25.1)	(17.3, 30.6)	(9.8, 39.6)	
Median time (h) between recovery room arrival and first postoperative fentanyl use	0.3	10.0	21.1	12.8	< 0.001
95 percent CI for median	(0.2, 0.4)	(0.8, 20.7)	(14.8, 28.0)	(4.0, 36.1)	
EREM, extended-release epidural morphine; CI, confidence interval; * p values for time to first postoperative fentanyl use are based on log-rank test for equality of product-limit survival curves.					

primary total arthroplasty was the most common procedure (72 percent, 86/120 patients). The mean duration of surgery was 2.2 hours (range one to six hours).

Efficacy

Fentanyl use. Mean total postoperative fentanyl usage from 0 to 24, 24 to 48, and 0 to 48 hours significantly decreased in a dose-related fashion with increasing dose of EREM ($p < 0.001$ dose response) (Table 2). Figure 1 illustrates the cumulative fentanyl usage throughout the 48-hour postoperative period. Fentanyl use by placebo-treated patients was consistently higher than by single-dose EREM patients, whereas the 20 and 30 mg single-dose EREM groups used the smallest amount of supplemental fentanyl (Table 2). Across all groups, patients ≥ 65 years old consistently used less total fentanyl than patients < 65 years old through the 24 hours following surgery (Figure 2).

Time to first postoperative fentanyl use among single-dose EREM-treated patients was significantly longer than among placebo-treated patients ($p < 0.001$ overall treatment difference) (Table 3). Through 24 and 48 hours following surgery, a larger percentage of patients in the single-dose EREM groups did not use fentanyl, compared with patients in the placebo group (33.3 percent vs. 3.7 percent, $p = 0.001$ at 24 hours; 15.0 percent vs. 3.6 percent, $p = 0.042$ at 48 hours).

Pain intensity evaluations. For up to 48 hours postdose, patients receiving EREM reported low pain intensity scores as measured by VAS (Figures 3 and 4) and CAT (data not shown). Placebo-treated patients had significantly higher pain intensity scores at rest and during activity, as measured by the VAS (Figures 3 and 4) and CAT, than EREM-treated patients from four through 18 hours ($p = 0.003$ at each time point). The single-dose EREM groups had significantly lower resting CAT scores at 24 hours compared with the placebo group (0.6 to 0.9 vs 1.1, $p = 0.032$). From four to 18 hours postdose, 3 percent to 15 percent of the EREM-treated patients reported moderate to severe pain at rest, whereas 41 percent to 63 percent of placebo-treated patients reported moderate to severe ratings of pain at rest ($p < 0.001$ for comparison of mean CAT scores at rest).

Patient ratings of study medications. At 24 and 48 hours postdose, patients receiving single-dose EREM rated their study medications significantly more favorably than those receiving placebo ($p < 0.001$ and $p = 0.021$, respectively). Approximately 55 to 75 percent of EREM-treated patients rated their study medication "very good" or "excellent," compared with 37 percent of placebo-treated patients (Figure 5).

Safety

The most common treatment-related AEs across EREM groups were pruritus (67 percent), nausea (66 percent), vomiting (46 percent), hypoxia (32 percent), and urinary retention (25 percent) (Table 4). The onset of opioid-related AEs primarily occurred before 24 hours postdose; the majority were mild, with less than 4 percent rated severe. Laboratory and chemistry measurements showed no consistent, clinically significant drug-related abnormalities.

Adverse events related to respiratory function in all patients occurred within 48 hours postdose; the majority occurred within the first 24 hours after dosing, and only three patients had decreases in respiratory function 24 to

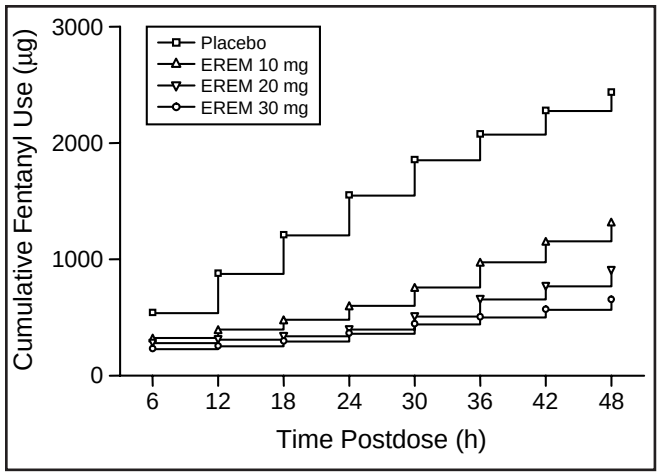

Figure 1. Cumulative fentanyl use over time postdose. Cumulative fentanyl use in six-hour intervals is plotted against the upper boundary for each interval. EREM = extended-release epidural morphine.

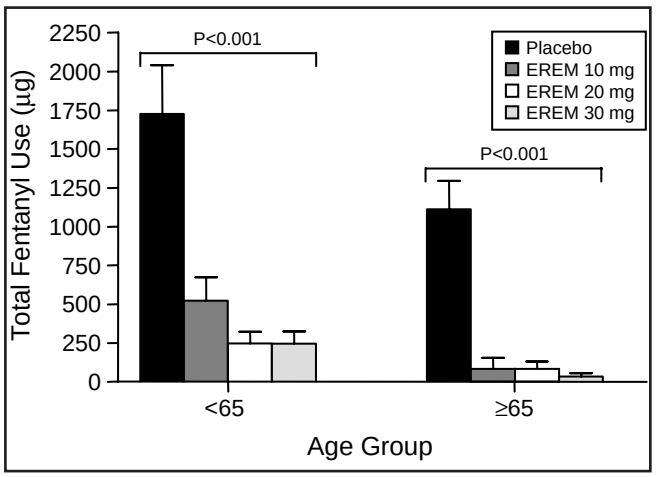

Figure 2. Total fentanyl use through 24 hours following surgery for < 65- and > 65-year age groups. Two-way analysis of variance in which main effects are treatment group and study site.

48 hours postdose (patient in each of the placebo and 10 and 30 mg single-dose EREM groups). Decreased hemoglobin oxygen saturation was recorded more frequently in the single-dose EREM groups (34 percent, 31 percent, and 58 percent for 10, 20, and 30 mg, respectively) than in the placebo group (7 percent) (Table 5). Most alterations of respiratory function were rated mild and resolved spontaneously or with oxygen therapy. Five cases of severe respiratory depression occurred 2.5 to five hours postdose and resolved with oxygen therapy and/or naloxone treatment (Table 6). Naloxone treatment as intermittent boluses or continuous infusion was administered to four patients for a duration of 20 to 62 hours, until resolution of the last respiratory event.

Serious AEs occurred in five single-dose EREM-treated patients, three patients in the 10 mg group and two patients in the 30 mg EREM group. One serious AE was considered possibly related to study medication. The case involved a 63-year-old woman who received 10 mg of single-dose EREM and developed somnolence and required a nasopharyngeal airway. She also developed oliguria and tachycardia during the postoperative period

Table 4. Number (percent) of patients with treatment-related adverse events*

Adverse event, n (percent)	Placebo (n = 27)	Single-dose EREM			
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	All (n = 93)
Constipation	1 (4)	6 (17)	7 (22)	6 (23)	19 (20)
Hypoventilation	1 (4)	4 (11)	7 (22)	4 (15)	15 (16)
Hypoxia	2 (7)	8 (23)	11 (34)	11 (43)	30 (32)
Nausea	9 (33)	20 (57)	20 (62)	21 (81)	61 (66)
Pruritus	6 (22)	22 (63)	21 (66)	19 (73)	62 (67)
Somnolence	2 (7.4)	5 (14)	8 (25)	5 (19)	18 (20)
Urinary retention	3 (11)	7 (20)	7 (22)	9 (35)	23 (25)
Vomiting	4 (15)	18 (51)	12 (38)	13 (50)	43 (46)

EREM, extended-release epidural morphine; * Adverse events reported more frequently by EREM than placebo and expected with opiate use.

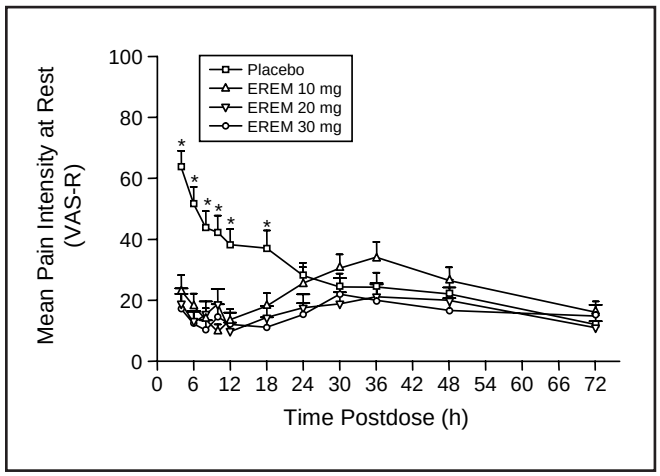

Figure 3. Pain intensity evaluation at rest over time (VAS-R). VAS-R = Visual Analog Scale-Rest; EREM = extended-release epidural morphine. * p = 0.003 at each time point from three through 18 hours.

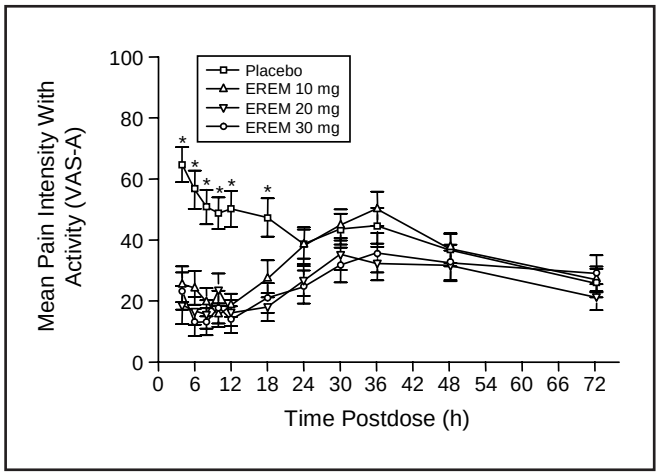

Figure 4. Pain intensity evaluation with activity over time (VAS-A). VAS-A = Visual Analog Scale-Activity; EREM = extended-release epidural morphine. * p ≤ 0.002 at each time point from four through 18 hours.

and was treated with IV fluids and a blood transfusion. All events resolved completely, and the patient was discharged four days after receiving study drug. The remaining four serious AEs were fat embolism syndrome, a dislocated right hip, non-Q-wave myocardial infarction, and an infection of the hip. No patients terminated the study due to an AE, and there were no deaths.

DISCUSSION

In the present study of patients undergoing hip arthroplasty, single-dose EREM provided dose-related efficacy in the management of postoperative pain for up to 48 hours postdose. The improved analgesia among EREM-treated patients was reflected in the reduced use of supplemental opioids and the longer time to first postoperative fentanyl use compared with placebo. The efficacy of single-dose EREM was also supported by the significantly greater proportion of EREM-treated patients requesting no supplemental postoperative fentanyl for pain control compared with placebo-treated patients. Although patients were instructed to self-titrate supplemental IV fentanyl to optimize pain relief, placebo-treated patients frequently reported moderate to severe pain reflecting undertreatment of pain, whereas most EREM-treated patients reported low pain intensity for up to 48 hours postdose. In this study, patients' ratings of pain reflected a combination of responses to study drug and supplemental pain medications. Single-dose EREM patients experienced predominantly mild pain, and when asked to rate their pain medication, they reported higher satisfaction with their study drug than did placebo-treated patients. This is consistent with previous studies that have evaluated single-dose EREM for the management of postoperative pain following hip surgery and abdominal surgery and reported higher patient ratings of pain control compared

Table 5. Alterations in respiratory function within 0 to 48 hours

Variable n (percent)	Placebo (n = 27)	Single-dose EREM			
		10 mg (n = 35)	20 mg (n = 32)	30 mg (n = 26)	All (n = 93)
Respiratory rate < eight breaths/minute	10 (37.0)	15 (42.9)	17 (53.1)	15 (57.7)	47 (50.5)
End-tidal CO_2 > 50 mm Hg	2 (7.4)	12 (34.3)	10 (31.3)	15 (57.5)	37 (39.8)
SaO_2 < 90 percent	1 (3.7)	4 (11.4)	2 (6.3)	0	6 (6.5)

EREM, extended-release epidural morphine.

Table 6. Patients with respiratory depression rated severe in intensity

Single-dose EREM	Age (y)	Time of onset postdose (h)	Lowest respiratory rate (breaths/min)	Highest end-tidal CO_2 (mm Hg)	Lowest SaO_2 (percent)	Therapy†	Duration of therapy (h)‡
10 mg	63	3.5	10	46	92	Oxygen	24
20 mg	73	5	6	49	93	Naloxone	22
20 mg	58	4	0*	50	94	Naloxone	62
20 mg	72	2.5	8	50	77	Naloxone	46
30 mg	54	3.5	8	56	96	Oxygen and naloxone	20.5

EREM = extended-release epidural morphine; * The zero value noted by telemetry was due to improperly functioning instrumentation; † Naloxone was administered as intermittent boluses or continuous infusion over time; ‡ From time of onset of first episode to resolution of last episode.

with standard epidural morphine sulfate or placebo control.[20,22] The improved patient satisfaction experienced by patients treated with single-dose EREM may indicate that patients are spending less time self-monitoring and self-treating postoperative pain, which may lead to a perception of improved care.

Inadequate pain control during patient mobilization can hinder patient rehabilitation and, consequently, patient recovery.[9,24] In general, PCA with opioids provides adequate pain relief at rest, but its effectiveness with movement has been questioned.[14] In this study, patients treated with single-dose EREM reported improved pain scores at rest and with activity for up to 18 hours postdose compared with placebo. The VAS with activity for all EREM-treated patients remained mild (below 40 mm), with the exception of 30- to 36-hour postdose periods at the 10 mg dose only. In contrast, the placebo-treated patients' VAS with activity remained above 40 mm until 48 hours postdose. Improved pain control at rest and with activity and the ability to deliver EREM without the need for epidural catheters and infusion pumps may lead to improved rehabilitation postoperatively.

In the present study, the AE profile of single-dose EREM was typical of that reported in the published literature in patients undergoing hip replacement surgery with epidural anesthesia and IV opioid administration for postoperative pain management.[25,26] The incidences of vomiting (34 to 55 percent) and pruritus (62 to 73 percent) in EREM-treated patients are similar to those previously reported in patients receiving epidural morphine (50 percent and 77

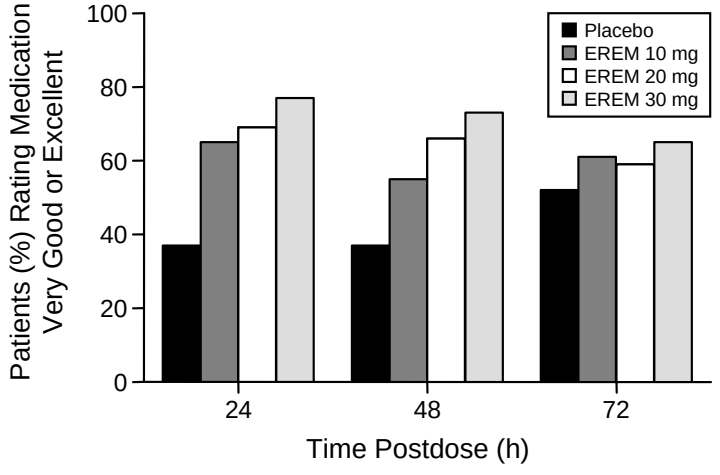

Figure 5. Patients rating pain medication "very good" and "excellent" at 24, 48, and 72 hours postdose. EREM = extended-release epidural morphine.

percent, respectively).[25,26] Although EREM-treated patients experienced a higher incidence of opioid-related AEs compared with placebo-treated patients, the majority (96 percent) of AEs were rated mild or moderate. These results, coupled with the general improvement in pain control, may explain why the majority of EREM-treated patients rated their medication "very good" or "excellent."

The rates of respiratory depression for epidural analgesics vary widely across studies because of differences in the monitoring methodology, the criteria for defining respiratory depression, and the types of analgesic techniques being assessed. When oxygen saturation is used to identify respiratory depression in the current study, the incidence of respiratory depression is 6 percent among EREM-treated patients, whereas the historical rate for epidural analgesics ranges from 5.6 percent to 34.8 percent (mean of 15.1 percent).[27] The rate of severe respiratory depression as indicated by opioid antagonist use observed here (5.4 percent) is higher than that previously published for epidural analgesics (range of 0.1 to 0.2 percent, mean of 0.1 percent).[27] However, given the small number of patients in this study and the variability in monitoring techniques, more controlled trials with well-defined endpoints are required to provide a more accurate assessment of the respiratory depression with EREM administration.

In this study, 57 percent of the respiratory AEs (hypoxia, hypoventilation, and respiratory acidosis) occurred within six hours after EREM administration, 93 percent within 24 hours of administration, and the remaining 7 percent within 24 to 48 hours of administration. Although the majority of AEs occurred within a few hours after study drug administration, all patients who receive EREM should be closely monitored for the first 48 hours, and any patient who develops a respiratory AE should be monitored until the respiratory AE resolves.

Recently, 10 to 20 mg dose levels of single-dose EREM were approved for treatment of postoperative pain in the United States.[28] Results of this study are consistent with these recommendations because the largest fentanyl-sparing effects appeared to occur between the 10 and 20 mg doses. Increasing the dose to 30 mg did not appear to offer significant additional benefits. Therefore, doses of EREM greater than 20 mg are not recommended. The present study also suggests that older patients may achieve analgesic benefits that are comparable to younger patients but at a lower dose of EREM than received by their younger counterparts.

It is also important to note that the goal of this Phase II registration study was to assess the efficacy of EREM as a single agent. As indicated by a recent meta-analysis, multimodal analgesia with nonsteroidal anti-inflammatory drugs (NSAIDS) can reduce morphine consumption through IV PCA with significant decreases in AEs (e.g., nausea, vomiting, and sedation).[29] In principle, multimodal analgesia with a preoperative low dose of EREM (e.g., 10 mg) could provide an analgesic foundation upon which nonopioid medications such as NSAIDs could be layered in the postoperative period. Such a strategy may help to maximize analgesia and tolerability and is an important subject for future study.

After joint replacement surgery, severe, persistent postoperative pain beyond the first 24 hours may necessitate an indwelling epidural catheter, which is contraindicated in patients receiving anticoagulation therapy.[16,30] This study shows that single-dose EREM provides up to 48 hours of pain relief and a reduced need for supplemental postoperative analgesics while avoiding the need for an indwelling epidural catheter, thus permitting prophylactic anticoagulation therapy in patients undergoing total joint replacement. Additional studies will be required to explore whether patients' decreased need for supplemental postoperative analgesics directly improves patient satisfaction and contributes to improved patient care and recovery.

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ORIGINAL ARTICLE

Relative abuse potential of opioid formulations in Canada: A structured field study

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ABSTRACT

Introduction: *While prescription opioids can improve quality of life through pain relief, they are susceptible to misuse. This field study characterizes the relative susceptibility and attractiveness of a new analgesic patch, with fentanyl embedded in a matrix material, compared to other opioid dose formulations.*

Methods: *Recreational opioid abusers (N = 42; 31 male, 11 female) from three Canadian sites participated in structured interviews. They were presented with nine products, some of which were hypothetical (fentanyl [F], hydromorphone [H], and oxycodone [O] in each of three formulations: matrix patch [M], reservoir-type gel patch [G], and tablet [T]). The attractiveness and tampering potential of each product was ranked using two 7-point Likert scales (Value of Product and Likelihood to Tamper), an index representing the product of the two scales, a 17-item Opiate Attractiveness Scale (OAS), relative street value, and rank order of overall desirability. Non-parametric analyses were used to compare each product to the FM.*

Results: *The FT, HT, and FM were highly valued and most likely to be tampered with. The products were ranked in decreasing order of desirability as follows: FT > HT > FM > FG > OT > HM > HG > OM > OG. On the OAS, FM was more attractive than all gel-patch products ($p < 0.001$), and OT was most attractive overall. FM was statistically similar to OT, FT, OM, and HT. Of the 42 subjects, 25 (60 percent) preferred the matrix patch to the gel patch. Of the 17 subjects who preferred the gel patch, 10 (59 percent) were from a region generally unfamiliar with that formulation.*

Conclusions: *Fentanyl is attractive to opioid abusers regardless of formulation. In Canada, a fentanyl matrix patch may be at higher risk for diversion, tampering, and abuse than other transdermal opioid formulations. These findings should be confirmed by epidemiological studies. Comparative risk management programs should be part of the development of any new narcotic delivery system.*

Key words: opioid, abuse, risk, matrix patch, formulation, tampering

INTRODUCTION

Prescription opioids bring important quality-of-life improvements to patients suffering pain.[1] Most opioid medications, however, have the potential to be abused. The challenge is to maintain the availability of opioid medications for therapeutic use while minimizing the risk of diversion for abuse.[2]

Tampering persists despite the incorporation of tamper-resistant features into several opioid products. A slow-release formulation of oxycodone (OxyContin®) was intended to have low abuse potential due to its lower peak concentrations and slower rate of entry into the brain.[3] However, abusers either crushed the tablets before ingestion or dissolved them in water for injection, thereby bypassing the slow-release mechanism. Similarly, the currently available transdermal fentanyl reservoir gel patch (Duragesic®) is designed to provide sustained pain relief with reduced likelihood of abuse, but abusers have extracted fentanyl from the hydroxyethyl cellulose gel for intravenous use[4,5] or chewed the patch for transmucosal delivery.[6-8]

A new analgesic patch has fentanyl dissolved directly into a polyacrylate copolymer adhesive layer in a flexible matrix material, creating a simplified transdermal system. The currently available form-and-seal patch has a reservoir containing the drug formulation in a hydroxyethyl cellulose gel, and it utilizes permeation enhancers and a rate-limiting diffusion membrane.[9] The newer matrix design results in a simplified two-layer drug-in-adhesive system. Hypothetical methods of tampering may include cutting the patch into smaller pieces for buccal use, or the use of readily available solvents (e.g., water, alcohol,

Table 1. Nine drug-formulation combinations presented to subjects		
Drug	**Formulation**	**Product status**
Fentanyl	Reservoir gel patch	Existent
	Matrix patch	Hypothetical*
	Controlled-release tablet	Hypothetical
Hydromorphone	Reservoir gel patch	Hypothetical
	Matrix patch	Hypothetical
	Controlled-release tablet	Existent
Oxycodone	Reservoir gel patch	Hypothetical
	Matrix patch	Hypothetical
	Controlled-release tablet	Existent
* Hypothetical for Canadian opioid users; formulation exists outside of Canada.		

vinegar) or heat to extract fentanyl for intravenous injection. These types of tampering methods are commonly employed by recreational drug users, who often share knowledge over the Internet.[10,11] This is in contrast to the reservoir gel patch, where the drug is neither readily soluble nor easily separated from the hydroxyethyl cellulose components, and where cutting the patch into smaller, more portable pieces results in complete gel extrusion. Therefore, the likelihood of tampering with the new matrix patch may be increased compared to the fentanyl gel patch, creating a new public health concern. Individuals intent on abusing drugs go to great lengths and take great risks to obtain and use opioids. It is imperative that new opioid formulations be carefully evaluated for abuse potential.[12]

Patterns of drug abuse and tampering methods vary among countries and regionally within a country.[13,14] The present study gathered Canadian data from recreational drug users and reviewed them in order to better understand the relative abuse risk of a proposed fentanyl matrix patch in Canada.

METHODS

The study protocol, consent form, amendments to the protocol, and advertisements for subject recruitment received Institutional Review Board approval (IRB Services, Aurora, Ontario).

Subject population

Prior to any study procedures, written informed consent was obtained from each subject. Subjects were excluded if they displayed positive breath alcohol or indication of intoxication at the study session or inability or unwillingness to complete study procedures in a useful and timely manner, or if study staff had concerns about the subject's reliability.

A total of 42 adults (31 male, 11 female; mean age 40.1 years, range 22 to 60 years) were enrolled from three sites across Canada: Toronto, Ontario (n = 18); Winnipeg, Manitoba (n = 12); and Dartmouth, Nova Scotia (n = 12). Each participant confirmed having engaged in recreational drug use in the last six months. Abuse of, or dependence upon, prescription opioids was confirmed by DSM IV criteria. All participants had knowledge of fentanyl, hydromorphone, and oxycodone and were required to provide specific, correct information about each drug. Participants were required to demonstrate that they had tampering experience by providing two specific examples of prescription pharmaceutical product tampering. Recent or current drug users were enrolled to prevent cue-induced relapse in recovering users. Each participant completed the study as per protocol.

Study design

This was a multicenter, noninterventional, single-session study. Each subject attended a three-hour session consisting of a structured interview, evaluation of choice procedures, and estimation of monetary street values comparing three opioid drugs in each of three formulations (Table 1). It is important to note that some of these formulations were hypothetical or not currently available in the Canadian marketplace. The interview format was finalized following a Toronto-based pilot study (n = 5, data not shown).

Table 2. Subject demographics, overall and by study site				
Parameter	**All subjects (N = 42)**	**Toronto (n = 18)**	**Winnipeg (n = 12)**	**Dartmouth (n = 12)**
Age (years)				
Mean	40.1	43.0	35.2	40.8
Range	22-60	31-60	22-54	26-51
Sex (n [percent])				
Male	31 (73.8)	15 (83.3)	7 (58.3)	9 (75.0)
Female	11 (26.2)	3 (16.7)	5 (41.7)	3 (25.0)
Race (n [percent])				
Caucasian	40 (95.2)	17 (94.4)	11 (91.7)	12 (100.0)
Black/African American	1 (2.4)	1 (5.6)	–	–
American Indian	1 (2.4)	–	1 (8.3)	–

Testing

Choice procedures. Subjects were required to assign a score for each product on two 7-point Likert scales, each anchored by "Strongly Disagree" and "Strongly Agree." The Value of Product scale (VPS) stated, "This drug would be highly valuable to me"; the Likelihood to Tamper scale (LTS) stated, "I would definitely tamper with this drug." Subjects also completed a validated 5-point scale (the 17-item Opiate Attractiveness Scale [OAS])[15,16] which presented specific drug features related to abuse attractiveness for each of the nine products (some hypothetical). Subjects then ranked the products according to overall desirability.

Street value. Subjects were asked to give a subjective street-sale dollar value to 13 reference drugs (both illicit and prescription, based upon a study assessing street values in Vancouver[1]); these were then ranked in descending order. Without assigning a specific street value to the test products, subjects were asked to rank each of the nine test products within the ranking of the 13 reference drugs. The street value for each test product was derived as the midpoint between the dollar values for the two closest reference drugs (i.e., the drug ranked immediately higher and the drug ranked immediately lower than the test product).

Product presentation. Samples of the three different formulations were available for subjects to view and/or handle. Multiple sizes of matrix and reservoir patches (containing no active ingredients) and photos of different tablets were used to illustrate different dosages of each compound; no actual tablets were presented. Each formulation was documented for the subject on a board along with basic information including the drug's brand name, street name(s), active ingredient, available doses, drug solubility, and potency relative to morphine.

Placebo reservoir (gel) and matrix patches were supplied by Janssen-Ortho, Inc. Existent tablet formulations used were OxyContin®, Purdue Pharma, and Dilaudid®, Abbott Laboratories. Triphasil® 28, Wyeth Pharmaceuticals, was used as a basis for the hypothetical fentanyl tablet formulation.

Data analysis

No formal sample-size calculation was performed. The Type I error for all hypothesis testing was set at 0.05 (two-sided). Two-sided 95 percent confidence intervals were used. No multiplicity adjustments were made for multiple testing because no primary endpoint was specified. Each of the following endpoints was considered equal: VPS, LTS, Value of Product-Likelihood to Tamper Index (VP-LT index, a product of the VPS and LTS), OAS, relative desirability of opioid formulations, monetary street value of opioid formulations relative to local street drugs, and description of potential tampering methods.

Nonparametric methods (Wilcoxon Rank-Sum test) were used to compare the derived street value of the fentanyl matrix patch to the values derived for each of the test products. Descriptive analysis was used to identify

Table 3. Description of opioid use history and preferences				
Opioid	**Subjects using in past six months (n = 42) N (percent)**	**Subjects with tampering experience (percent of subjects using opioid in past six months) n (percent)**	**First opioid of choice n = 40* n (percent)**	**Second opioid of choice n = 38** n (percent)**
Methadone	40 (95.2)	14 (35.0)	0 (0)	0 (0)
Morphine	30 (71.4)	24 (80.0)	7 (17.5)	14 (36.8)
Codeine	27 (64.3)	11 (40.7)	3 (7.5)	0 (0)
Oxycodone	26 (61.9)	20 (76.9)	7 (17.5)	5 (13.2)
Hydromorphone	22 (52.4)	21 (95.5)	14 (35.0)	10 (26.3)
Fentanyl	14 (33.3)	13 (92.9)	0 (0)	5 (13.2)
Heroin	13 (31.0)	6 (46.2)	6 (15.0)	2 (5.3)
Hydrocodone	7 (16.7)	2 (28.6)	1 (2.5)	2 (5.3)
Oxymorphone	5 (11.9)	4 (80.0)	2 (5.0)	0 (0)

* Missing data for two subjects; ** Missing data for four subjects.

the mean price ± standard deviation for each opioid drug and formulation combination.

Data for the three opioid drugs, in each of three formulations, were categorized into relevant groupings prior to analysis. The VP-LT Index was analyzed as for Likert scales. Nonparametric analysis was used to evaluate rankings.

In the structured interview and open-ended questions, the respondents also provided narrative descriptions of tampering methods.

Data were keyed into PDS Express, version 3.4 (Phoenix Data Systems, Inc., King of Prussia, PA). All statistical analyses were performed using SAS version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Subject demographics were similar across study sites (Table 2). All subjects reported using opioids within the six months prior to the study, including at least one of the following: methadone (95 percent), morphine (71 percent), codeine (64 percent), oxycodone (62 percent), hydromorphone (52 percent), fentanyl (33 percent), heroin (31 percent), hydrocodone (17 percent), or oxymorphone (12 percent). Tampering experience was highest among heroin and fentanyl users (96 percent and 93 percent, respectively) (Table 3).

Value of Product and Likelihood to Tamper scales

Overall, and independent of formulation, fentanyl was statistically similar to hydromorphone in its perceived value and likelihood to be tampered with, but it was significantly more valued ($p < 0.001$) and more likely to be tampered with ($p = 0.01$) than oxycodone. When formulation type was considered independent of drug, tablets were most valued (tablet vs. matrix: $p = 0.01$) and were more likely to be tampered with, although the probabilities for tampering with tablet, matrix, and gel products were not significantly different. The matrix and gel patches were not ranked significantly differently on either the VPS or LTS.

On the VPS, the fentanyl matrix patch was statistically similar to the three tablets, the fentanyl gel patch, and the hydromorphone matrix patch. The fentanyl matrix patch was perceived as being more valued than the hydromorphone ($p = 0.02$) and oxycodone ($p < 0.001$) gel patches and the oxycodone matrix patch ($p < 0.001$). A similar trend was observed for the LTS (data not shown).

Table 4. Rank, from highest to lowest, of products on the Value of Product-Likelihood to Tamper (VP-LT) Index		
Product	**All subjects (N = 42)**	
	p value	**Rank**
Fentanyl tablet	0.02	1
Hydromorphone tablet	ns	2
Fentanyl matrix	–	3
Oxycodone tablet	ns	4
Hydromorphone matrix	0.03	5
Fentanyl gel	ns	6
Hydromorphone gel*	0.002	7
Oxycodone matrix	< 0.001	8
Oxycodone gel**	< 0.001	9
* Indicates three missing data points; ** Indicates two missing data points; ns = not significant; p value based on comparisons to the fentanyl matrix patch (bolded).		

The VP-LT Index for the fentanyl tablet was significantly higher than for the fentanyl matrix patch (p = 0.02) (Table 4). The fentanyl matrix patch was ranked similarly to the other tablet formulations and the fentanyl gel patch and was of more interest to subjects than were both of the matrix patches and the hydromorphone and oxycodone gel patches.

Overall desirability

The overall desirability of each of the three drugs, three formulations, and nine products is provided in Table 5, in decreasing order of desirability. Independent of the drug involved, the tablet was the most desirable dosage form, followed by the matrix patch and then the gel patch. Regardless of formulation, fentanyl was significantly more desirable than both hydromorphone and oxycodone. As a result, the (hypothetical) fentanyl tablet was ranked consistently as the most desirable product and was significantly more desirable than the fentanyl matrix patch. The fentanyl matrix patch was statistically similar in terms of desirability to the hydromorphone and oxycodone tablet formulations and to the fentanyl gel patch, and it was significantly more desirable than both types of (hypothetical) hydromorphone and oxycodone patches.

Opiate Attractiveness Scale

Mean scores for the OAS are presented in Table 6. Results were similar among study centers (not shown). The oxycodone tablet ranked as the most attractive formulation. The fentanyl matrix patch was significantly more attractive than all three gel-patch products, and it was statistically similar in attractiveness to all three tablet formulations and the oxycodone matrix patch.

Estimation of street value

The mean subjective street values of reference drugs and study products are presented in Table 7. Of the 13 reference street drugs presented to subjects, ketamine, *d*-amphetamine, Hycodan®, and Demerol® could not be assigned dollar values due to a lack of experience in the majority of subjects; these have been excluded from Table 7.

The range of mean dollar values for the reference drugs was large and, on average, the values assigned were either "low" (< $20) or "high" (> $70). Each of the nine study products ranked intermediately between the "low" and "high" value categories of the reference drugs.

Overall, the fentanyl matrix patch had the highest derived dollar value of the test products, followed by the fentanyl tablet and fentanyl gel patch; however, the difference between fentanyl formulations was not statistically significant.

Table 5. Overall desirability of drug, formulation, and product			
		All subjects (N = 42)	
		p value	Rank
Drug	**Fentanyl**	–	1
	Hydromorphone	< 0.001	2
	Oxycodone	< 0.001	3
Formulation	Tablet	< 0.001	1
	Matrix	–	2
	Gel	0.03	3
Product	Fentanyl tablet	0.001	1
	Hydromorphone tablet	ns	2
	Fentanyl matrix	–	3
	Fentanyl gel	ns	4
	Oxycodone tablet	ns	5
	Hydromorphone matrix	0.002	6
	Hydromorphone gel	< 0.001	7
	Oxycodone matrix	< 0.001	8
	Oxycodone gel	< 0.001	9
Products are ranked from most to least desirable, using fentanyl, a matrix patch, and the fentanyl matrix patch as comparator references (bolded).			

Feedback on matrix and gel formulations

Subjects were asked for feedback on any safety concerns, as well as how they might tamper with and share the formulations to get high (data not shown). In addition, subjects were asked which fentanyl product they would prefer to use to get high.

Of the 42 subjects interviewed, 25 (60 percent) said they would prefer to use the matrix patch, as it was perceived to be easier to prepare for intravenous use (soluble in water and without hydroxyethyl cellulose gel, making it "cleaner" to use).

More than half of the subjects preferring to use the gel patch over the matrix patch (10 of 17, or 59 percent) were from Dartmouth. The most common reason for Toronto and Winnipeg subjects' preference for the gel patch was familiarity; the most common reason for Dartmouth subjects was that they could see the gel (i.e., the drug).

DISCUSSION

This study compared the likelihood and potential for tampering with a fentanyl matrix patch to that of other

Table 6. Mean scores for the Opiate Attractiveness Scale				
Product	**N**	**Mean score**	**p value**	**Rank**
Oxycodone tablet	42	4.01	ns	1
Fentanyl tablet	42	3.93	ns	2
Oxycodone matrix	42	3.85	ns	3
Fentanyl matrix	42	3.82	–	4
Hydromorphone tablet	42	3.68	ns	5
Hydromorphone matrix	42	3.57	0.03	6
Fentanyl gel	42	3.30	< 0.001	7
Oxycodone gel	42	3.29	< 0.001	8
Hydromorphone gel	42	3.22	< 0.001	9
Ranked from most to least attractive; p value based on comparison to the fentanyl matrix patch (bolded).				

opioid formulations among Canadian recreational opioid users. Based on self-reported histories, hydromorphone was the preferred opioid and was the one with which subjects had most often tampered.

Regardless of dosage form, fentanyl is highly sought by abusers. The theoretical fentanyl tablet was the most preferred product on all scales except the OAS, where it ranked second after the oxycodone tablet.

In general, tablet formulations were preferred, followed by matrix patches and then gel-patch formulations. The preference for tablet formulations may reflect the subjects' previous experience with opioids that are available in tablet formulations (i.e., hydromorphone and oxycodone). Many commonly abused prescription drugs are available in tablet formulations, and tampering by chewing, crushing, or dissolving for oral, intranasal, or intravenous administration is fairly routine among recreational drug users.[10] In addition, tablets may have been perceived as easier to obtain in greater quantities due to the number of tablets per prescription compared to patches, making them easier to divert, divide, and resell. Subjects considering such aspects may also have weighed the perceived familiarity or preferences of potential buyers. Of the matrix-patch formulations, the fentanyl matrix was most desired and ranked comparably to tablet formulations. The fentanyl gel patch was ranked higher than the hydromorphone and oxycodone gel formulations, and it was consistently ranked lower than the fentanyl matrix patch. The exception was in overall desirability by Dartmouth subjects (Eastern Canada), who tended to prefer the gel-patch formulations (primarily because they could see the gel). This regional difference may reflect unfamiliarity with the gel patch and limited experience tampering with this formulation, as those who expressed knowledge of the extraction process with gel patches generally preferred other formulations.

The few inconsistencies in the ranking of products among scales may reflect differences in scale properties, form, and instructional control. For example, the OAS measures the effect of individual product characteristics on attractiveness; the other scales measure choice or attractiveness based upon the subject's baseline knowledge. Additionally, the results appear to have been influenced by product familiarity and experience.

Given the choice to tamper with either a matrix or gel-patch formulation, 60 percent of subjects chose the matrix patch, primarily because it was perceived as being easier to extract opioids from for intravenous use. Of those choosing the gel patch, 59 percent were from

Table 7. Mean subjective street values of reference and study products			
Drug (unit)	**n**	**Mean dollar value/unit (± SD)**	**p value**
Heroin (g)	33	216.06 (96.28)	
Cocaine (g)	41	85.96 (28.19)	
Fentanyl matrix (patch)	42	61.68 (42.17)	–
Fentanyl tablet (pill)	42	61.47 (51.77)	ns
Fentanyl gel (patch)	42	57.65 (45.02)	ns
Hydromorphone matrix (patch)	42	45.21 (32.79)	0.04
Hydromorphone gel (patch)	42	41.46 (30.89)	0.01
Oxycodone gel (patch)	42	35.54 (26.48)	0.001
Oxycodone matrix (patch)	42	34.70 (23.61)	< 0.001
Hydromorphone tablet (pill)	42	27.20 (21.54)	< 0.001
Oxycodone tablet (pill)	42	24.27 (21.96)	< 0.001
MDMA (pill)	33	18.44 (7.88)	
MS Contin (pill)	40	16.55 (12.26)	
Methadone (20 mg)	39	14.20 (18.17)	
Fiorinal $C_{1/2}$ (pill)	22	4.08 (5.14)	
Percodan (pill)	42	3.97 (1.32)	
Tylenol 4 (pill)	36	2.06 (1.27)	
Valium (pill)	40	1.66 (2.07)	
Note: Drug names in italics are reference drugs; p value based on comparison to the fentanyl matrix patch (bolded).			

Dartmouth and, as discussed, were less familiar with the fentanyl gel patch than subjects from Toronto (Central Canada) and Winnipeg (Western Canada). The fentanyl matrix patch had the highest derived street value compared to the other eight products, a value lower than those of only heroin and cocaine. The high estimated value, plus overall desirability, suggests a higher incentive for diversion of the fentanyl matrix patch than for the existing gel patch and other currently marketed products (hydromorphone and oxycodone tablets). However, the differences between street values derived for fentanyl formulations were not statistically significant.

Our data suggest that the risk for misuse of various formulations may differ regionally and that drug users' preferences may be based on past experience. There was a tendency for subjects to prefer drugs with which they were familiar. However, the highly rated desirability and attractiveness of the matrix patch (a hypothetical product

not yet marketed in Canada) raises concern regarding the abuse potential of such a product in Canada. With availability and tampering experimentation, baseline knowledge of the fentanyl matrix patch would increase, perhaps substantially increasing its attractiveness to opioid users. The relevance of the current data to other global regions or countries is unknown.

Despite differences in what the scales measured and the confounding influence of comparing hypothetical to existing products, all scales consistently showed the fentanyl matrix patch to be more valued, more likely to be tampered with, more desired, and more attractive than the fentanyl gel patch. This suggests that the fentanyl matrix patch may have greater abuse potential than the existing reservoir gel patch.

Fentanyl in any form is highly attractive to opiate abusers, even in a tamper-resistant formulation. Although not conclusive, these results suggest that a fentanyl matrix formulation has characteristics indicating an increased risk of diversion and tampering in Canada. Such risk should be evaluated by prospective epidemiological studies or comparative risk management programs (RMPs). RMPs should be part of the development of any new narcotic delivery system.

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ORIGINAL ARTICLE

The influence of chief complaint on opioid use in the emergency department

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ABSTRACT

The aim of this study was to explore factors influencing emergency department (ED) clinicians' use of opioids in treating selected patients. Patients who either received or did not receive opioids in the ED, as well as their nurses and physicians, were interviewed before patient discharge. We found that the decrease in patients' mean (SD) pain intensity from the time of admission to the ED (7.3 ± 2.4 on a 0 to 10 numeric rating scale) to discharge (5.0 ± 2.9) was statistically significant (t_{93} = 8.4, p < 0.001, 95 percent CI = 1.7, 2.8) for all groups except those with trauma-related pain. The factor that most frequently led physicians of patients with abdominal pain and nurses in general to administer no opioids was that the patient was "not in that much pain." However, the patients in question had self-reported pain scores that indicated moderate pain. Our findings lead us to conclude that clinicians inaccurately infer severity of patient pain. This in turn can influence the prescription of opioids and the patient's decrease in pain.

Key words: pain, pain assessment, pain treatment, emergency department, decision making, opioids

INTRODUCTION

Certain patients are at particular risk of not receiving aggressive or adequate pain management in hospital emergency departments (EDs). Opioids have been withheld from ED patients because of the following clinical concerns: 1) that the patient will become too sedated and unable to safely leave the ED,[1] 2) that physicians will not be able to make an accurate diagnosis in patients with abdominal pain because symptoms or physical findings might be "masked" by analgesics,[2] 3) hesitancy to provide opioids to patients with chronic painful conditions and/or drug dependencies,[3-5] and 4) that trauma patients will suffer hemodynamic instability or a decrease in respiratory drive following administration of opioids.[6] We hypothesized that the ED patient's pain experience and clinicians' utilization of opioids in the management of patient pain would be influenced by the patient's chief complaint (abdominal, chronic, abscess, or trauma pain). Understanding how pain in various patient groups is treated and what factors lead clinicians to be concerned about treating patient pain with opioids could provide guidance for future interventions for ED patients in pain.

METHODS

Study design

This prospective, descriptive, comparative study was conducted in the EDs of two Level I trauma centers in teaching hospitals in Northern California, Stanford University Medical Center and San Francisco General Hospital. Study approval was obtained from the institutional review boards at both sites, as well as from the Committee on Human Research at the University of California, San Francisco.

Study setting and population

The study population was selected from patients who presented to the ED with a chief complaint of abdominal, chronic, abscess, or trauma pain. Abdominal pain was categorized as any pain in the abdominal area that began less than 10 days prior to ED admission. For the purpose of this study, chronic pain was defined as pain lasting longer than 10 days, to differentiate it from the many other acute, painful conditions that lead patients to seek ED care. Chronic pain has traditionally been defined as pain lasting for longer than three months.[7] However, ED researchers have defined chronic pain as having a duration of longer than 48 hours[8] or longer than one month.[9]

Table 1. Sample demographics							
	All patients (N = 94)	**Patients with abdominal pain (n = 31)**	**Patients with chronic pain (n = 18)**	**Patients with abscesses (n = 25)**	**Patients with trauma pain (n = 20)**	**Physicians (N = 78)**	**Nurses (N = 43)**
Age (mean/SD)	41.2/12.6	38.8/12.2	45.1/15.2	43.5/5.90	36.6/10.6	31.6/6.4	38.2/8.4
Gender							
Male (percent)	53 (56.4)	22 (46)	19 (68)	24 (73)	23 (66)	46 (59)	11 (26)
Female (percent)	41 (43.6)	26 (54)	9 (32)	9 (27)	12 (34)	32 (41)	32 (74)
Ethnicity							
Caucasian (percent)	49 (52)	18 (38)	15 (54)	19 (58)	24 (69)	48 (63)	34 (79)
African American (percent)	26 (28)	15 (32)	9 (32)	12 (37)	5 (14)	4 (5)	2 (5)
Hispanic (percent)	12 (13)	10 (21)	2 (7)	1 (3)	5 (14)	3 (4)	1 (2)
Asian Pacific (percent)	5 (5)	4 (8)	1 (4)	0 (0)	1 (3)	16 (21)	5 (12)
Other (percent)	2 (2)	1 (2)	1 (4)	1 (3)	0 (0)	5 (7)	1(2)

We included patients presenting with abscesses because, in our EDs, they are often injection drug users and, as such, may be subjected to a conservative approach by clinicians regarding opioids. Patients with trauma pain were included if they were categorized as second-tier trauma activations (i.e., without life-threatening injuries). Patients were excluded if they didn't speak English, were younger than 18 years of age, or had life-threatening or unstable conditions or altered mental status.

Measurements

The research instruments were separate questionnaires for patients, nurses, and physicians. The questionnaires were developed by research team members who were experts in pain, emergency nursing, and/or emergency medicine. Nurses received the same questionnaire for all patients, and physicians received questionnaires specific to each patient's chief complaint (abdominal pain, chronic pain, abscess pain, or trauma pain). Content validity of the instruments was determined through pilot testing of three ED nurses and five ED physicians. In one question on the questionnaire, clinicians were offered a variety of reasons for why they might decide not to administer an opioid to a particular patient or, if an opioid was selected, to use only a low dose. They checked all reasons that they felt were relevant to the particular patients for whom they were providing care. We intentionally did not define "low-dose opioids," believing that there is considerable variation in clinicians' beliefs about what would constitute a low dose. In this study, a provider's own interpretation of a low opioid dose was what we considered to be important. The questionnaires also contained numeric rating scales (NRSs) where 0 = no pain and 10 = worst pain imaginable.[10,11] (Questionnaires available upon request.) Upon discharge from the ED, patients rated their degree of pain intensity at admission and at discharge using separate 0 to 10 NRSs for each rating. Information about patient demographics and whether patients received opioids or other analgesics during their ED stays was obtained through chart abstraction.

Study protocol

If a patient met study criteria, the patient and the patient's primary nurse and physician were asked to participate in the study, and informed consent was obtained.

Table 2. Changes in pain intensity from admission to discharge (NRS)*					
Type of pain	**Pain at admission (M/SD)†**	**Pain at discharge (M/SD)†**	**t**	**p**	**95 percent CI‡**
All types (N = 94)	7.3/2.4	5.0/2.4	8.4	< 0.001	1.7, 2.8
Abdominal pain (n = 31)	7.5/2.0	4.2/3.0	7.3	< 0.001	2.3, 4.2
Chronic pain (n = 18)	7.4/2.5	5.5/3.0	4.5	< 0.001	0.98, 2.7
Abscess pain (n = 25)	7.6/2.5	5.6/2.8	4.1	< 0.001	0.97, 3.0
Trauma pain (n = 20)	6.4/2.8	4.8/2.8	2.1	< 0.053	-0.03, 3.2

* NRS = Numeric Rating Scale; † M/SD = mean/standard deviation; ‡ confidence intervals

Research assistants were nurses who participated in training sessions and regularly scheduled review sessions to ensure standardization of enrollment and administration of the questionnaires. Each patient's nurse and physician completed their surveys soon after assessing and treating the patient. When patients were being prepared for ED discharge or hospital admission, they were given the option to complete their questionnaires themselves or have research assistants read the questions to them. All questionnaire responses were blinded from other respondents. Time required for completion of the questionnaires did not exceed five minutes.

Data analysis

Data were analyzed using Statistical Program for the Social Sciences (SPSS) 12.0 for Windows. Descriptive statistics (e.g., frequencies, means, and standard deviations) were used for analysis of demographic data. Fisher's Exact tests were used for analyses of categorical data, and

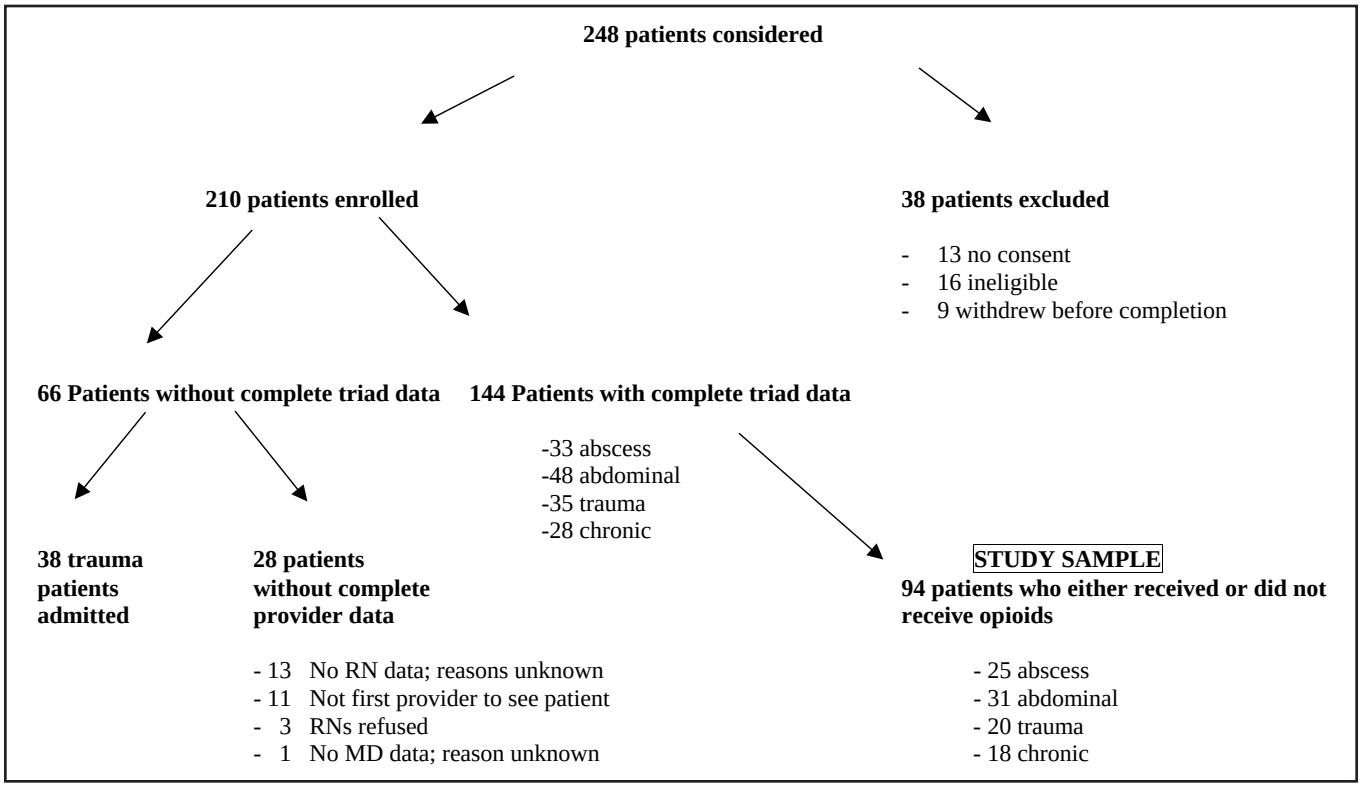

Figure 1. The process of patient enrollment into the study.

Table 3. Specific factors influencing nurses' decision to administer opioids			
Factor (number of nurses who selected factor)	**Number (percent) of patients who received opioids (n = 59)**	**Number (percent) of patients who did not receive opioids (n = 35)**	**Level of significance**
Patient's vital signs (12)	9 (15.3)	3 (8.6)	ns
Patient's chief complaint (7)	4 (6.8)	3 (8.6)	ns
Patient has chronic pain (6)	3 (5.1)	3 (8.6)	ns
Opioids interfere with diagnosis (4)	3 (5.1)	1 (2.9)	ns
Patient not in that much pain (32)*	11 (18.6)	21 (60)	< 0.001
Opioids not appropriate (11)	4 (6.8)	7 (20.6)	< 0.05
* Ten (56 percent) were patients with chronic pain			

t-tests and analysis of variance (ANOVA) were used for analyses of continuous data. An α level of significance of < 0.05 was considered statistically significant.

RESULTS

We identified 248 patients presenting with a chief complaint of abdominal pain, chronic pain, abscess pain, or trauma-related pain. Of those, 144 had complete triad data (patient, nurse, physician) for analysis. Of the 144, 94 either received only opioids for pain or did not receive any analgesics. It is this sample of 94 that we report on here. (See Figure 1 for the patient enrollment process and Table 1 for sample demographics.)

Pain intensity at ED admission

Our 94 patients reported moderate to severe pain upon arrival at the ED, with an overall mean NRS score of 7.3 ± 2.4. Patients with abscess pain reported the highest pain intensity (7.6 ± 2.5), while the patients with trauma pain reported the lowest pain intensity (6.4 ± 2.8) (Table 2). A one-way ANOVA determined that the difference among the four groups in pain intensity at admission was not statistically significant.

Opioid administration

During their stay in the ED, 59 patients received only opioids for pain, and 35 patients received no analgesics. Among the four pain groups, the difference in the number of patients who received opioids versus no analgesics was not significant. For those who received opioids, the average opioid dose (in morphine equivalents) differed considerably between those whose chief complaint was of abdominal pain and those with chronic pain. Doses ranged from 8.9 ± 7.5 mg (administered to patients with abdominal pain [n = 19]) to 19.8 ± 19.8 mg (administered to those with chronic pain [n = 10]). Trauma pain (n = 11) and abscess pain (n = 19) patients received an average of 14 ± 11.4 mg and 14.4 ± 14.3 mg, respectively. A one-way ANOVA determined that the differences in opioid doses among groups were nonsignificant. This may have been an artifact resulting from the small number of patients in each group who received opioids.

Factors that could influence clinicians' use of opioids

The physicians and nurses were asked to choose a reason or reasons that would lead them to administer low doses of opioids or no opioids at all to their patients. We provided them with an extensive list of possible factors that could influence opioid administration decisions, derived from research and our own clinical practices. (Complete list of factors available on request.) We used Fisher's Exact tests to examine the relationships between selected factors and whether patients did or didn't receive an opioid. Only six factors, from the entire list of 12 potential factors, were selected by more than 5 percent of the nurses as being important to them when determining whether an opioid should be administered to a particular patient. Table 3 presents the factors selected by the nurses. A choice against opioid administration was significantly related to a nurse's determination that the "patient was not in that much pain" ($p < 0.001$) and that "opioids were not appropriate" ($p < 0.05$).

Table 4. Specific factors influencing physicians' decision to administer opioids				
Chief complaint	**Selected factor (number of physicians selecting factor)**	**Number (percent) of patients who received opioids**	**Number (percent) of patients who did not receive opioids**	**Level of significance**
Abdominal pain		n = 18	n = 12	
	Pending consult (2)	2 (11)	0 (0)	NS
	Opioids may interfere with diagnosis (3)	3 (17)	0 (0)	NS
	Patient not in that much pain (14)	4 (22)	10 (83)	$p < 0.001$
	Opioids not appropriate (7)	2 (11)	5 (42)	$p = 0.053$
	Patient going to CT (1)	0 (0)	1 (8)	NS
	Medications will interfere with timely discharge (1)	1 (5.6)	0 (0)	NS
Abscess pain		n = 19	n = 6	
	Abscess best treated by incision and drainage (3)	2 (11)	1 (17)	NS
	Abnormal vital signs (3)	2 (11)	1 (17)	NS
	Altered mental status (2)	2 (11)	0 (0)	NS
Chronic pain		n = 11	n = 8	
	Patient should be treated by primary provider (1)	0 (0)	1 (17)	NS
	Patient given other pain medications (3)	2 (18)	1 (13)	NS
Trauma pain		n = 11	n = 9	
	Suspected abdominal injury in trauma patient (1)	1 (9)	0 (0)	NS
	Not a high priority (3)	2 (18)	1 (11)	NS

Only 13 factors, from the entire list of 59 potential factors on the four physician questionnaires, were selected by more than 5 percent of the physicians as important when determining whether an opioid should be administered to a particular patient. Table 4 presents the factors selected by the physicians. Opioid administration was significantly related to the determination that a "patient was not in that much pain" ($p < 0.001$) by physicians of patients with abdominal pain. Significantly fewer abdominal pain patients received opioids if their physicians thought this factor was an important influence on the decision to administer an opioid. The idea that "opioids were not appropriate" for abdominal pain patients almost reached statistical significance ($p = 0.053$).

Physicians and nurses frequently noted that there were "other" factors (besides those on the questionnaire) that influenced their decisions concerning opioids. However, the following "other" factors were the only ones written in: a) "other medications would be better selections" (n = 1), b) "patient refusal of pain medication" (n = 3), c) patient did not want "mind-altering drugs" (n = 1), d) patient was taking heroin/methadone (n = 2), and e) patient had no IV access (n = 1).

Patients "not in that much pain"

Fourteen physicians of patients with abdominal pain

Table 5. Patient- and nurse-reported pain intensity scores for patients (N = 94) and resultant opioid doses

	Patient-reported score	Nurse-reported score	Number of patients who received opioids	Opioid dose* administered
Nurse chose "not in that much pain" (n = 32)	5.8 ± 2.3[a]	3.5 ± 2.3[a]	11	8.0 ± 5.7 mg[c]
Nurse did not choose "not in that much pain" (n = 62)	8.1 ± 2.2[b]	6.0 ± 2.5[b]	48	14.7 ± 12.6 mg[c]

* As morphine equivalent; a = $p < 0.001$; b = $p = 0.003$; c = $p < 0.02$.

and 32 nurses (over half of them nurses of chronic pain patients) noted that their patients were not in enough pain to warrant an opioid. Because of this finding, we examined the self-reported pain intensity of these particular patients at admission. Patients determined by their nurses to not be in much pain reported an average pain intensity of 5.8 ± 2.3 at admission (their nurses rated their average pain intensity as being 3.53 ± 2.3) (Table 5). The 14 abdominal pain patients whose physicians believed they were not in much pain reported an average pain intensity of 6.7 ± 2.2 at admission; their physicians rated their pain as being 2.7 ± 1.3. These differences in pain intensity scores between nurses and patients and between physicians and abdominal pain patients were significant ($p < 0.05$ and $p < 0.001$, respectively). Patients who were considered to not be in much pain received significantly lower doses of opioids than the other patients (nurses' patients = 8.0 ± 5.7 mg vs. 14.7 ± 12.6 mg, respectively; abdominal pain patients = 4.0 ± 1.6 mg vs. 10.2 ± 2.2 mg, respectively). (See Tables 5 and 6.)

Change in pain intensity from admission to discharge

Overall, our 94 patients' pain at discharge had decreased significantly, from an admission pain intensity of 7.3 ± 2.4 to a discharge pain intensity of 5.0 ± 2.9 (t^{93} = 8.4, $p < 0.001$, 95 percent CI = 1.7, 2.8). (Table 2.) The decrease in pain intensity was statistically significant in all of the groups except the trauma patients. In spite of the significant decrease in pain, 54 percent of our patients reported pain scores of 5 or greater upon discharge, and only 5.3 percent reported no pain at discharge. An NRS pain score of 5 or greater is considered to reflect moderate pain.[12]

DISCUSSION

We studied four different groups of ED patients who we believe are at particular risk for undertreatment of pain: patients with abdominal pain, chronic pain, abscess pain, or trauma-related pain. Our goal was to elucidate possible reasons for their undertreatment. Unlike previous studies in the ED setting, we questioned not only the patients but also the patients' nurses and physicians to determine the basis of clinicians' decisions regarding opioid administration.

Forty-one percent (n = 59) of the 144 patients in our sample received opioids alone for pain, a frequency different from those seen in previous studies.[6,13,14] The 94 patients we isolated for this report rated their pain as severe upon arrival at the ED. Pain decreased significantly over time when considering the group as a whole and three of the four chief complaint groups. While the amount of opioids administered to these patients was not statistically different, patients with abdominal pain received a substantially lower average opioid dose (8.9 mg) than did patients with chronic pain (19.8 mg). That abdominal pain patients received the lowest doses of opioids may not be too surprising, given the traditional surgical dogma dictating that analgesics be withheld from such patients until a diagnosis is established, so they don't affect the physical examination. It is also sometimes believed that opioids can mask symptom progression or prevent the accurate and timely diagnosis of serious disease. In our study, physicians caring for patients with abdominal pain believed that they "weren't in that much pain" and an opioid was unwarranted. The lower dose of opioids received by abdominal pain patients did not seem to prevent a change in pain intensity over time, since their pain intensity scores at discharge were significantly lower than at admission. Factors other than opioid administration that influence or decrease abdominal pain were not explored in this study.

While trauma patients had the lowest pain intensity scores (NRS = 6.4) at admission, those scores were close to what is considered to be severe pain (NRS = 7 to 10).[12] Although 11 out of 20 of our patients with trauma pain received opioids, trauma pain did not decrease significantly over the patients' time in the ED. There was no documented concern on the part of clinicians that these trauma patients had unstable vital signs or altered mental status. There was, however, a documented concern from

Table 6. Patient- and physician-reported pain intensity scores for abdominal pain patients (n = 30) and opioid doses				
	Patient-reported score	**Physician-reported score**	**Number of patients who received opioids**	**Opioid dose* administered**
Physician chose "not in that much pain" (n = 14)	6.7 + 2.2[a]	2.7 + 1.3[a]	4	4.0 + 1.6 mg[c]
Physician did not choose "not in that much pain" (n = 16)	8.1 + 1.7[b]	6.1 + 2.2[b]	14	10.2 + 2.2 mg[c]
* As morphine equivalent; a = $p < 0.001$; b = $p = 0.003$; c = $p < 0.02$.				

a few physicians that treatment of the trauma patients' pain was not a priority. The patients that we studied were second-tier trauma activation, and thus of lower urgency than first-tier trauma patients. Perhaps this accounted for some of the physicians' decision that treatment of pain was not a priority. Careful consideration should be given regarding administering opioids in a timely manner to trauma patients (unless specifically contraindicated).

While many nurses of chronic pain patients felt that opioids were "not appropriate," 10 chronic pain patients received the highest doses of opioids provided to patients in any group. These may have been situations where a physician's prescription for opioids was carried out by the nurse in spite of the nurse's own belief that the patient wasn't in much pain. Patients with chronic pain often adapt behaviorally and therefore may not exhibit common pain behaviors when seeking care in an ED.[15] It may have been a lack of outward signs of pain that led nurses in this study to believe that opioid administration was not appropriate. Future research could explore the influence of pain-exhibiting behavior on nurses' judgments about chronic pain patients' level of pain and appropriate analgesic interventions.

The reason most often given by clinicians for administering low-dose opioids or no opioids at all was that the patient was "not in that much pain." Yet those patients who were deemed by their clinicians to be "not in that much pain" were, by self-report, experiencing moderate pain at admission. For emergency clinicians, current challenges in pain management may be to believe the patient's report of pain and its intensity, to use treatments and medications appropriate for the level of pain reported, to reassess the efficacy of these interventions, and to provide additional treatment as needed. Other investigators have noted that only patients who reported severe pain received frequent pain assessments.[16] Whether those frequent assessments resulted in greater analgesic administration or pain relief was not reported, but Tcherny-Lessenat and colleagues[9] found that patients who reported mild to moderate pain received fewer analgesics and obtained less relief than did patients reporting higher pain intensity. It may be that those patients with higher pain scores were more demonstrative and therefore received more attention.

Like others,[8,17,18] we found a significant discrepancy between the patients' self-reports of pain and clinicians' assessments of their pain, with patients reporting they were in significantly more pain than assessed by their nurses or physicians. The reasons for this underestimation are unclear. It has been theorized that true underestimation may occur because a patient's pain is evaluated by proxy, and since pain is a subjective experience it cannot be fully appreciated by the clinician. Some postulate that the daily observation of pain by clinicians may blunt their ability to appreciate pain.[19] This issue is indeed complex and may need to be studied through the use of clinicians' narratives concerning their decision-making processes and patients' narratives concerning factors influencing their pain reports.

In summary, we initially hypothesized that an ED patient's pain experience and clinicians' opioid management of the patient's pain would be influenced by the patient's chief complaint. Contrary to that hypothesis, we found that admission pain intensity scores and amount of opioids received did not differ significantly among the patient groups. Still, there were important differences in treatment and outcome. Nurses and physicians of patients with abdominal pain were influenced by their (inaccurate) belief that their patients weren't in much pain, and they made decisions regarding opioids according to this belief. In addition, the pain experienced by trauma patients did not decrease across their time in the ED, while other patients saw significant decreases in their pain. These findings highlight the complexity of pain assessment and treatment and should prompt further investigation of opioid management practices in EDs.

Limitations

Although we limited patients in our study to four categories of chief complaint, there still could have been several other factors that influenced their clinicians' decisions

about opioid use. However, since we used actual patient encounters and reported on actual opioid use, in terms of both frequency and amount, we had a greater chance of identifying factors that influenced unique patient-provider situations. Despite presenting clinicians in our study with a detailed list of potential factors (based on prior research and clinical experience) that could have influenced their treatment decisions, many clinicians noted that other factors influenced them. We agree with Tamayo-Sarver[20] that "the decision to prescribe opioids is complicated." Finally, the decision-making process of nurses regarding the administration of a prescribed "pro re nata" opioid has not been fully explored in this study.

CONCLUSION

Our patients with abdominal, chronic, abscess, or trauma pain arrived in the ED with moderate to severe pain. The amount of opioids they received was greater than reported in some studies, yet improvement of pain intensity depended more on the patient's chief complaint. Clinicians often think that opioids are not an appropriate treatment because they believe the patient's pain severity level does not warrant opioids. Identification of factors that may influence patients' reporting and clinicians' pain assessment and clinical decisions may provide a basis for focused research on appropriate pain management techniques aimed at decreasing pain in ED patient populations who are at risk for inadequate pain control.

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Renal effects of opioid exposure: Considerations for therapeutic use

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ABSTRACT

In recent years, the discovery of peripheral opioid receptors has challenged the dogma of opioids interacting exclusively with the central nervous system. In this article, we describe the current understanding of the roles of opioids and opioid receptors in renal physiology and pathophysiology. The renal response to opioid exposure varies depending upon the specific opioid agonist, dose, and duration of exposure. The known acute effects of opioids on the kidney impact salt and water balance. The chronic effects of opioid exposure on kidney function are largely unknown, but collapsing glomerulopathy has been associated with chronic heroin abuse. Opioid exposure can lead to both physiological and architectural renal changes, and this may have important clinical implications. Since opioids are often used for pain management in patients with existing kidney disease, their role in kidney function warrants attention.

Key words: opioid, morphine, kidney, renal function, endothelium

INTRODUCTION

Opioids have been used for nearly six centuries for pain control, including by Hippocrates (460-377 BC), considered the founding father of medicine.[1] The clinical use of opioids for pain control has exploded as more opioid agonists have become available. However, the clinical significance of opioid use goes well beyond pain control and requires an understanding of the drugs' role in organ disease, especially when treating patients with pre-existing conditions. Opioid actions, previously believed to be confined to the central nervous system, have attracted considerable attention for their existence and possible functions in peripheral systems.[2-4] Increased understanding of opioid signaling pathways has opened the door to new vistas in terms of understanding their role in growth, survival, and vital physiological functions such as vasodilation.[5] Our laboratory, at the University of Minnesota, showed that morphine stimulates angiogenesis-dependent tumor growth and ischemic wound healing.[6,7] We also found evidence that opioids and opioid receptors play an important role in the maintenance of normal kidney physiology in mice.[8] Data are beginning to emerge that suggest both exogenous and endogenous opioids have important actions on the kidney. The renal response to opioid exposure varies depending upon the specific opioid agonist, dose, and duration of exposure (acute vs. chronic). The text to follow explicates the renal effects of endogenous and exogenous opioids, their receptors, and the potential renal consequences of acute and chronic opioid exposure.

OPIOID RECEPTORS

Opioid receptors (ORs), once thought to be expressed exclusively in the central nervous system, have also been identified in the kidney, and acute opioid administration has been shown to have various renal effects.[3,4] To date, four different ORs have been cloned: μ, δ, κ (MOR, DOR, and KOR, respectively), and nociceptin (ORL1).[9,10] Like other receptors, opioid receptors have specific agonists and antagonists.

Agonist selectivity is thought to be attributed to the first and third extracellular loops of MOR, the second extracellular loop of KOR, and the third extracellular loop of DOR. Opioid receptors have about 60 percent identity, with the highest homology in the transmembrane region and the most diversity in the N and C termini.[11] DOR was first characterized in the mouse vas deferens. There are several isoforms of OR, with various affinities for opioid ligands. KOR has a high affinity for dynorphin A. MOR has a high affinity for morphine, although morphine interacts with all ORs. ORL1 has been identified in humans, rats, and mice, with over 90 percent conserved homology between species.[9] ORL1 is included in the OR family based on structural characteristics, in spite of little pharmacologic homology. Opioid receptor expression can be modulated by proinflammatory cytokines and growth factors.[11] For example, interleukins (IL) 1 and 6 and vascular endothelial growth factor (VEGF) stimulate MOR expression, while nerve growth factor and IL4 stimulate DOR expression in different cell types.[12] Thus, the

changing microenvironment in different pathological conditions may have an effect on opioid receptor activity, depending upon the receptors' expression.

SIGNALING

Opioid receptors belong to a superfamily of seven transmembrane G-protein-coupled receptors (GPCRs). Upon activation, opioid receptors are coupled to Gi/Go proteins, which interact with several downstream effectors to inhibit adenylate cyclase and voltage-gated Ca^{++} channels.[11] However, chronic activation leads to cyclic adenosine 3',5'-monophosphate (cAMP) superactivation and increased cAMP.[9] Because cAMP is a survival factor for endothelial cells, acute and chronic activation can be a matter of death and survival, respectively, in endothelium. Endothelium and vasculature play critical roles in kidney pathology and function. Therefore, in this context, it is reasonable to believe that short- and long-term effects of opioid exposure on the kidney can be opposite each other.

ORs (similar to other GPCRs) are capable of signaling via the family of mitogen-activated protein kinases (MAPKs). MAPKs constitute a family of seronine/threonine kinases that are important in cell processes such as growth, response to external stimuli, and apoptosis.[13] Three major subfamilies of MAPK exist, including the p44/p42 (ERK1/ERK2), JNK, and p38. The p44/p42 pathway is activated by growth factors, while the JNK and p38 MAPK pathways are also stimulated by external stressors such as inflammation. It is theorized, and shown in vitro, that activation of MAPK allows GPCR agonists to modulate such diverse molecular events as cell proliferation, differentiation, and survival.[14] MOR, DOR, and KOR have the ability to signal through MAPKs in various cell types.[15-17] MOR, DOR, and KOR activation in endothelial cells results in stimulation of the p44/p42 MAPK pathway and subsequent proliferation.[6]

Figure 1 shows that ORs have the ability to signal through cAMP and PI3 kinase in addition to MAPK.[18-20] ORs stimulate vasodilatory, cytoprotective, and growth-promoting signaling by activating nitric oxide, hemoxygenase-1, cycloxygenase-2, and signal transducer and activator of transcription. Classical activation of these pathways involves growth factor stimulation of a receptor tyrosine kinase (RTK), which ultimately leads to downstream signaling and p44/p42 MAPK activation.[21] However, transactivation of RTK by GPCR has been well described.[22,23] This is also true for opioid receptors. For example, MOR transactivates epidermal growth factor receptor[24] and VEGF receptor 2/Flk-1.[25] DOR and KOR have also been indirectly associated with RTK transactivation.[15] Stimulation of vasodilatory, cytoprotective, and growth-promoting mechanisms by ORs may be critical in kidney function (Figure 1).

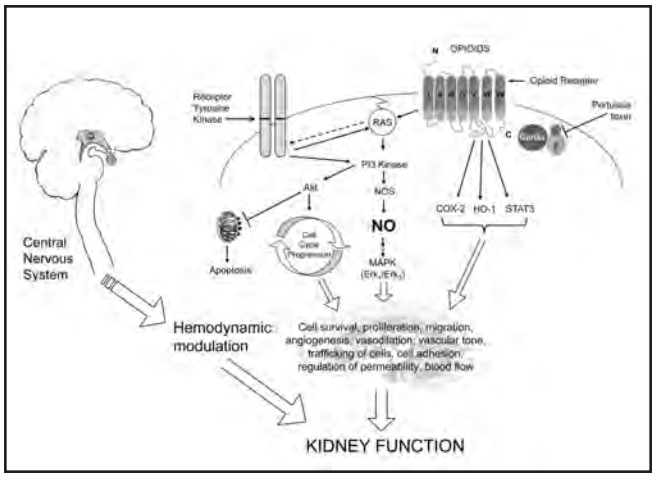

Figure 1. Proposed effect of opioids on kidney function. NOS, nitric oxide synthase; NO, nitric oxide; MAPK, mitogen-activated protein kinase; COX-2, cyclooxygenase-2; HO-1, hemoxygenase-1; STAT3, signal transducer and activator of transcription.

RENAL EFFECTS OF ENDOGENOUS OPIOIDS

Endogenous opioids have a profound effect on kidney homeostasis of salt and water balances (Table 1). Surgically manipulated, stressed rats have an antinatriuretic response to administration of the endogenous opioid dermorphin, without changes in renal blood flow, glomerular filtration rate (GFR), or blood pressure; this response was blocked by naloxone.[26] In a different study, low-frequency renal nerve stimulation led to an antinatriuretic response that was also inhibited by naloxone.[27] When viewed together, these studies outline the importance of stress-induced activation of the peripheral endogenous opioid system on kidney function.

Considerable evidence supports the participation of endogenous opioids in renal function.[2,28-31] Under basal conditions, the opioid system remains quiescent, but when dietary sodium is restricted, central opioid pathways are activated as a mechanism to retain a maximum of sodium.[30,32,33] Other data suggest that opioids modulate renal function via central and sympathetic nervous system dependent and independent pathways.[34] For example, intracerebroventricular (ICV) injection of dermorphin produced an increase in urine flow rates in denervated animals as well as in controls.[32] These animals also displayed decreases in urine sodium excretion, without alterations in GFR or effective renal plasma flow. These alterations were assumed to have been prevented by pretreatment with a selective MOR antagonist, suggesting a direct effect on renal tubular absorption via renal MOR. KOR agonists induce a profound diuretic and antinatriuretic response involving both central and peripheral mechanisms which are yet to be defined.[30,33,35-37] Beyond their physiological effects,

Table 1. Role of opioid receptors in renal function				
	MOR agonist	**DOR agonist**	**KOR agonist**	**ORL1 agonist**
Renal physiologic effects	Antidiuretic (H)[43]	Aquaresis Natriuresis[46]	Aquaresis Antinatriuresis[30,33,35-37,45]	Aquaresis[47]
Kidney cell effects	Proliferation of: – interstitial cells[50] – mesangial cells[8,51] – epithelial cells[49]	Undefined	Proliferation of mesangial cells[8]	Undefined
CNS dependence	+/-	+	+/-	+/-
Therapeutic uses	Uremic pruritis (naltrexone as an antagonist)[57]		Diuretic (Nirvoline)[58]	

endogenous opioids may promote pathological structural changes within the kidney. β-endorphin amplifies the proliferative effect of IL1 on cultured mesangial cells.[38] Given this data, it is interesting to consider whether endogenous opioids play a pathologic role in the progression of chronic kidney disease. Indeed, significantly elevated plasma β-endorphin levels were found in patients with uremia and chronic renal failure and in patients on dialysis.[39-41]

RENAL EFFECTS OF EXOGENOUS OPIOIDS

Acute effects

Morphine induces a transient, dose-dependent reduction in blood pressure and a dose-dependent elevation in atrial natriuretic peptide (ANP) in both control and denervated animals.[42] The reduction in systemic arterial blood pressure caused by morphine and other MOR agonists can cause a marked reduction in urine output as a result of a secondary decrease in renal hemodynamics and inhibition of baroflex pathways. These lead to an increase in antidiuretic hormone secretion and augmentation of central sympathetic outflow to the kidneys, thus bringing about the diminished output. Renal responses to morphine exposure are dependent upon the integration of several different actions, including ANP release, decreased arterial pressure, subsequent activation of sympathetic nerves, and direct effects on the kidneys.[34]

Morphine, a MOR agonist, is one of the most common substances used in clinical settings. Acute administration of morphine in relatively high doses leads to a decrease in urine output, while lower doses lead to increased urine output and an increase in GFR.[43] The reduction in systemic arterial blood pressure caused by morphine can also decrease GFR. Acute KOR-agonist administration produces a profound diuretic and antinatriuretic response, the mechanism of which is unclear.[44,45] DOR agonists acutely promote diuretic and natriuretic effects.[46] Stimulation of the ORL1 receptor induces a dose-dependent aquaresis by vasopression-independent inhibition of aquaporin 2.[47]

Opioid exposure results in myriad effects outside the realm of antinociception and has been shown to induce a proliferative phenotype in a variety of kidney cell types. Seven days of morphine exposure significantly altered the presence of microprojection on podocytes, as assessed by scanning electron microscopy.[48] Morphine exposure over 48 hours was shown to lead to proliferation of glomerular epithelial cells at low doses and apoptosis at higher doses.[49] Renomedullary interstitial cells underwent proliferation and had increased matrix deposition in response to morphine compared to vehicle.[50]

Chronic effects

The renal consequences of chronic exposure to specific opioid receptor agonists are unknown. The only example of an opioid potentially inducing renal injury is the poorly characterized heroin-induced nephropathy (HIN), which is characterized by collapsing glomerulopathy, a variant type of focal and segmental glomerulosclerosis (FSGS).[1,3,51,52] There is also debate as to whether HIN truly exists or is related to contaminants injected with heroin. The data for or against HIN itself are based largely on case reports and speculation. However, there is a growing literature on the in vitro effects of morphine (a metabolite of heroin) on kidney cells of various types. Morphine exposure induces proliferation of cultured rat mesangial cells, suggesting that

opioids may play a significant role in mesangial expansion.[50] Furthermore, morphine has been shown to increase superoxide production in kidney cells.[49] Oxidative stress is a potential mechanism by which opioids may in some way contribute to the progression of chronic kidney disease. One study showed that rats exposed to long-term intraperitoneal morphine had elevated creatinine values and increased vacuolization in tubular cells compared to controls.[53] It is important to note that classic lesions of FSGS are initiated with mesangial cell hyperplasia and mesangial expansion.[54,55]

THERAPEUTIC CONSIDERATIONS

Peripheral effects of opioids may have clinically beneficial aspects, as well. For example, naltrexone has been used to treat the pruritis associated with chronic kidney disease.[56] Furthermore, opioid receptor agonists can potentially be used as diuretics to treat edematous states associated with cirrhosis or congestive heart failure. Niravoline, a KOR agonist, has been shown in rats to produce a superior aquaresis compared directly to an ADH V2 receptor antagonist.[57]

CONCLUSION

Given the increased utilization of opioids for acute and chronic pain control in a number of disease processes, it is timely to define nonanalgesic renal effects of opioids. Experimental data show that opioids are likely to have physiological renal effects. It remains to be seen whether the observed stimulation of proliferation of kidney cells enacted by endogenous and exogenous opioids translates into a clinically relevant effect. Furthermore, the differential effects of opioid receptors on renal structure and function raise therapeutic implications. Thus, a better understanding of the mechanisms by which opioids exert renal effects is required in order to use them in a more clinically beneficial manner.

In the year 2000, the number of patients with chronic kidney disease (CKD) progressing to a point necessitating renal replacement therapy was over 370,000. This number is projected to double by 2010.[58] This alarming figure represents a public health crisis in terms of morbidity, mortality, and healthcare costs. The possibility that opioids may in any way contribute to the progression or therapy of CKD is a novel idea that requires more attention.

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