Journal of Opioid Management™

A medical journal for proper and adequate use

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Official Journal of Opioid Management Society

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AD

OPIOID CERTIFICATION PROGRAM

Presented by

OPIOID MANAGEMENT SOCIETY™

In association with

Journal of Opioid Management™

This 2-day program, held at The Conference Center at Harvard Medical in Boston and led by a renowned group of specialists, is designed to inform primary care physicians, pain specialists, and other opioid prescribers in the uses, abuses, and legal ramifications of opioids.

Upon completion of the entire program, the Society will issue a framed certificate verifying that you have completed the program.

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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).*

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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.

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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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Journal of
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A medical journal for proper and adequate use

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

The law and pain

Christopher V. Rowland, Jr., MD

Marshall Kapp opens this issue with a fine editorial on the law and assisted suicide. A recent Supreme Court's decision is quite narrow, and the matter will be shifted from the judicial to the legislative arena. There it will concern all who prescribe opioids.

In a second legal contribution, Jennifer Bolen takes on the daunting task of explicating the Drug Enforcement Administration's positions on controlled substances for treatment of pain. These in turn lead to federal legal and regulatory standards, which seem to be shifting under the weight of revisions of revisions. A final revision is promised, but there seems to be no time when. If she, as an attorney in this field, finds unclear boundaries and inconsistencies, the rest of us have every right to be anxious.

Anthony Guarino, et al., take up just this point with the use of oral transmucosal fentanyl for the treatment of patients with noncancerous pain. The FDA declares in a black box warning that its only use is for cancer breakthrough pain for patients already on opioids. This study follows 29 patients treated for noncancerous pain in an academic setting and finds that the medication is both safe and works well. Are the authors and patients to be congratulated or jailed?

Ruth Zalansky, and colleagues, present a paper on the early use of oral morphine after orthopedic surgery. IM morphine is widely used, but works poorly. IV and patient-controlled epidural routes work well but are expensive, more work, and of limited availability. Oral morphine given early postoperatively was found to be safe, easily administered, and effective.

Mafrica and Fodale consider the problem of opioid use for patients with Down's syndrome. Neurotransmission abnormalities involve opioid receptors and pain transmission, so that special evaluation and care must be taken to avoid respiratory arrest and other complications in this group. If so, the goals of sedation, anesthesia and analgesia may be achieved.

Lim, Wilson, and Katz take up the issue of patient-controlled epidural pethidine after caesarean section, compared to intermittent, nurse-controlled administration. Patients in the first group had improved pain scores at rest and when moving during the 48 hours post-operatively, and there was increased nurse satisfaction with this procedure. There was also a slightly earlier trend to return to activities of daily living and caring for newborns in the first group. Sometimes patients know what works best.

To end up this issue, Turner, Lane, Kott, and Hauk write about the use of the emergency department across New York State by HIV+ drug users. They find that repeated visits were greatest in rural areas and small cities (40.7%) and least in New York City (24.1%). They conclude that the availability of long-term treatment for this cohort is likely better, less costly, and makes more sense than using the ED as a primary care physician for these complicated patients.

In the end, what do we want from the opioids? The law must be there, but we do not want the law to be our physician. Die we must, but not with more pain than we can bear and hopefully not alone.

Christopher V. Rowland, Jr., MD
Editor

WELCOME TO OMS CONFERENCE

OPIOID MANAGEMENT SOCIETY
470 Boston Post Road
Weston, MA 02493

Dear Colleagues,

It is with great pleasure that I anticipate welcoming many of you to Boston and the Conference Center at Harvard Medical for the Opioid Management Society's first annual Opioid Certification Program on April 22-23.

As my fellow members of the Society's educational advisory board know all too well, as do many of you, the readers of this journal, there are a number of pressing and critical issues to address surrounding the use, management, abuse, and legal ramifications of these powerful painkillers—issues we will present, discuss, and grapple with throughout this intensive, two-day conference. To get an idea of the breadth and depth of this conference, as well as future ones we will hold, I invite you to review the complete program schedule listed here on pages 68 and 69.

If you've registered and are looking forward to a full and compelling weekend, I don't think you'll be disappointed. If you were unable to come, don't worry; the Society is already planning future conferences, not just in Boston, but in a number of locations across the country.

If you think you'd like to attend one of our future conferences, please let us know. Simply go to *www.opioidmanagementsociety.org*, click on "Upcoming Conferences," fill out the simple form, and we'll send you periodic updates to keep you informed.

So, if I don't see you in Boston, perhaps I'll see you in Chicago, or Miami, or San Francisco!

Very truly yours,

Robert E. Enck, MD

Robert E. Enck, MD
Opioid Management Society
Professor of Medicine
Division of Medical Oncology
Thomas Jefferson University
Philadelphia, PA

Day One* – Saturday, April 22, 2006 8:00 AM – 4:30 PM

INTRODUCTION

Rationale for OMS, JOM, Opioids and Usage

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

Pain is a worldwide problem causing needless suffering along with a significant economic burden. Opioid drugs are the cornerstone to addressing this problem but are often underused and misunderstood. The goal of this conference is to provide a remedy to understanding opioid management for acute and chronic pain. Education, both from a medical and regulatory view, is the lighting rod to start this process.

DEA—The Federal View of Drug Diversion Drug Use: A National Perspective

Mark J. Rubbins, Director, Drug Diversion Department

Drugs, Documentation and the DEA

Jennifer Bolen, JD, Founder, The Legal Side of Pain®

Many practitioners fear repercussions from the DEA when prescribing controlled substances to treat pain. Living in fear of the DEA or any other legal/regulatory entity will not help pain professionals care for patients in pain, but understanding the interplay of law and medicine will encourage a proper perspective and quality medical care. The goal of this lecture is to give pain professionals some perspective on legal/regulatory issues and provide them with tools and resources to assess the current state of their compliance with federal and state legal/regulatory materials on prescribing controlled substances to treat pain and make necessary improvements in medical record documentation.

This lecture will cover recent DEA enforcement activity, current federal and state legal/regulatory material on prescribing controlled substances to treat pain, and common challenges pain professionals face in daily practice.

Legal and Ethical Standard for Palliative Care Involving Opioid Use

Marshall B. Kapp, JD, MPH, Dr. Arthur W. Grayson Distinguished Professor of Law, School of Law, Southern Illinois University

This presentation will explore the various factors that help influence the development of legal standards of care regarding the provision of palliative care to patients experiencing physical pain and emotional suffering, with special attention to the role of opioid prescription as a component of palliative care. By comparing legal standards of care with the ethical requirements of good palliative care, this presentation will ask whether the law can exert a positive, therapeutic influence on medically effective and humane patient treatment in this context.

Opioids in Everyday Practice—Legal Aspects

Tomasz Stefaniak, MD, PhD, Department of General, Endocrine, and Transplant Surgery, Medical University of Gdansk, Poland

Since the introduction of the WHO analgesic ladder, serious changes have taken place in worldwide care. First, progress in the treatment of malignancies has provided patients with much longer duration of survival. Second, further research into the adverse effects of opioids has been undertaken, presenting various problems associated with use of those medications. Therefore, it has been postulated that the indications for use of the WHO analgesic ladder should be reconsidered, and other treatment methods for pain, including psychological, surgical, and complementary medicine should be considered.

It should be emphasized that opioid use may mean legal problems resulting from addiction and underprescribing. Therefore, re-evaluation of the WHO analgesic ladder should be performed, and strict criteria evaluated for the use of opioids as well as precise standards of diagnosing and treating iatrogenic addiction.

Legal Issues Among Opioid Prescribers: One Physician's Viewpoint

Paul Alexander Sloan, MD, Professor, Department of Anesthesiology and Oncology, University of Kentucky Hospital

Federal laws allow for appropriate physician prescription of opioids for the management of chronic pain. Governing regulations can both help and hinder the physician in the practice of pain therapy. This session will briefly give one physician's viewpoint regarding the appropriate use of opioid therapy using current guidelines and regulations. Specific patient examples will be used to engage audience participation.

Psychopharmacology, Antidepressants, Drugs, Opioids: Acute and Chronic Pain—A Pharmaceutical Overview

Robert L. Barkin, MBA, PharmD, FCP, DAAPM, Associate Professor, Departments of Anesthesiology, Family Medicine, Pharmacology, and Psychology, Rush University Medical Center

The clinician, following this presentation, should be able to discriminate acute pain from chronic pain and somatization presenting as pain. The clinician will be able to utilize pharmacotherapeutic (pharmacology, pharmacodynamics, pharmacokinetics), differences among analgesics, NSAIDs (Cox I and COX II), opiates/opioids, antiepileptic drugs (AEDs), antidepressants, centrally acting agents, skeletal muscle relaxants, anxiolytics, sedative/hypnotics, in a patient specific manner.

Pain—How to Deal with It

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

Pain is a complex neurophysiologic response to a noxious stimulus which is screened and adapted by each person's brain. Younger persons express pain differently from older persons due to the filtering effect of lifelong experiences. Culture has a significant modulating influence on the perception of pain as well. There certainly are other factors, both internal and external, which in combination or singly must be appreciated to manage any person with pain.

Physicians tend to underestimate a person's pain intensity by a third. Part of this under perception is often related to a failure to understand these complicating external factors. Therefore, it is important to educate physicians, both young and old, in the recognition and management of confounding issues in pain management.

Managing Pain Without the Use of Opioids

Gilbert J. Fanciullo, MD, Associate Professor of Anesthesiology, Pain Management Center, Dartmouth-Hitchcock Medical Center

The presence of acute pain from cancer and other noncurable progressive illnesses almost always precludes the option to exclude opioids from our treatment regimen. Patients suffering from chronic pain and addiction, patients who have diverted their prescription drugs, or patients incarcerated for drug related offenses who may not have objective evidence of a painful disorder may not be candidates for opioid treatment, but other acceptable options exist to help diminish their pain. Behavioral interventions often improve quality of life and diminish suffering and pain. Treatment of coexisting psychological or psychiatric disorders including addiction, depression, anxiety, and personality disorders can be effective, and utilizing physical medicine treatments and advice will almost always help. Injection therapy, implantable devices, and neurolytic procedures also exist in the nonopioid armamentarium and should be utilized whenever possible. Attention to diet should not be overlooked. Complementary/alternative treatments are useful for some individuals.

Day Two* – Sunday, April 23, 2006 8:00 AM – 3:30 PM

History of Opioids

Ricardo Vallejo, MD, PhD, FIIP, Director of Research Staff, Pain Medicine, Millennium Pain Center

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.

Science of Opioids

Mellar P. Davis, MD, FCCP, Medical Director, The Harry R. Horvitz Center for Palliative Medicine, Taussig Cancer Center, The Cleveland Clinic

Opioids function under the opponent process theory which is that pleasant and/or aversive effects of drugs are automatically opposed by centrally mediated mechanisms that progressively reduce the intensity of drug effect. In opioid pharmacology the opponent theory is synonymous with opioid tolerance.

Opioid tolerance is a clinical fact based upon the correlation of animal data, clinical experience, the opioid withdrawal syndrome, and well documented cases of opioid facilitated pain. Opioid withdrawal is a result of pronociceptive counter-opioid responses due to chronic opioid receptor activation. Intracellular pronociceptive neuroplastic responses to opioid receptors include: 1) activation of protein kinase C, 2) activation of NMDA receptors, 3) production of prostaglandins and nitric oxide, and 4) up regulation of kinase due to increased intracellular calcium, which in turn inactivates opioid receptors. Intercellular events include up regulation of CCK in the rostroventral medial medulla and spinal dynorphin, both of which activate downward facilitatory pathways through the dorsolateral funiculus to the dorsal horn. In addition, surrounding glia is activated by morphine.

Rotation of Opioids

Gilbert J. Fanciullo, MD, Associate Professor of Anesthesiology, Pain Management Center, Dartmouth-Hitchcock Medical Center

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. Many practitioners create an arbitrary upper limit on opioid daily dose, particularly in their chronic pain patient population. A rational and useful option in situations where the ceiling has been reached but higher opioid doses may help to reduce pain is opioid rotation.

Opioid rotation takes advantage of incomplete opioid cross-tolerance which implies that an equianalgesic dose of a different opioid—one that the patient has not been exposed to 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.

Types of Opioids

Gary M. Reisfield, MD, Assistant Professor; Director, Division of Palliative Medicine, University of Florida Health Science Center

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. nonanalgesic. 5) By federal schedule (CI-CV). 6) By receptor affinity. 7) Legal vs. illegal. 8) Agonist vs. partial agonist vs. antagonist.

Uses for Opioids

George R. Wilson, MD, Associate Professor and Chairman, Department of Community Health and Family Medicine, University of Florida Health Science Center

There are many uses for opioids. Some examples: 1) Analgesia (This, of course, will be the major focus of the talk. It will touch briefly on the other uses listed. They're fascinating and most people are not aware of many of them). 2) Anesthesia (e.g., high-dose fentanyl, sufentanil). 3) Antitussive (chiefly codeine). 4) Antidiarrheal. 5) Antispasmodic (belladonna and opium suppositories). 6) Drug abuse (heroin as well as licit opioids). 7) Opioid maintenance treatment (methadone, LAAM, buprenorphine). 8) Opioid detoxification (buprenorphine). 9) Vasodilatation/smooth muscle relaxation (papaverine): a. Erectile dysfunction; b. Vasospasm. 10) Antiterror (The Russians used aerosolized opioids against Chechen separatists in the 2002 Moscow hostage crisis).

Interventional Techniques Used in Pain Management

Ramsin M. Benyamin, MD, DABPM, FIPP, President, Millennnium Pain Center, Bloomington, Illinois; Staff Anesthesiologist, BroMenn Hospital

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. In addition, slides of actual procedures will be presented to help illustrate the techniques.

Non-Opioid Strategies for Dealing with Pain

Ronald J. Kulich, PhD, Attending Psychologist, Harvard Medical School and Tufts School of Dental Medicine

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 regiment 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.

**Program subject to change*

CALENDAR

Opioid Management Society/
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Opioid Certification Program
April 22-23, 2006
The Conference Center
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American Pain Society
25th Annual Scientific Meeting
May 3-6, 2006
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& Marriott River Center
San Antonio, Texas

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American Society of Addiction Medicine
37th Annual Meeting and Medical-Scientific Conference
May 4-7, 2006
San Diego Sheraton Hotel and Marina
San Diego, California

For registration information, contact:
American Society of Addiction Medicine
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4601 North Park Ave., Suite 101
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AFFIRMATION OF STATES' AUTHORITY

The Supreme Court of the United States has ensured that states, through their legislatures, professional licensing boards, and citizens' initiatives, will continue to decide what uses of medications are for a legitimate medical purpose.

In Gonzales v. Oregon, the US Department on Justice (DOJ) was seeking authority through the Drug Enforcement Administration (DEA) to make decisions about the legality of prescriptions in all situations, not just end-of-life care. DOJ could, for example, have ruled that under all circumstances the prescribing of Schedule II barbiturates for insomnia is not a legitimate medical purpose, or that prescribing Schedule II opioids for longer than 60 days is not a legitimate medical purpose. This is not to say DOJ would have done this, but it could if the Attorney General had won the case.

The Supreme Court ruling agreed with two lower federal courts that the states have the authority to determine what prescriptions have been issued for a "legitimate medical purpose." For more information on Gonzales v. Oregon ruling go to *www.webmd.com*. (Source: Medscape from WebMD news release, March 8, 2006.)

KNOWING HOW TO PLAY THE GAME; ABUSERS' PAIN RELIEF

The Model of "Knowing How to Play the Game" was developed on the basis of participants' descriptions of their experiences and consisted of two core action categories "Feeling Respected/Not Respected" and " Strategizing to Get Pain Relief." The study examined 18 hospitalized substance abusers', 14 men and four women, strategies for obtaining pain relief. They had many suggestions about nursing actions that were helpful or not helpful in assisting them to obtain pain relief. Nursing practice, education, research, and policy implications were discussed.

The Purpose of this study was to identify and explore the experiences of people who have substance abuse problems who sought pain relief during hospitalization for a medical problem. The research questions were: 1) how do participants with substance abuse problems manage painful medical conditions during hospitalization? 2) what difficulties do they encounter in getting adequate help with pain while hospitalized? and 3) how do participants with substance abuse problems understand their interactions with nurses around issues of pain?

In summary, research examining the issue of pain management in people with substance abuse problems has only been examined over the last decade. Research from the perspective of patients with pain and substance abuse problems is needed to identify problems, strategies to manage the pain, and difficulties that arise in the interactions between patients with these problems and the healthcare professionals who care for them. All participants had a painful medical/surgical problem for which they were hospitalized. Their age ranged from 32 to 60 years. (Source: *Pain Management Nursing*, March 2006; 7(1):31-41.)

ACUTE PAIN AND NARCOTIC USE DOES NOT IMPAIR THE ABILITY TO PROVIDE INFORMED CONSENT

From the Department of General Surgery, Naval Medical Center, Portsmouth, Virginia: Patients evaluated in acute pain will often have narcotics withheld until after the patient has been evaluated by a surgeon and has given informed consent. Concern that the patient would have impaired judgment due to narcotic effects often prevent the administration of timely pain relief. The Hopkins Competency Assessment Tool (HCAT) is a validated instrument for both psychiatric and medical patients; it has not been validated to evaluate drug effects on judgment. Thirty consecutive patients agreed to participate in the trial over a 12-month period. The HCAT was administered prior to the planned major elective procedure and repeated on each postoperative day up to and including postoperative day five. Narcotic use (as morphine equivalents), HCAT scores, demographic data, and surgical procedures were recorded. The average of our patients was 53 years. Twenty-seven patients passed the initial HCAT, and one patient failed subsequent exams. No correlation was seen between HCAT score and narcotic dose. Narcotic administration sufficient for pain control does not impair the ability to provide informed consent. The only patient who failed the HCAT after an initial passing score was somnolent on the narcotic dose. (Source: *American Surgery*, February 2006; 72(2): 154-7.)

MASSIVE AMOUNTS OF PAIN MEDICATION

It is common practice in pain management to use a long-acting analgesic titrated to an appropriate level to control baseline chronic pain and to add a second, short-acting agent on an as-needed basis to treat occasional

breakthrough pain. It is recommended to determine whether therapy improves patient functionality prior to embarking on a course of long-term opiate therapy. If clear pain relief and improved functionality are not demonstrated, then other medication classes should be considered, as should nonpharmacologic alternatives to achieve patient-specific pain goals.

The rationale for prescribing two long-acting opioids (e.g., methadone and MS Contin) is questionable and appears to be a duplication of therapy. The duration of this particular prescribing regimen is not known; thus, it cannot be determined whether there is intent to wean the patient from extended-release morphine sulfate (MS Contin) and convert to methadone as a single long-acting agent, or otherwise switch to a different long-acting agent. The need for simultaneous prescribing of more than one long-acting opiate and the lack of a short-acting agent for breakthrough pain relief should be questioned.

The pharmacokinetics of methadone are reviewed briefly as follows: methadone acts at μ-receptors, inhibits NMDA receptors, and inhibits monoamine reuptake. The duration of analgesia is approximately three to six hours at the start of therapy and extends to eight to 12 hours with repeated dosing. Plasma levels of methadone generally stabilize within five to seven days due to its long half-life; dosing more frequently than every eight hours is not recommended. There are protocols available to rapidly discontinue the previously prescribed long-acting opiate and replace it with methadone or taper off the previously prescribed opiate with a concomitant upward titration of methadone. Additional information about converting to methadone dosing can be found in the package insert or in the references cited in this summary.

Patients may be at increased risk for respiratory depression with initial therapy, particularly if they are opiate naive, or if comorbid conditions exist (e.g., sleep apnea, heart failure, obesity, severe asthma, or respiratory conditions). Patients who concurrently take other sedative drugs may also be at risk. Caution should be exercised during upward titration because toxicity may not be apparent for up to five days following dosage change. (Source: Medscape Pharmacists, March 2, 2006.)

EDITORIAL

The US Supreme Court decision on assisted suicide and the prescription of pain medication: Limit the celebration

Marshall B. Kapp, JD, MPH

Most physicians who prescribe opioid medications to treat patients' severe pain problems, including otherwise intractable pain symptoms experienced by patients in the final stages of life, are chronically nervous about various aspects of the legal environment in which they function professionally. One source of legisogenic, or law-derived, anxiety has been concern about exposure to possible federal criminal prosecution for violation of the Controlled Substances Act (CSA). In the past few years, this particular worry has been understandably exacerbated by action taken by the US Department of Justice (DOJ), through the Office of the Attorney General (AG), in response to an Oregon state statute pertaining to physician-assisted suicide.

By way of background, a 1971 regulation published by the AG required that prescriptions written for substances that fall within the CSA be used "for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice." In 1994, Oregon voters enacted through the referendum process the Oregon Death With Dignity Act (ODWDA), which explicitly exempts from civil or criminal liability a state-licensed physician who, in compliance with ODWDA's specific safeguards, dispenses or prescribes a lethal dose of drugs upon the request of a terminally ill patient. In 2001, the AG issued an Interpretive Rule to address the implementation and enforcement of the CSA in light of the ODWDA, declaring that using controlled substances to assist suicide is not a legitimate medical practice and that dispensing or prescribing them for this purpose is unlawful under the CSA.

The state of Oregon initiated litigation to challenge the authority of the AG to issue and enforce that Interpretive Rule. After protracted wrangling in the lower federal courts, on January 17, 2006, the US Supreme Court in *Gonzales v Oregon* (126 S.Ct. 904.) invalidated the Interpretive Rule. The announcement of this judicial decision was accompanied by loud celebration on the part of a variety of proponents of effective pain management for suffering patients. Typical, was this jubilant statement in the January 22, 2006, edition of the *Washington Post*: "Doctors who specialize in pain management and their advocates are hoping that last week's Supreme Court decision upholding Oregon's assisted-suicide law will boost their efforts to defend colleagues accused by the government of illegally prescribing narcotic painkillers to their patients."

The problem, however, is that enthusiastically optimistic assessments of what the Supreme Court did in *Gonzales v Oregon* overwhelmingly have emanated from observers who are responding to the case's particular outcome, but because they have not closely (or actually) read the legal majority and dissenting opinions of the Court in this case, they have not formulated an appreciation of the narrowly confined legal reasoning underlying the majority's decision. A closer reading and appreciation of the majority's opinion in *Gonzales v Oregon*, I believe, may substantially subdue the enthusiasm of pain control advocates about the real impact of this case on the legal environment surrounding pain control clinical practice.

According to Justice Anthony Kennedy, writing for the six-Justice majority in *Gonzales v Oregon*:

> [T]he question before us is whether the Controlled Substances Act allows the United States Attorney General to prohibit doctors from prescribing regulated drugs for use in physician-assisted suicide, notwithstanding a state law permitting the procedure. . . . The dispute before us is in part a product of . . . political and moral debate, but its resolution requires an inquiry familiar to the courts: *interpreting a federal statute* to determine whether Executive action is authorized by, or otherwise consistent with, [the CSA]. … The [AG's] Interpretive Rule's validity under the CSA is the issue before us. (emphasis added)

Under Constitutional principles (the "delegation doctrine") and the federal Administrative Procedure Act, an executive branch agency, such as the DOJ, may promulgate only those administrative rules or regulations that Congress, within a specific statute it has enacted, has

empowered that agency to promulgate. Put differently, a cabinet officer, such as the AG, does not have legal authority to initiate a regulation just because he or she thinks it is desirable as a public policy matter; rather, every regulation must be justified with a specific statutory basis provided by the democratically elected legislative branch of government.

Thus, the legal question decided in *Gonzales v Oregon* was the rather narrow one of statutory interpretation; namely, whether the CSA, as currently written, authorizes the AG to promulgate an administrative rule that defines what is a "legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice." The Supreme Court did *not* find that Congress is *precluded* from authorizing the AG to promulgate such a regulation but did find that Congress had *not chosen* to include such administrative law-making authorization in the language of the CSA, as presently written.

The big concern for advocates of effective pain control, including the option for physicians to prescribe opioids when necessary and appropriate, ought to be that Congress still does have the power under the Constitution to statutorily authorize the AG to promulgate precisely the kind of regulation that was promulgated (without proper statutory authority at the time) in 2001, and that the Supreme Court's *Gonzales v Oregon* decision may inspire Congress to take exactly that action. Or even worse, Congress could directly use an amended CSA to bypass the DOJ altogether and directly outlaw the prescription of lethal drugs within the physician-assisted suicide context. There have already been significant political rumblings in the halls of Congress proposing these very legislative actions.

Hence, for advocates of effective pain control, celebration of the Supreme Court's important but limited decision in *Gonzales v Oregon* must be short lived and restrained. Attention must now be shifted from the judicial arena to the legislative arena to preserve physicians' legal freedom to use their clinical experience and expertise ethically to behave benevolently toward their suffering patients.

Marshall B. Kapp, JD, MPH, Garwin Distinguished Professor of Law and Medicine, Southern Illinois University, Carbondale, Illinois.

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A summary of current Drug Enforcement Administration positions and resulting federal legal and regulatory "standards"

Jennifer Bolen, JD

This article contains a quick summary of the Drug Enforcement Administration's (DEA) current position on using controlled substances to treat pain. My discussion covers three key sources:

1. The Code of Federal Regulations section 1306.04 pertaining to valid prescriptions;

2. *The Interim Policy Statement on Dispensing Controlled Substances for the Treatment of Pain*, published by the DEA in the *Federal Register* on November 16, 2004; and

3. The *Clarification Statement on the Controlled Substances Act and the Use of Schedule II Controlled Substances for the Treatment of Pain*, published by the DEA in the *Federal Register* on August 23, 2005.

In a "back to school" sense, I recommend that you cut out Figure 1, laminate it, and keep it as a quick reference card. The DEA is in the process of drafting a final policy statement on the dispensing of controlled substances for the treatment of pain, but the agency has not said when it will publish this final policy statement. Use our website, *www.legalsideofpain.com*, to stay current on DEA releases. As you read this article, realize that I share your frustration about the lack of clear boundaries and the inconsistency between regulatory and health plan approaches to prescribing controlled substances to treat pain. I, and many others, continue to work for balance and clarity on your behalf.

21 CFR §1306.04–*PURPOSE OF ISSUE OF PRESCRIPTION*

When you receive a federal drug registration number, the DEA expects you to follow federal controlled substances laws, regulations, and policies. Citing federal law, the DEA expects its registrants to administer, dispense, and prescribe controlled substances for **a legitimate medical purpose while acting in the usual course of professional practice**.[1] These two concepts, often viewed formally as a single standard, are well established in federal law. The Code of Federal Regulations (CFR), which explains most of the Controlled Substances Act (CSA) of 1970, contains the "legitimate medical purpose" standard.

In relevant part, 21 CFR §1306.04, entitled *Purpose of Issue of Prescription*, states:

> (a) A prescription for a controlled substance to be effective **must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice**. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, **but a corresponding responsibility rests with the pharmacist who fills the prescription**. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.[2]

A related CFR provision is 21 CFR §1306.05, entitled *Manner of Issuance of Prescriptions*, states:

> **All prescriptions for controlled substances shall be dated as of, and signed on, the day when issued[3] and shall** bear the full name and address of the patient, the drug name, strength, dosage form, quantity prescribed, directions for use and the name, address and registration number of the practitioner. A practitioner may sign a prescription in the same manner as he would sign a check or legal document (e.g., J.H. Smith or John H. Smith). Where an oral order is not

> permitted, prescriptions shall be written with ink or indelible pencil or typewriter and shall be manually signed by the practitioner. The prescriptions may be prepared by the secretary or agent for the signature of a practitioner, but the prescribing practitioner is responsible in case the prescription does not conform in all essential respects to the law and regulations. **A corresponding liability rests upon the pharmacist who fills a prescription not prepared in the form prescribed by these regulations.**[4]

Many states adopt the federal "legitimate medical purpose" standard and incorporate it into state licensing board regulations. Make sure that you know your state's position on what constitutes "legitimate medical purpose within the usual course of professional practice" and that you read all applicable state laws, regulations, and guidelines on controlled substance prescribing and pain management. Use our website, *www.legalsideofpain.com*, to locate these materials.

THE DEA'S *INTERIM POLICY STATEMENT*

In November 2004, following the publication and retraction of a document called *Prescription Pain Medications: Frequently Asked Questions* (the FAQ), the DEA published an *Interim Policy Statement* (IPS) on dispensing controlled substances to treat pain.[5] In part, the DEA published the IPS to explain what the agency characterizes as "misstatements" in the FAQ. The IPS covers, among other things, four key areas of the DEA's concern about the use of controlled substances to treat pain. The DEA published the IPS in the *Federal Register*, meaning that it is the agency's official statement on matters related to the CSA. Also, it means that the DEA will use the IPS when it performs agency functions relating to registrants and prescribed controlled substances. The DEA acknowledges that both chronic pain and the abuse and diversion of controlled substances to treat it are large problems in the United States.

THE IPS AND THE DEA'S ABILITY TO COMMENCE INVESTIGATIONS

The DEA contends the FAQ contains language that suggests the "DEA must meet some arbitrary standard or threshold evidentiary requirement to commence an investigation of a possible violation of the Controlled Substances Act."[6] Federal law does not require the DEA to meet any such standard. It is a "longstanding legal principle—that the Government 'can investigate merely on suspicion that the law is being violated, or even just because it wants assurances that it is not.'"[7]

Thus, the DEA first uses the IPS to remind registrants that it may initiate an investigation of a registrant at any time and for any reason without jumping through any "hoops."[8]

In the IPS, the DEA states the "FAQ erroneously stated '[t]he number of patients in a practice who receive opioids, the number of tablets prescribed for each patient, and the duration of therapy with these drugs *do not, by themselves, indicate a problem*, and they should not be used as the sole basis for an investigation by regulators or law enforcement.'"[9] The DEA acknowledges that these factors, while not "necessarily determinative," *"may indeed be indicative of diversion."*[10] The DEA cites a federal case called *United States v Rosen*[11] in support of its arguments and highlights several factors cited by the *Rosen* court regarding "certain recurring concomitance of condemned behavior:

> (1) An inordinately large quantity of controlled substances was prescribed.
>
> (2) Large numbers of prescriptions were issued.
>
> (3) No physical examination was given.
>
> (4) The physician warned the patient to fill prescriptions at different drug stores.
>
> (5) The physician issued prescriptions to a patient known to be delivering the drugs to others.
>
> (6) The physician prescribed controlled drugs at intervals inconsistent with legitimate medical treatment.
>
> (7) The physician involved used street slang rather than medical terminology for the drugs prescribed.
>
> (8) There was no logical relationship between the drugs prescribed and treatment of the condition allegedly existing.
>
> (9) **The physician wrote more than one prescription on occasions in order to spread them out.**"[12]

Under the CSA, the DEA has both the ability and the responsibility to investigate allegations that a registrant has failed to follow the federal law relating to controlled substances. The DEA uses both its administrative and criminal investigative authorities to fulfill its mission. In many ways, the DEA's responsibility to investigate violations of the CSA is analogous to a state medical licensing board's responsibility to investigate allegations that a licensee has practiced medicine in a manner inconsistent with state standards.

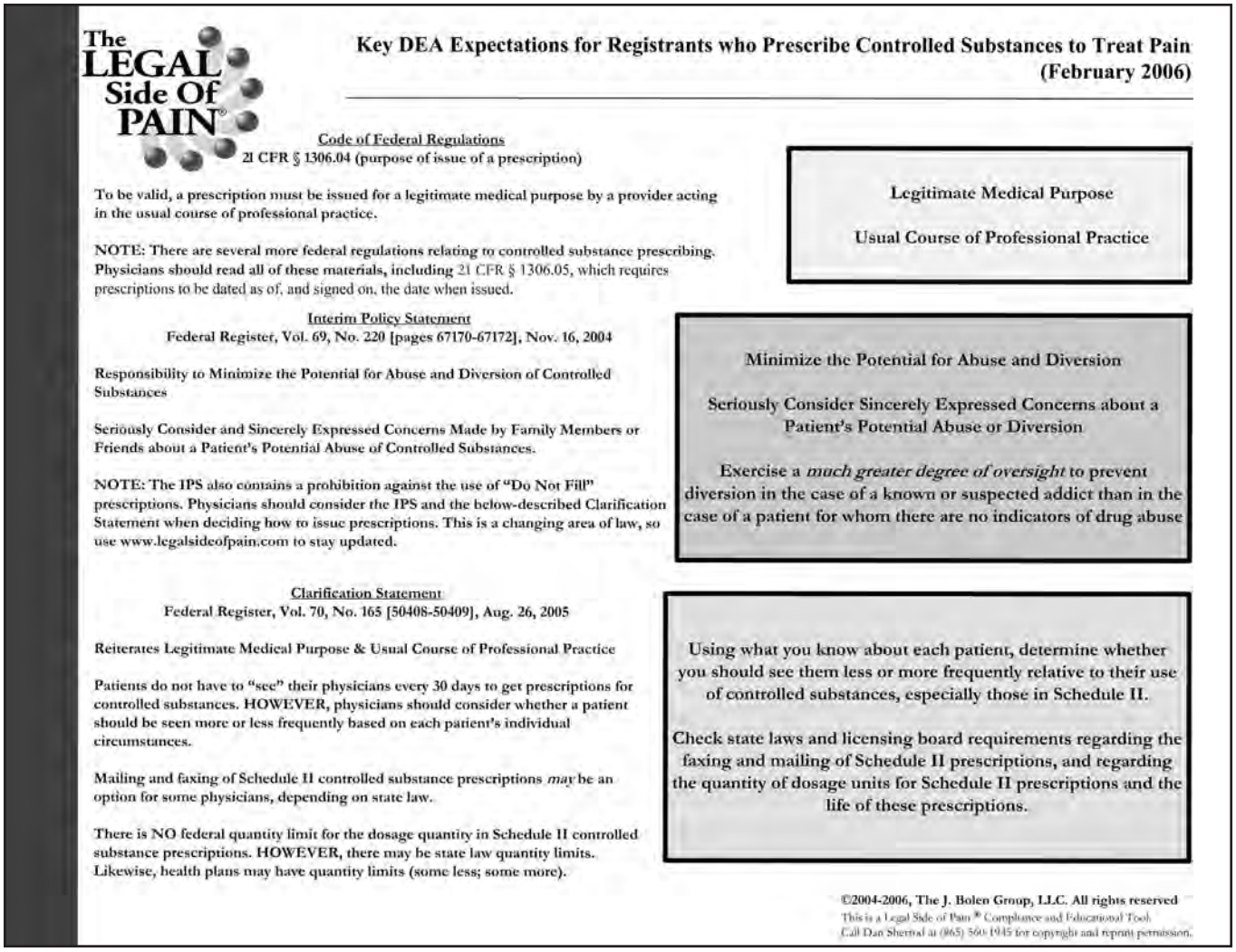

Figure 1. DEA expectations.

THE IPS AND "DO NOT FILL" PRESCRIPTIONS

The DEA's second problem with the FAQ concerns the following language:

> Schedule II prescriptions may not be refilled; however, *a physician may prepare multiple prescriptions on the same day with instructions to fill on different dates.*[13]

The DEA states in the IPS that "the first part of this sentence is correct, as the CSA expressly states: 'No prescription for a controlled substance in schedule II may be refilled.'"[14] However, the DEA contends that the CSA does not allow for the activity described in the italicized portion of the FAQ language above.[15] Instead, **the DEA uses the IPS to take the position that physicians who "prepare multiple prescriptions on the same day with instructions to fill on different dates"[16] are essentially "writing a prescription authorizing refills of a schedule II controlled substance, [and doing so] conflicts with one of the fundamental purposes of section 829(a)."**[17]

The DEA supports its argument by discussing factors quoted in *United States v Rosen*,[18] and comments that "writing multiple prescriptions on the same day with instructions to fill on different dates is a recurring tactic among physicians who seek to avoid detection when dispensing controlled substances for unlawful (nonmedical) purposes."[19] The DEA's reliance on *Rosen* is flawed because the facts in *Rosen* involve "postdated" prescriptions (dated improperly) rather than "do not fill" prescriptions (dated properly but containing instructions to the dispensing pharmacist about the dispensing period).[20] Thus, the DEA's position against "do not fill" prescriptions is one that requires additional analysis and may actually promote abuse and diversion rather than minimize it.[21]

THE IPS, RESELLING OF MEDICATIONS, AND THE REGISTRANT'S RESPONSIBILITY TO "MINIMIZE THE POTENTIAL FOR ABUSE AND DIVERSION"

The DEA cites a third problem with the FAQ, claiming that the FAQ [allegedly] understated "the degree of caution that a physician must exercise to minimize the likelihood of diversion when dispensing controlled substances to known or suspected addicts."[22] The DEA states the "FAQ listed a number of behaviors, or 'red flags,' that are 'probable indicators of abuse, addiction, or diversion,'" including the sale of medications. The FAQ "suggested that certain steps be taken to deal with such indicators, including 'appropriate management' and possible referral to an addiction specialist. However, the FAQ also stated that these behaviors (including reselling medications) 'should not be taken to mean that a patient does not have pain or that opioid therapy is contraindicated.'" Regarding the phrase "appropriate management," the FAQ stated: "management may or may not include continuation of therapy, depending on the circumstances." Thus, according to the FAQ, "if continued opioid therapy makes medical sense, then the therapy may be continued, even if drug abuse has occurred. The DEA recommends that physicians engage in "additional monitoring and oversight of patients who have experienced such an episode." The DEA retracted its support on several of these FAQ statements, as discussed below.

The DEA confirms that "the behaviors listed in the August 2004 FAQ as 'red flags'" are indeed indicators of possible diversion, . . . but the FAQ understated the degree of caution that a physician must exercise to minimize the likelihood of diversion when dispensing controlled substances to known or suspected addicts." If a physician is aware that a patient is a drug addict, has resold prescription narcotics, or both, it is not merely "recommended'" that the physician engage in additional monitoring of the patient's use of narcotics.

The DEA uses the IPS to explain that **registrants have "a responsibility to exercise a much greater degree of oversight to prevent diversion in the case of a known or suspected addict than in the case of a patient for whom there are no indicators of drug abuse."**[23] Thus, the DEA believes that physicians *must* "engage in addition monitoring of the patient's use of narcotics" when the physician "is aware that the patient is a drug addict and/or has resold prescription narcotics."[24] The DEA also believes the federal law prohibits physicians from "dispensing controlled substances [to any patient] with the knowledge that they will be used for a non-medical purpose or that they will be resold by the patient."[25] The DEA leaves the method of monitoring to the individual clinician and the states. The IPS contains a discussion of monitoring examples.[26]

THE IPS AND THE DEA REGISTRANT'S RESPONSIBILITY TO "SERIOUSLY CONSIDER" ANY "SINCERELY EXPRESSED CONCERNS" BY FAMILY MEMBERS ABOUT A PATIENT

The DEA's fourth criticism of the FAQ is that it "incorrectly minimized the potential significance of a family member or friend expressing concern to the physician that the patient may be abusing the pain medication."[27] In this regard, the FAQ states:

> Family and friends, or health care providers who are not directly involved in the therapy, may express concerns about the use of opioids. These concerns may result from a poor understanding of the role of this therapy in pain management or from an unfounded fear of addiction; they may be exacerbated by widespread, sometimes inaccurate media coverage about abuse of opioid pain medications.[28]

The DEA believes that "family members are not always determinative of whether the patient is engaged in drug abuse," but thinks "the above-quoted [FAQ] statement is incorrect to the extent it implies that physicians may simply disregard such concerns expressed to them by family members or friends."[29]

Because "a family member or friend might be aware of information that the physician does not possess regarding a patient's drug abuse,"[30] the DEA also believes:

> (1) the addictive and sometimes deadly nature of prescription narcotic abuse,
>
> (2) the tremendous volume of such drug abuse in the United States, and
>
> (3) the propensity of many drug addicts to attempt to deceive physicians in order to obtain controlled substances for the purpose of abuse,[31]

requires physicians to "seriously consider any sincerely expressed concerns about drug abuse conveyed by family members and friends."[32]

Unfortunately, the DEA did not explain in the IPS its interpretation of "sincerely consider" or "sincerely expressed concerns." Consequently, when a family member or friend contacts you about a patient's behavior regarding controlled substances, document the contact and do something that shows you addressed the matter with the patient. In all cases, your response should include monitoring measures that minimize the potential for abuse and diversion of the controlled substances you prescribe. Often you can meet this DEA standard through focused follow-up visits, laboratory testing, psychological and substance abuse counseling, changes in the treatment plan, consultations, and referrals.

THE DEA'S *CLARIFICATION STATEMENT*

In August 2005, the DEA used its authority to *clarify* its position on the CSA in a document called *Clarification of Existing Requirements under the Controlled Substances Act for Prescribing Schedule II Controlled Substances.*[33] The DEA once again pronounced its belief that the CSA of 1970 and federal regulations on controlled substances prohibit the use of "do not fill" prescriptions.[34] However, the DEA acknowledged that since its release in November 2004, many people wrongly interpreted the *Interim Policy Statement* as a federal law requiring clinicians to see patients using schedule II medications every thirty days. Because of the confusion, and the many letters sent to the DEA following the *Interim Policy Statement*, the DEA chose to address this point in the *Clarification Statement*, stating the *Interim Policy Statement* [and federal law] does not require patients to see their physicians every thirty days to get their prescriptions for schedule II controlled substances.[35]

Nonetheless, the DEA expects its registrants to **"consider whether a patient should be seen more or less frequently depending on their individual circumstances."**[36] This comment by the DEA **implies that registrants have a burden to balance what they know about a patient and his/her history (medical, substance abuse, and behavioral) during the course of the physician-patient relationship when deciding how frequently to see a patient who requires schedule II medications**. Generally, the more risks a patient presents, the more frequently you should see them personally and the more monitoring measures you should consider.

The DEA also points out in the *Clarification Statement:*

> **. . . in each instance where a physician issues a prescription for any controlled substance, is that the physician properly determine there is a legitimate medical purpose for the patient to be prescribed that controlled substance and that the physician be acting in the usual course of professional practice.**[37]

The DEA recognizes that "schedule II controlled substances, by definition, have the highest potential for abuse, and are the most likely to cause dependence, of all the controlled substances that have an approved medical use."[38] Thus, the DEA expects physicians to:

> **use the utmost care in determining whether their patients for whom they are prescribing schedule II controlled substances should be seen in person each time a prescription is issued or whether seeing the patient in person at somewhat less frequent intervals is consistent with sound medical practice and appropriate safeguards against diversion and misuse.**[39]

The DEA also expects physicians to "abide by any requirements imposed by their state medical boards with respect to proper prescribing practices and what constitutes a bona fide physician-patient relationship."[40]

Assuming the DEA is correct[41] when it says "do not fill" prescriptions are illegal under federal law, what other options do you have for getting patients their schedule II medications? The DEA uses the *Clarification Statement* to point out that a clinician who regularly sees a patient and issues him/her a prescription for a schedule II controlled substance for a legitimate medical purpose and without seeing the patient in person may **"mail the prescription to the patient or pharmacy."**[42] Of course, your ability to mail prescriptions is further subject to state law and some states disallow mailing, whereas others impose a "patient permission" requirement. In addition, mailing has its own problems—like ensuring receipt by the patient, which may entail the added cost of certified or registered mail.

The DEA uses the *Clarification Statement* to confirm yet another alternative to getting patients their schedule II medication—faxing the prescription:

> A prescription for a schedule II controlled substance may be transmitted by the practitioner or the practitioner's agent to a pharmacy via facsimile equipment, provided that the original written, signed prescription is presented to the pharmacist for review prior to the actual dispensing of the controlled substance, except as noted [elsewhere in this section of the regulations].[43]

Remember, however, your ability to fax schedule II prescriptions is further subject to state law. Make sure that you understand your state's position on this matter before you use the faxing alternative.

As a final point, the DEA uses the *Clarification Statement* to explain the **federal law does not contain dosage limits for schedule II prescriptions**.[44] However, some states do impose dosage limits on the amount of a schedule II controlled substance that clinicians may prescribe.[45] Find out your state's position, and factor it into your daily prescribing practices. Many states require clinicians to "control the drug supply," especially to patients with a substance abuse history or other indications of abuse potential. Thus, **increasing the number of dosage units may not be the right answer because it may actually encourage abuse and diversion in certain patient populations**.

The DEA expects its registrants to issue a controlled substance prescription **for a legitimate medical purpose in the usual course of professional practice. "Physicians and pharmacies have a duty as DEA registrants to ensure that their prescribing and dispensing of controlled substances occur in a manner consistent with effective controls against diversion and misuse, taking into account the nature of the drug being prescribed."**[46]

THE DEA AND A FINAL POLICY STATEMENT

The DEA will issue a final policy statement on the use of controlled substances for the treatment of pain, and every physician who prescribes controlled substances should find a good source to help them stay current on these matters. In all cases, physicians and physician extenders must make every effort to stay current with existing federal and state legal and regulatory materials and must be prepared to reevaluate their practices for compliance purposes.

This is a Legal Side of Pain educational tool: I intend for this article to serve as an educational tool for pain management practitioners, and I do not intend for it to serve as specific legal advice. If you need help on legal questions, contact me at 865-560-1945 or *jbolen@legalsideofpain.com*.

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

NOTES

1. 21 CFR 1306.04 - Prescriptions.
2. 21 CFR 1306.04.
3. This language relates to current issues surrounding the legality of "Do Not Fill" prescriptions. Federal case law tells us that those who "post date" prescriptions (do not date and sign prescriptions on the date issued) violate federal law. Do Not Fill prescriptions, however, are dated properly but contain instructions to the dispensing pharmacist about the timing of dispensation. The DEA claims Do Not Fill prescriptions are the same as postdated prescriptions. The case law suggests otherwise. For more on this issue, see Bolen J: Commentary. DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
4. 21 CFR 1306.05.
5. US Drug Enforcement Administration, Interim Policy Statement on Dispensing Controlled Substances for the Treatment of Pain, November 16, 2004, as published in the Federal Register: Volume 60, Number 220, Pages 67170-67172. Available at *http:// waisaccess.gpo.gov* (DOCID:fr16no04-82). Accessed January 10, 2006. Although the DEA used the term "dispensing" in the IPS, the DEA will apply its interpretation to other conduct, including administering and prescribing controlled substances to treat pain.
6. Interim Policy Statement, see note 5 above.
7. United States v. Morton Salt Co., 338 US 632, 642-643 (1950). Despite the DEA's ability to initiate investigations without satisfying any initial burdens, the DEA may not continue investigations or charge individuals without meeting basic criteria.
8. Interim Policy Statement, see note 5 above.
9. Interim Policy Statement, see note 5 above.
10. Interim Policy Statement, see note 5 above.
11. United States v. Rosen, 582 F.2d 1032, 1035-36 (5th Cir. 1978).
12. Rosen, 582 F.2d at 1035-1036 (internal cases citations omitted). Point 9 is the one the DEA relies on to claim that Do Not Fill prescriptions are improper. You can read more about this debate in Bolen, J. Commentary. DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
13. To find the FAQ, conduct an Internet search using the following terms: DEA, FAQ, Prescription Pain Medications. The DEA retracted the FAQ from its website on or about October 6, 2004. Thus, there is no formal citation to the document available.
14. Interim Policy Statement, see note 5 above. See also 21 U.S.C. § 829(a).
15. Interim Policy Statement, see note 5 above.
16. Interim Policy Statement, see note 5 above.
17. Interim Policy Statement, see note 5 above.
18. Rosen, 582 F.2d 1032, 1035-1036.
19. Rosen, 582 F.2d 1032, 1035-1036.
20. Bolen J: Commentary, DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
21. Bolen J: Commentary, DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
22. Interim Policy Statement, see note 5 above.
23. Interim Policy Statement, see note 5 above.
24. Interim Policy Statement, see note 5 above.
25. Interim Policy Statement, see note 5 above.
26. Interim Policy Statement, see note 5 above.
27. Interim Policy Statement, see note 5 above.
28. Interim Policy Statement, see note 5 above.
29. Interim Policy Statement, see note 5 above.
30. Interim Policy Statement, see note 5 above.
31. Interim Policy Statement, see note 5 above.
32. Interim Policy Statement, see note 5 above.
33. US Drug Enforcement Administration, Clarification of Existing Requirements Under the Controlled Substances Act for Prescribing Schedule II Controlled Substances, August 26, 2005, as published in the *Federal Register*. 2005; 70(165): 50408-50409. Available at *http://wais.access.gpo.gov* (DOCID:fr26au05-139). Accessed January 10, 2006.
34. For a complete discussion of the DEA's position on "Do Not Fill" prescriptions and case law surrounding this issue, see Bolen J: Commentary, DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
35. The exact language from the Clarification Statement is as follows: "the IPS did not state that patients must visit their physician's office every month to pick up a new prescription. There is no such requirement in the CSA or DEA regulations." Clarification Statement, see note 8 above.
36. Clarification Statement, see note 33 above.
37. Clarification Statement, see note 33 above.
38. Clarification Statement, see note 33 above.
39. Clarification Statement, see note 33 above.
40. Clarification Statement, see note 33 above.
41. I am not convinced the DEA is correct in its claim that "Do Not Fill" prescriptions are improper under federal law. For more information on this topic, see Bolen J: Commentary, DEA and Schedule II "Do Not Fill Prescriptions" - Disappointing Enforcement Activity. *Pain Medicine.* 2006; 7(1): 80-85.
42. Clarification Statement, see note 33 above.
43. Clarification Statement, see note 33 above.
44. Clarification Statement, see note 33 above.
45. Clarification Statement, see note 33 above.
46. Clarification Statement, see note 33 above.

CASE REPORT

A descriptive case series: Oral transmucosal fentanyl use in patients with noncancerous pain

Anthony H. Guarino, MD
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ABSTRACT

Transmucosal fentanyl is indicated for patients with cancer who are opioid tolerant, but it is also used for the treatment of noncancerous pain. The following is a survey study of the use of transmucosal fentanyl in 29 patients with noncancerous pain in an academic, community-based pain management practice. Transmucosal fentanyl was found to be safe and efficacious in the patients studied.

Key words: Transmucosal fentanyl, Actiq, noncancerous pain, breakthrough pain, opioid

INTRODUCTION

Oral transmucosal fentanyl (OTFC) is currently approved solely for the management of breakthrough cancer pain in patients who are already receiving and tolerating opioid therapy for underlying persistent pain. The package insert for OTFC (Actiq) has a black box warning stating that this is the only indication approved by the Food and Drug Administration.[1] Despite this warning, clinicians have greatly expanded OTFC's use in the management of noncancerous pain over the last several years. We report the experiences of 29 patients prescribed OTFC for noncancerous breakthrough pain.

OTFC has proven efficacy in the management of cancer pain.[2-8] The clinical significance of the change in a patient's perception of pain with this medication has been addressed.[9] The clinical safety for the use of OTFC in patients without cancer has been established.[10,11] Patients who have chronic pain, regardless of the cause, commonly have transient pain flares, referred to as breakthrough pain (BTP).[12-16] Even in a noncancerous pain state, BTP is common despite the long-term use of opioids.

Patients who present to our pain management clinic traditionally have pain states that are chronic, meaning pain that has persisted for six months or longer. While we utilize the World Health Organization's Analgesic Ladder as a reference, it is not our treatment algorithm. We routinely tailor our treatment plans to the needs of the patients and the nature of their pain conditions. If a patient is presenting to our clinic for the first time, a detailed medication history is obtained, including medications that have not worked in the past. This information is used to determine what level of pain management is needed in order to improve the patient's quality of life. For example, if a patient presents with a pain flare but the underlying pain condition (e.g. low back pain) has not changed, these patients may be treated conservatively with nonsteroidal anti-inflammatory medications. If the pain state is moderate to severe, a stepwise approach to medication management is taken. If the patient has tried a short-acting medication (e.g. hydrocodone or oxycodone) and has been taking the medication every four hours around the clock, we provide the patient with a long-acting opioid (e.g. morphine or oxycodone). Our intent is to obtain a steady concentration of medication with a lower yield of BTP that may require additional short-acting medication.

Despite a maintenance dose that provides effective management of chronic pain, patients will experience BTP episodes. OTFC has been tested and approved in patients with cancer who experience BTP episodes. Pain specialists frequently prescribe OTFC off-label to treat BTP episodes in patients that do not have cancer. OTFC dosing in these patients is individualized according to the premise that the dose should be approximately equivalent to the dose of other short-acting BTP medications that a patient has previously taken. Equivalent dosing is not an exact science with OTFC because 25 percent of the dose is absorbed through the mucosal tissue, and only 25 percent of the swallowed dose is absorbed through the stomach. Thus dosing becomes an educated guess that is based on the assumption that only 50 percent of the dose is absorbed. Using the number of BTP episodes, the severity of the episodes, and the patient's

Table 1. Survey questions	
Demographics	Age, weight
General medical information	Nonpain related medical problems requiring continual care
Current pain diagnosis	Diagnosis, length of time of diagnosis
	Pain medications other than OTFC
OTFC information	Dose, start date
Specific questions	How long does your pain relief last after using OTFC? (0, 1, 2, 4, 5, >5 h)
	Rate the amount of pain reduction you experience using OTFC (none, slight, good, very good, excellent)
	Rate your level of sleepiness after using OTFC (none, slight, somewhat, very, cannot stay awake)
	Rate your level of nausea after using OTFC (none, slight, some, very, extreme)
	Rate your level of dizziness after using OTFC (none, slight, some, very, extreme)
	Rate your level of constipation after using OTFC (none, slight, some, very, extreme)
	Rate your level of breathing difficulty after using OTFC (none, slight, some, very, extreme)
Comparison of OTFC with medications used to control pain	Darvocet-N, Vicodin, Lortab, Norco, Demerol, other
	Tylenol with codeine, Talwin, Fiorinal, Percocet, morphine and Dilaudid (better, same, not as good, not applicable)
Miscellaneous questions	How many episodes of BKP do you have each day? (none, 1, 2, 3, 4, 5, >5)
	In general, how long have you been taking pain medications for this condition?
	How often do you feel impaired from taking OTFC? (never, sometimes, most of the time, always)
	How often do you feel impaired from any other pain medications? (never, sometimes, most of the time, always)
BTP, breakthrough pain; OTFC, transmucosal fentanyl	

history with the use of other BTP medications, the physician determines the best dose. Therefore, the intent of this study was to report one physician's off-label use of OTFC for BTP in 29 patients who had chronic noncancerous pain that was being managed with opioids.

METHODS

This study was a retrospective survey of patients with chronic noncancerous pain who experienced BTP episodes. The Washington University Human Studies Committee gave approval to administer the survey. The 29 patients, with a variety of pain diagnoses, attended a community-based academic pain management clinic. Patients asked to complete the survey 1) had chronic pain; 2) were using optimized dosages of opioids, either long-acting or around-the-clock short-acting, for chronic pain management; 3) indicated that current chronic pain management had resulted in a 50 percent or greater reduction in the original pain level, and 4) had BTP episodes that had been treated with a stable dose of OTFC for a minimum of one month.

Survey instrument

To facilitate the gathering of information, the investigator developed a questionnaire to collect both subjective and objective information from the patient. Collected information included 1) demographics, 2) current medical information, 3) current pain diagnosis, 4) information on current OTFC usage, 5) known side effects experienced, 6) length of pain relief, and 7) perception of impairment from OTFC and other pain medications (Table 1). All patients seen from July 2003 through October 2003 who met the inclusion criteria were asked to complete the questionnaire.

Statistical methods

The data were analyzed with SPSS for Windows (SPSS 12.0; SPSS Inc., Chicago, Illinois). Both descriptive and inferential statistical methods were used. All testing was based on determining statistical significance at a two-sided α level of 0.05. The study sample was described with measures of central tendency (mean and median) and dispersion (standard deviation and range) for continuous variables and frequency and percentage for categorical variables. The Spearman's rho statistic was used to evaluate the association between continuous and ordinal-scaled variables. The Mann-Whitney U test was used to compare the distribution of continuous and ordinal-scaled variables between two categories of categorical variables. The Kruskal-Wallis test was used to compare the distribution of continuous and ordinal-scaled variables among three or more categories of categorical variables.

RESULTS

Patient characteristics

Patient characteristics are presented in Table 2. The patients represented a middle-aged or older white (93 percent) population who had used pain medications for an average length of 5.4 years. The patients' pain was attributed to a variety of diagnoses, but it was predominantly due to spine-related disorders. Fifteen patients reported a pain diagnosis related only to the spine, seven reported only a nonspine-related pain diagnosis, and seven reported both a spine-related and nonspine-related diagnosis for pain.

Long-acting pain medications

The subjects were taking a variety of long-acting or around-the-clock opioids to maintain their chronic pain states at an acceptable level (Table 3). Fourteen (48 percent) of the subjects were using a fentanyl patch alone for chronic pain management, four (14 percent) were using a fentanyl patch and short-acting around-the-clock opioids, nine (31 percent) were using only short-acting around-the-clock opioids, and two (7 percent) were using another form of long-acting opioid medication for chronic pain management. The doses of the chronic pain medications had been stabilized before OTFC was prescribed for BTP. The average daily dose of long-acting opioid medication was 285 (± 235) morphine equivalents (mg).[17]

Side effects experienced

The patients' perceptions of several known side effects related to the use of OTFC are presented in Table 4. The most common side effects experienced were sleepiness and constipation. The least common side effects were breathing difficulties, nausea, and dizziness. None of the patients reported the side effects as being severe, although three patients reported they were very constipated, one was very sleepy, and one was very dizzy. No information was obtained to determine whether the subjects had been experiencing any of the side effects before the start of OTFC.

Effectiveness of transmucosal fentanyl

Patients were asked to rate their perception of the effectiveness of OTFC in the reduction of the pain from their BTP episodes in terms of no effect, slightly effective, good, very good, and excellent. Six patients (21 percent) rated OTFC as excellent, 12 (41 percent) rated it very good, 10 (34 percent) rated it good, and one (3 percent) rated it slightly effective. None of the patients indicated that OTFC had no effect on reducing pain.

Table 2. Patient characteristics (N = 29)	
Sex	
Male	12 (41.4)
Female	17 (58.6)
Race	
White	27 (93.1)
African American	2 (6.9)
Age (years)	50.4 ± 11.8
Body Mass Index	28.2 ± 7.1
Pain medication usage (years)	5.5 ± 5.4
Medical diagnosis related to pain (multiple diagnosis present in 16 patients)	
Spine-related disorders	
Degenerative disc disease (n = 5)	17.2
Failed back surgery (n = 5)	17.2
Lumbago (n = 6)	20.7
Radiculopathy (cervical and lumbosacral) (n = 7)	24.1
Spinal enthesopathy (n = 2)	6.9
Spinal stenosis (n = 4)	13.8
Other: Spondylosis, compression fracture, scoliosis, CRPS (n = 4)	13.8
Nonspine-related disorders	
Degenerative joint disease (n = 6)	20.7
Fibromyalgia (n = 3)	10.3
Other: Intestinal cystitis, peripheral neuropathy, esophageal spasms, pancreatitis, polyneuropathy, rectal pain, Shy-Drager syndrome (Total n = 7; n = 1 for each disorder)	24.1
Values are mean (± SD) or frequency (percentage); CRPS, complex regional pain syndrome.	

Table 3. Long-term pain medications	
Opioids	**n (percent)***
None	3 (9)
Fentanyl	18 (57)
Oxycodone	5 (16)
Morphine	4 (13)
Methadone	3 (9)
Nonopioid medications used for pain	**n (percent)***
Muscle relaxants	8 (25)
Anticonvulsants	5 (16)
Nonsteroidal anti-inflammatories	4 (13)
Hydrocodone	2 (6)
Other analgesics	4 (13)
Antidepressants	1 (3)
* Percentages do not total 100 because several patients were taking more than one long-acting medication.	

When patients were asked to compare OTFC with other BTP medications they had used, OTFC was rated better by 80 percent or more patients, except in the case of morphine, in which only 41 percent of the patients rated OTFC better. The results of these comparisons are presented in Table 5.

Transmucosal fentanyl dose relationships

To determine whether side effects were associated with higher daily doses of OTFC, we compared the distribution of the daily OTFC dose and the patients' perceptions of each side effect (none, slight, somewhat, very, and severe). When compared with the daily dose of OTFC, the responses were not significant for any of the side effects. The results of these comparisons are presented in Table 6.

The correlation between the total daily OTFC dose and the number of BTP episodes resulted in a Spearman's rho of 0.520 (rho = 0.002). The average total daily dose of OTFC was 1710 ± 967 μg, and the average number of breakthrough episodes was 3.7 ± 1.6. The correlation between a single dose of OTFC and the length of pain relief resulted in a Spearman's rho of -0.384 (rho = 0.030). The average single dose of OTFC was 600 ± 251 μg, and the average length of pain relief was 3.3 ± 1.5 hours. Thus, a moderately strong positive association was present between dose and number of BTP episodes, and a moderately strong negative correlation was present between dose and the length of pain relief.

DISCUSSION

In this limited population of 29 patients using OTFC for noncancerous BTP, the patients perceived the medication to be effective with a minimum of tolerable side effects. The patients were not opioid naïve and had tried a variety of opioids for BTP before OTFC was prescribed. Ninety-seven percent of the subjects rated OTFC good to excellent in effectively reducing their BTP episodes.

OTFC has an onset of effect at five minutes and a peak effect at 20 minutes.[1] The lasting effect can be several hours. In this study, the pain relief reported lasted an average of 3.3 ± 1.5 hours.

In this study the side effects were minimal. The most common side effects were constipation and sleepiness.

Table 4. Reported side effects of transmucosal fentanyl*					
	None	Slight	Somewhat	Very	Extreme
Sleepiness	13 (45)	6 (21)	9 (31)	1 (3)	0
Nausea	26 (90)	3 (10)	0	0	0
Constipation	18 (62)	3 (10)	5 (17)	3 (10)	0
Dizziness	24 (83)	4 (14)	0	1(3)	0
Breathing problems	28 (97)	0	1 (3)	0	0

* The total for each category is 29. The values reported are frequency (percentage).

None of the patients reported any of the side effects as being severe, although one patient reported being very sleepy, one very dizzy, and three very constipated. No correlation was seen between the daily dose of OTFC taken and the side effects. Side effects are common with opioids, and OTFC is no exception.

The moderately strong positive association between dose and number of BTP episodes and the moderately strong negative correlation between dose and the length of pain relief may indicate that subjects taking higher doses of OTFC are experiencing more BTP with shorter periods of relief, or they may suggest higher doses of OTFC are associated with less effectiveness. This study was not designed to determine the psychosocial behavior of the patients. Therefore, the correlations may represent a finding that is consistent with patients with drug-seeking behavior. The reports of shorter periods of effectiveness and increased numbers of BTP episodes in patients with the higher doses might represent patients who are seeking more opioids. In this clinical practice, patients are asked to sign a contract before starting opioid therapy that states they understand the consequences of opioid therapy and drug-seeking behavior. The physician conducts random drug testing if there are concerns. Even with guidelines in place, however, drug-seeking behavior is not always detected.

Table 5. Comparison of OTFC with other analgesics used by patients				
	n*	Better†	Same†	Not as good†
Propoxyphene acetaminophen	22	22 (100)	0	0
Hydrocodone acetaminophen	26	21 (81)	3 (12)	2 (8)
Meperidine	13	11 (85)	2 (15)	0
Acetaminophen codeine	24	23 (96)	1 (4)	0
Naloxone pentazocine	1	1 (100)	0	0
Butalbital aspirin	5	5 (100)	0	0
Oxycodone acetaminophen	23	21 (91)	2 (9)	0
Morphine	17	7 (41)	5 (29)	5 (29)
Hydromorphone	7	6 (86)	1 (14)	0

* Of the 29 patients completing the questionnaire, n represents the number of patients who had taken the respective medication; † Values represent the number of responses with percentages determined with the total number of patients who have taken the medication (n [percent]); OTFC, transmucosal fentanyl.

Table 6. Comparison results of side effects with daily OTFC dose (μg)					
	None	**Slight**	**Somewhat**	**Very**	**P**
Sleepiness	1,523 (± 847)	1,500 (± 1,010)	2,089 (± 1,141)	*	0.389
Nausea	1,677 (± 973)	2,000 (± 1,058)			0.612
Constipation	1,511 (± 857)	2,200 (± 1,732)	1,680 (± 912)	2,467 (± 702)	0.315
Dizziness	1,825 (± 959)	850 (± 661)		*	0.062
Breathing problems	*		*		
Values are mean ± SD; * Statistical analysis not done when n < 3; OTFC, transmucosal fentanyl.					

This study was designed only as a point-in-time retrospective survey of patients who were using OTFC for BTP. The study has several limitations. First, the subject-inclusion criteria dictated that only patients who had used OTFC for at least one month were to be studied. Most patients using a medicine tend to discard it fairly quickly if the desired effects are not reached or unwanted side effects are experienced. Second, no standardized tools were used to evaluate the patients' chronic pain or BTP. Third, because all clinic patients with chronic noncancerous pain using OTFC for BTP, regardless of dosage, were asked to participate in this study, the amount of chronic medication prescribed and the amount of OTFC prescribed were not controlled. Fourth, patients were not evaluated for baseline side effects before starting the OTFC. Although the questionnaire asks patients to rate their side effects as related to the OTFC, patients frequently have difficulty separating the two. A prospective study done at the start of OTFC administration would help to clarify this issue. Finally, patients were asked to rate only known side effects. There is a possibility that patients experienced other side effects that did not fit into the categories listed on the survey and thus went unreported.

In summary, in this limited population, OTFC was reported to be effective with a minimum of side effects. We recommend a larger controlled study to support the findings.

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Early administration of oral morphine to orthopedic patients after surgery

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ABSTRACT

Current pain treatment guidelines advise against providing analgesics for postoperative pain using intramuscular injections, as this generally provides poor pain relief. However, this route remains the most prevalent treatment method. Intravenous or epidural patient-controlled-analgesia methods reduce pain effectively but are expensive, labor intensive, and available to only a limited number of patients. We propose administering the analgesics using oral analgesics and have developed a simple protocol for treating postoperative pain by use of oral morphine. After a variety of orthopedic surgeries, patients were given "around-the-clock," oral, immediate-release morphine. Efficacy of the treatment (pain scores and adverse effects) was assessed 24 ± 2 hours after surgery. Data were collected prospectively from 95 patients, who received an average of 61 ± 30 (SD) mg morphine. Average pain scores were 2.4/10 (± 1.4) at rest and 4.0/10 (± 1.4) during movement in bed. Nausea and vomiting, the most common adverse effects, were reported by 22 (23 percent) patients. Naloxone was not administered to any of the patients. Oral morphine given in the early postoperative time to patients after a variety of orthopedic surgeries was effective and safe.

Key words: postoperative pain, oral analgesics, oral morphine, orthopedic surgery

INTRODUCTION

Pain after orthopedic surgery can be severe.[1] In one study, 40 percent of orthopedic patients reported severe pain during the first 24 hours after surgery.[2] It is widely accepted that effective analgesia for postoperative pain is a component of good care,[3] as pain relief is a "universal human right."[4] It is also known that alleviation of pain facilitates early ambulation and may thus be important in reducing the incidence of postoperative complications.[5] Indeed, prevention and treatment of pain in its acute phase may even prevent the progression to chronic pain.[6]

Management of pain remains a complex issue in healthcare despite the proliferation of drugs and treatment techniques.[7] Surveys continue to indicate that it is still undertreated.[8] In a review of 21 studies published over the last 40 years, there is no change in the 30 to 70 percent of patients reporting moderate to severe levels of pain after surgery.[9] One possible explanation for this may be the widespread practice of providing analgesics by intramuscular administration, on a "patient-demand" basis.[10] This route continues to be the most prevalent method for providing analgesics postoperatively, despite contrary recommendations from current treatment guidelines.[5,11]

Intravenous or epidural patient-controlled analgesia or physician-controlled epidural treatment provides "state-of-the-art" analgesia but is available to only a limited number of postoperative patients (10 to 25 percent), even in major university hospitals.[12] The limited availability is due to such reasons as the high cost of labor and materials, need for intensive and complex monitoring,[12] and the need for major reorganization of medical and nursing services before these techniques can be widely implemented.

A majority of postoperative patients can achieve adequate analgesia simply, safely, and effectively without the need for expensive and sophisticated methods. However, achieving this goal requires finding hospital-wide solutions to problems such as systematic assessment of pain, provision of analgesics "around-the-clock," titration of

analgesics to individual requirements, and combination of opioid and nonopioid medications.[5,11,12] These principles were applied in a number of studies using intramuscular injections to provide the analgesics.[12,13]

Scores of ≤ 3/10 represent pain that is "mild" and can be regarded as the "zone of analgesic success."[14] We therefore aimed at obtaining such scores for rest- and movement-related pain in orthopedic surgical patients by following the currently recommended pain management practices while providing morphine by the oral rather than the intramuscular route.

In this report, we assess the efficacy of providing morphine by the oral route in the early postoperative timeframe by assessing two clinical outcomes: pain relief and frequency of morphine-related adverse effects.

METHODS

Participants and procedure

This was an open, observational, prospective survey conducted in the Orthopedics Department at the Rambam University Medical Center in Israel. Data were collected between August 1999 and March 2000. Institutional Review Board approval was obtained prior to initiating treatment and collecting data. Administration of oral morphine postoperatively was the standard method of treating postoperative pain in the department of orthopedics where the survey took place. We present results obtained from patients for which full documentation was available in their medical record regarding the dosage of morphine in the first 24 hours after surgery, pain at rest and movement, and adverse effects.

Postoperative analgesic medication

Patients were prescribed immediate-release morphine tablets (Morphine Immediate Release [MIR]; Rafa Laboratories, Israel). Onset of action of MIR is 20 to 30 minutes, and duration of action is four to five hours. With MIR, peak blood plasma concentration occurs at 1.1 hours; it has a half-life of two to three hours and bioavailability of 20 to 40 percent (per manufacturer's datasheet). Dosing was based on patient age rather than on weight.[15] We used the recommended parenteral dose to treat postoperative pain and converted it to the oral dose based on an equianalgesic ratio of 1:3.[5,11,15] The recommended dose for patients up to the age of 65 years was 15 or 30 mg, six times daily, and for patients over 65 years, 7.5 or 15 mg, six times daily. A "rescue dose" of 7.5 or 15 mg morphine was available for patients for whom pain relief was insufficient. The specific dose prescribed to each patient was determined by the attending surgeon. Morphine tablets were made available to patients immediately upon their return from the post-anesthesia recovery room, where they typically had remained for one to two hours after surgery. At night, patients were not awakened from sleep to administer the medication, but it was made available if required. This regimen was followed until reported pain levels were sufficiently low to switch over to nonopioid medication, typically 24 to 72 hours after surgery.

Patient assessments

Intensity of patient pain was assessed during the first 24 ± 2 hours after surgery. The pain was estimated by the patient with one of three nurses participating in the survey by means of a numerical pain scale (0 = "no pain" to 10 = "unbearable pain"). Patients were asked to grade current pain at rest, while lying still in bed, and also when moving the surgically treated limb (movement-related). Assessments were made independently of when the medication was administered. The rationale for this evaluation procedure was that the objective of the treatment regimen was to achieve pain scores ≤ 3/10 for both rest and movement throughout the day rather than at a specific time after administration of the analgesic.

We also assessed 1) the incidence of adverse effects related to morphine: nausea and vomiting, dizziness, sedation, confusion, cessation of treatment due to adverse effects, and respiratory depression necessitating treatment by naloxone; 2) the dose of oral morphine administrated; and 3) the type of surgery and type of anesthesia.

Type of surgery was determined by two of the authors (BP and DNR), who classified all surgical procedures of patients in the study into five categories (Table 1), based on the type of tissue involved in the surgery (bone or soft), type of surgery (emergency or elective), and extent of surgery (minor or major). Data were pooled by type of surgery, and an analysis of variance was performed to determine the overall effectiveness of the oral treatment with respect to the different types of surgeries. Additionally, the Tukey-Kramer HSD test was applied to reveal variant results based on surgery type.

The Student t-test was performed to determine whether type of anesthesia (general vs. regional) had an effect on postoperative pain scores.

JMP version 4.01 (SAS Institute, Cary, NC) and Excel for Windows NT (Microsoft Corp, Redmond, WA) were used for the statistical analysis. A value of $p < .05$ was regarded as statistically significant.

RESULTS

Data were obtained from 95 patients (59 women and 36 men; age range, 19 to 93 years; average ± SD age, 58.8 ± 21 years).

Table 1. Types of surgical procedures and number of patients in each category, dosage of oral morphine and pain scores for each surgical category

Category	Surgical procedure	Number of patients	Average morphine (mg)/ 24 hours (± SD)	Range (mg)	Pain at rest average (± SD)	Movement-related pain average (± SD)
1	Neck of femur fractures	11	46 (± 28.0)	15 – 90	3 (± 1)	4.8 (± 1.4)
2	Other fractures (open or closed treatments)	22	70 (± 27)	30 – 105	3.0 (± 1.7)	4.0 (± 1.7)
3	Major elective surgery, e.g., total hip or total knee replacement	38	60 (± 30)	15 – 120	2.2 (± 1.1)	3.9 (± 1.1)
4	Other lesser elective procedures	8	71 (± 32)	30 – 120	1.9 (± 1.5)	2.4 (± 1.2)
5	Soft tissue surgery with minimal bone involvement	16	58 (± 28)	15 – 90	2.9 (± 1.6)	4.4 (± 1.5)
	Total	95	61 (± 30)	15 – 120	2.4 (± 1.4)	4.0 (± 1.4)

Pain scores

The average pain score at rest was 2.4 ± 1.4. Average movement-related pain was 4.0 (±SD 1.4) The breakdown of average pain scores according to type of surgery are listed in Table 1.

Adverse effects

Adverse effects and their prevalence are listed in Table 2.

Dosage of oral morphine

Doses of oral morphine administered during the first 24 hours after surgery are shown in Table 1. The data are grouped by type of surgery. No significant difference in consumption of oral morphine was found between the groups ($p = 0.21$).

Effect of surgical parameters on pain scores

Type of surgery. When types of surgery were compared to pain scores at rest and during movement, a trend was found for both rest ($p = 0.056$) and movement-related pain ($p = 0.057$). Further inspection of the data suggested that one patient, at rest, had an unusually high pain score, and his data were eliminated. This did not change the statistical trend ($p = 0.075$). The trend is probably due to patients in group four ("Other lesser elective procedures") and, to a lesser extent, group three ("Major elective surgery, e.g., total hip or total knee replacement"), having slightly lower pain scores (Table 1).

Our findings indicate that on the whole, type of surgery is not tightly associated with postoperative pain of these orthopedic patients.

Type of anesthesia

Of the 95 patients, 42 (44 percent) were operated on under general anesthesia, 51 (54 percent) received regional anesthesia, and two patients received combined anesthesia. The latter two patients were excluded from the analysis. Pain scores were not associated with the type of anesthesia (pain score: rest, not significant [$p = 0.4$]; movement-related, not significant [$p = 0.44$]).

DISCUSSION

The main finding of this survey is that morphine administered orally during the first 24 hours after surgery to patients having undergone a variety of orthopedic surgical procedures enabled most to have mild pain at rest. Movement-related pain, while not reduced to such low levels, came fairly close. Furthermore, the treatment regimen was safe. The medication was effective equally in patients after general anesthesia or regional anesthesia.

The motivation for this study was the high incidence of poor postoperative pain relief among patients in our

Table 2. Incidence of adverse effects in patients (n = 95) receiving oral morphine	
Adverse effect	**Frequency n (percent)**
None	62 (63.5)
Nausea and vomiting	22 (23)
Dizziness	4 (4.2)
Confusion	7 (7.3)
Sedation	3 (3.1)
Cessation of treatment due to adverse effects	6 (6.25)
Use of naloxone	0 (0)

hospital. It is impractical and unnecessary to provide treatment with intravenous or epidural patient-controlled analgesia to many postoperative patients. Oral administration of analgesics is the mainstay treatment for chronic and cancer pain, due to ease of titration, relatively steady blood levels obtained, convenience to patients and staff, and low costs in both labor and equipment associated with their administration.

Oral administration is generally regarded as unsuitable during the early postoperative period due to such reasons as postoperative ileus leading to decreased gastrointestinal motility and, therefore, poor drug absorption, and nausea and vomiting that may also limit patients from oral intake.[16] Consequently, it is common practice to provide oral analgesics only after detecting gastric motility indicating a return of gastrointestinal functioning.[17,18] As orthopedic surgery does not involve open intra-abdominal procedures, ileus in the small bowel where morphine is absorbed, is transient,[17] or is not manifest.[18] Therefore, after this type of surgery, opioids can be absorbed early on in the postoperative period. Nausea and vomiting can be treated with antiemetics.[19] Many patients post-nonabdominal surgery can tolerate sips of fluid in the early period following surgery. If "patients can have soup for supper and are taking other medications orally, there is little reason to give their analgesics parenterally."[20]

We chose immediate-release morphine tablets for the following reasons: morphine is the "gold standard" for treatment of severe pain. The immediate-release form provides fairly rapid analgesia, as onset of action is 20 to 30 minutes following administration. This is similar to onset after intramuscular administration. Provision of the medication "around-the-clock," with additional doses when the pain is not sufficiently reduced, enables easy titration. These are essential features of a 24- to 72-hour routine to be used for the treatment of acute pain.[21]

A number of studies have described use of oral analgesia in the early postoperative period in orthopedic patients, once patients are awake from surgery and are able to drink: 20 mg of liquid morphine, every four hours[21]; 15 mg of liquid morphine, on a patient-controlled basis[22]; and 20 mg sustained release morphine, twice daily.[13] The principal finding of each of these studies is that oral morphine given at this early postoperative stage provides effective analgesia, and that medication given around the clock was more effective than when provided on a patient-demand basis. Adverse effects were similar in both oral and control groups.[13,21]

The principal differences between those previous studies and the current one relate to their relatively small number (n = 39, n = 23, n = 20)[13,21,22] of patients. Additionally, in the other studies, all patients received regional anesthesia. In this survey, patients divided almost equally between those who received regional and general anesthesia. We found that even the latter patients were able to ingest oral medication a few hours after surgery.

Nausea and vomiting composed the principal adverse event patients experienced in this survey. Our finding of an incidence of 23 percent is well within the expected range when morphine is provided by other routes. Nausea and vomiting were reported by up to 30 percent of patients receiving intrathecal and epidural opioids[23] and by up to 64 percent of patients receiving morphine by intramuscular injection.[24] Up to 25 percent of patients experience nausea and vomiting within the first 24 hours after surgery, and this may be even as high as 70 to 80 percent in high-risk patients, in response to the anesthesia.[19]

The most feared adverse event connected to use of opioids is respiratory depression. None of the patients we followed required treatment with naloxone. Clearly, a much larger sample of patients is necessary to provide a more clinically significant picture regarding the frequency of adverse events in response to oral morphine.[25]

CONCLUSIONS

Our findings support a number of previous studies, demonstrating that oral morphine administered in the early postoperative period appears to be simple, effective, and safe in a variety of orthopedic surgical procedures.

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ORIGINAL ARTICLE

Opioids and Down's syndrome

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ABSTRACT

Opioids are used in clinical practice for sedation, anesthesia, and analgesia. Their effects depend on their pharmacokinetic and pharmacodynamic characteristics. The liver is the major site for the biotransformation of most opioids. The major metabolic pathway is oxidation. Metabolism influences distribution, clearance, onset, and offset of opioid drugs. Action also depends on the coupling of opioids with the class of receptors involved and on localization of specific receptors. Three major types of opioid receptors, designated as μ, δ, and κ, present in the central nervous system, are coupled to G proteins and inhibit adenylyl cyclase. Down's syndrome is a congenital condition characterized by mental retardation and particular physical features. Neurotransmission alterations are important. Alteration in the concentration of opioids in the cortex of these patients has been demonstrated. Neurobiological abnormalities and, in some, abnormalities in the neurotransmission systems, anxiety, and, in particular, nociception all suggest that structural and functional alterations of opioid receptors may be present. A clear knowledge of these multiple abnormalities is essential for skillful management of the perioperative period and for a good outcome for patients with Down's syndrome.

Key words: opioids, Down's syndrome, neurotransmission alterations, neurobiological abnormalities

INTRODUCTION

In the operating room and in intensive care, the anesthetist must provide unconsciousness, analgesia, and muscular relaxation.[1] Opioids have a predominant action regarding one of the components of anesthesia, analgesia. However, each agent, when used in combination, not only produces its own expected effect but can also modify the effect of another agent acting on a different component.[2] Their metabolism is closely related to their chemical structure. Opioids are subject to O-dealkylation, N-dealkylation, ketoreduction, or deacetylation leading to phase I metabolites. Phase II metabolites are formed by means of glucuronidation or sulfonation. Some metabolites of opioids have an activity themselves and contribute to the effects of the parent compound.[3]

Endogenous opioid peptides and opiates, like morphine, produce pharmacological effects through the membrane-bound opioid receptors.[4] Each class μ, δ, κ, and ε of opioid receptors has a characteristic distribution pattern in the nervous system, which may, however, exhibit differences in unlike species. The effects of opioid receptor stimulation depend on the class of receptors involved and on their localization.[5]

The development of selective receptor ligands and the recent cloning of each receptor have greatly contributed to our increasing knowledge of the neuropharmacological profile of each type of opioid receptor.[6]

All types of opioid receptors are coupled to G proteins, because agonist binding is diminished by guanine nucleotides and because agonist-stimulated GTPase activity has been identified in several preparations.[7] The consequences of activation of any of the opioid receptors in a given cell type depend more on the profile of the G proteins and effectors expressed than on the type of opioid receptor present in the cell.[8]

The use of opioids has long been accepted as the standard care in patients with cancer and acute pain. While the development of tolerance and physical dependence are known effects of opioids in cancer and noncancer pain populations, these patients cannot be regarded as addicted. However, long-term therapy with short-acting opioids predisposes to tolerance and addiction.[9]

CLINICAL USE OF OPIOIDS

Sedation and analgesia in intensive care unit

Sedation and analgesia are relevant aspects for the adequate treatment of patients in an intensive care unit (ICU). Recent drug developments and new strategies for ventilation provide improved sedation management, allowing better adaptation to the clinical background and individual needs of the patient.[10]

Opioids are used in the ICU for sedation and analgesia.

The main indications for opioid analgesia and sedation in the ICU include anxiety, pain, and agitation; immediate postoperative period after major surgery; short-term invasive procedures; cardiac protection; and neuroprotection.[11] The cytoprotective effects of opioids have recently been recognized. A new form of cytoprotection has been identified, where it has been observed that prior exposure to opioids provides protection against cell ischemia (opioid preconditioning). In the heart, this opioid preconditioning-induced protection has been well documented by multiple studies and may be mediated by δ receptors, G(i/o) proteins, protein kinase C, ATP-sensitive potassium channels, and free radicals. A study suggests that opioid preconditioning also induces neuroprotection that involves δ1 receptors, mitochondrial ATP-sensitive potassium channels, and free radical production.[12]

Opioids such as morphine, fentanyl, and remifentanil are considered first-line agents for treating pain. All of these agents are equally effective at equipotent doses, and the choice of agent depends on both drug and patient characteristics. Sedatives with amnesic properties are desirable to prevent or relieve anxiety and agitation.[13]

Use of opioids in anesthesia

Multiple drugs are used to provide anesthesia. Volatile anesthetics are commonly combined with opioids. Several studies have demonstrated that small doses of opioids (i.e., within the analgesic range) result in a marked reduction in minimum alveolar concentration (MAC) of the volatile anaesthetic, which will prevent purposeful movement in 50 percent of patients at skin incision.[14]

Alfentanil, fentanyl, and sufentanil are synthetic opioid analgesics acting on specific opioid receptors. These opioids are widely used as analgesics to supplement general anesthesia for various surgical procedures or as primary anesthetic agents in very high doses during cardiac surgery. Opioid analgesics are mainly administered intravenously. However, other techniques of administration, including epidural, intrathecal, transdermal, and intranasal applications have been demonstrated.[15]

The MAC reduction of isoflurane by remifentanil is similar to that produced by other opioids. Although remifentanil is given at extremely high concentrations in the absence of isoflurane, it does not provide adequate anesthesia. A 50 percent isoflurane MAC reduction is produced by 1.37 ng/ml remifentanil, as opposed to previously published plasma concentrations of fentanyl of 1.67 ng/ml or sufentanil of 0.14 ng/ml.[16]

The definition of TIVA is a combination of hypnotic agents, analgesic drugs, and muscle relaxants, excluding simultaneous administration of any inhaled drugs. Midazolam, ketamine, and propofol are used as hypnotic agents, and fentanyl, alfentanil, sufentanyl, or remifentanil is administered for analgesia during surgery. Based on pharmacokinetic studies, continuous intravenous administration of these agents is strongly recommended, and infusion pumps with or without computers may be used for this purpose.[17]

Use of opioids in pain management

Opioids are the oldest and most effective agents for the short- and long-term control of severe pain, particularly chronic cancer pain palliation.[18] A number of opioids are available for clinical use, including morphine, hydromorphone, levorphanol, oxymorphone, methadone, meperidine, oxycodone, and fentanyl, and their advantages and disadvantages for the management of pain have been, and are currently being, discussed. An understanding of the pharmacokinetic properties, as well as issues related to opioid rotation, tolerance, dependence, and addiction, are essential aspects of the clinical pharmacology of opioids for pain.[19]

Opioids are widely used as effective analgesic therapy for cancer pain. Despite years of controversy, their use has also been accepted in chronic noncancer pain. Compared with morphine, oxycodone has a higher oral bioavailability and is about twice as potent. Pharmacokinetic-pharmacodynamic data support oxycodone as a pharmacologically active opioid that does not require conversion to oxymorphone for pharmacological activity.[20] Hydromorphone can be a safe analgesic alternative for long-term intrathecal management of nonmalignant pain among patients where morphine fails because of pharmacological side effects or inadequate pain relief.[21]

As more extensive and painful surgical procedures (e.g., laparoscopic cholecystectomy, laminectomy, knee and shoulder reconstruction, hysterectomy) are being performed on an outpatient basis, the availability of sophisticated postoperative analgesic regimens is necessary to optimize the benefits of day surgery for both the patient and the healthcare provider. However, outcome studies are needed to evaluate the effects of these newer therapeutic approaches with respect to postoperative side effects, cost, and important recovery variables.[22]

The consequences of acute pain include clinical, economical, and patient-reported outcomes; therefore, advance in the treatment of postoperative pain has the potential of improving healthcare from a broad perspective. Opioids remain the cornerstone of treatment of postoperative pain. Multimodal analgesia also has the potential of improving the pharmacotherapy of postoperative pain.[23]

Anesthesiologists must therefore take preventive measures, as well as apply techniques during and after surgery, to diminish the intensity of pain and the incidence of nausea or vomiting.[24]

OPIOIDS AND DOWN'S SYNDROME

Down's syndrome (DS) is the most common genetic birth defect associated with mental retardation. The underlying mechanism of the neuropathology of DS is not completely understood. Different hypotheses have been advanced to explain this mystery, including the gene dosage effect, amplified developmental instability, and the molecular misreading concept.[25] Two different hypotheses have been speculated to better understand the disease. One maintains that increased gene dosage contributes to phenotypic abnormalities; the other correlates genetic imbalance with DS pathogenesis.[26]

Neurophysiological and functional information are needed to understand the mechanisms of mental retardation in DS. The trisomy-16 murine models provide windows into the molecular and developmental effects associated with abnormal chromosome numbers. The distal segment of murine chromosome-16 is homologous to nearly the entire long arm of human chromosome 21.[27] Trisomic mice present an overall depressed responsiveness to nociceptive stimulation.[28]

The most recent pain and anxiety control techniques employed in patients with DS are described in relation to how cooperative the patient is and what assessment is made of his or her general condition.[29] Pain assessment in people with intellectual disabilities is a frequent and difficult problem, especially for nurses working with people with intellectual disabilities on a daily basis. Nurses have used a wide range of indicators to assess pain in these patients. Functional abilities and the level of disability seem to influence the indicators used.[30]

The initial treatment of pain should include agents such as acetaminophen, nonacetylated salicylates, celecoxib, or tramadol. If pain is not relieved, opioid analgesics should be considered. However, doses should be initiated at the lowest effective dosage and gradually increased, depending on response. Frequent monitoring for adverse outcomes should also be performed. If a daily opioid is needed, routine assessment of bowel function and use of a bowel regimen are recommended to prevent constipation.[31]

A 17-year-old boy with DS, weighing 48 kg, was scheduled to undergo laparotomy for duodenal obstruction and gastrostomy tube insertion. Combined general and continuous epidural anesthesia was selected as anesthetic. The patient awoke without distress and was discharged from the ward with subsequent good pain control from a continuous epidural infusion of bupivacaine 0.1 percent with 1 mcg/ml fentanyl at 4 to 6 ml/hr.[32]

A nine-year-old boy with DS was admitted to the pediatric ICU for treatment of septic shock and respiratory failure. Sedation was provided by continuous infusion of fentanyl and midazolam starting at 2 mcg/kg/hr and 0.05 mg/kg/hr, respectively. The doses were gradually increased up to a dosage of fentanyl at 4 mcg/kg/hr and of midazolam at 0.2 mg/kg/hr by the end of day four. The patient was enrolled in a study involving the correlation of the BIS with ICU sedation scale to demonstrate the development of tolerance to sedative drugs during sedation in the pediatric ICU. During the following five days, a two-fold increase in the dose of midazolam and a three-fold increase in the dose of fentanyl were required to maintain the same BIS value and desired level of sedation.[33]

Patients with DS are afflicted by multiple congenital anomalies, which affect almost all of their organ systems. Skillful management during the perioperative period is essential for a good outcome for patients with multiple congenital abnormalities in the cardiopulmonary and musculoskeletal systems.[34] A ketamine, midazolam, and vecuronium infusion was used for total intravenous anesthesia in a patient with DS with a ventricular septal defect and pulmonary hypertension. This simple technique, and ventilation with 100 percent oxygen, maintained tissue oxygenation and cardiovascular stability.[35]

There is a widespread clinical impression that it is difficult to achieve adequate sedation and that, following cardiac surgery, these patients require higher doses of morphine and additional sedative agents compared to patients without DS. It is in accordance with the report that DS patients are also more likely to receive additional sedatives and skeletal muscle relaxants.[36]

A seven-year-old Saudi boy with trisomy-21 was admitted to the hospital for dental surgery under general anesthesia. This was his first general anesthetic; there was no history of environmental allergies, respiratory tract diseases, or congenital heart malformation or any recent fever, cough, or sore throat. After connection of the monitors and before preoxygenation, a 50 mcg IV bolus of fentanyl (2 mcg/kg) was injected. Within 30 seconds, he began to cough explosively and struggled to a sitting position; the cough was unproductive and persisted in spasmodic bursts for a further two to three minutes until anesthesia was induced with propofol (60 mg) and atracurium (15 mg IV). After tracheal intubation and before surgery, numerous conjunctival and periorbital petechiae were noticed but had begun to fade by the end of the first postoperative day.[37]

Several recent reports have indicated that opioid blockers are effective in attenuating self-injurious behavior (SIB). In a study, four patients with SIB were challenged with four fixed doses (0, 25, 50, 100 mg) of naltrexone. The results suggest that endogenous opioids are implicated in SIB and that naltrexone is a powerful tool for examination of this treatment-resistant behavior.[38] Also, the data from another study on the effect of naltrexone on the frequency of SIB suggest that disturbances of the endogenous opioid systems may be involved in the pathophysiology of SIB of certain patients.[39]

An autistic eight-year-old boy with DS and unspecified

mental retardation was treated for SIB with naltrexone, which is a long-acting opioid antagonist. This treatment is based on the hypothesis that abnormal opioid systems mediate such behavior. The dose used on this patient was far above the consensus dose of 0.5 mg/kg to 2 mg/kg. After two weeks, the frequency of SIB had decreased.[40]

Endogenous opioids in the frontal cortex of adult patients with DS have been investigated, post mortem, in a study. The results of this study show that there is an increase in the levels of leu-enkephalin and dynorphin-A in the frontal cortex of patients with DS compared to the control group.[41]

Other alterations that involve neurotransmission in subjects with DS include the cholinergic system, which presents an important decrease; the GABA system; the noradrenergic system; and glutamate transmission. Moreover, another aspect that should be noted in the use of opioids in patients with DS is the special drug metabolism of this syndrome. Alterations in hepatic and kidney functions modify the pharmacokinetics and pharmacodynamics of drugs.

The "Down's syndrome critical region" (DSCR) is a chromosome 21 segment purported to contain genes responsible for many features of DS.[42] Neither the pathogenesis nor the etiology of DS is clearly understood. Numerous studies have examined whether clinical features of DS are a consequence of specific chromosome 21 segments being triplicated.[43]

Although numerous biochemical abnormalities accompanying the syndrome have not yet been completely clarified, the antioxidant defense system enzymes have been shown to be altered due to increased gene dosage on chromosome 21 and overproduction of superoxide dismutase (SOD-1 or Cu/Zn SOD).[44] It has been emphasized that increased oxidative damage may be present in DS and that SOD-1 seems to play a role in the pathogenesis of this disorder.[45] This is an example of a consequence of genetic anomalies in DS.

The human liver-type subunit of the key glycolytic enzyme, phosphofructokinase (PFKL), is encoded by a gene residing on chromosome 21. This chromosome, when triplicated, causes the phenotypic expression of DS (trisomy 21). Increased PFKL activity, a result of gene dosage, is commonly found in erythrocytes and fibroblasts from DS patients.[46]

Transient myeloproliferative disorder (TMD), an acute leukemia-like disorder in neonates with DS, is characterized by spontaneous regression of abnormal blast growth.[47] Knowing the cellular mechanism of hepatic fibrosis and its modulation by growth factors (e.g., platelet-derived growth factor), a pathogenetic link between TMD and the development of liver fibrosis in DS neonates seems probable. An association of this triad of findings no longer appears to be accidental.[48]

A range of renal diseases has been previously described in patients with DS. With increased survival, it appears that a growing number of these patients present with chronic renal failure. Definition of underlying causes of renal failure could potentially lead to prevention of progressive renal dysfunction in this population.[49] A variety of urological abnormalities and glomerulopathies have been reported in this population, and some DS patients develop chronic renal failure. Renal disease in patients with DS is not as rare as previously thought, although the majority of findings are of minor relevance. According to the variety of pathologies, and in order to detect early irreversible renal injury, it seems quite reasonable to perform regular monitoring of renal function in these patients.[50]

Sleep apnea syndrome occurs when, during sleep, breathing stops for 10 seconds or longer, with an index of five times an hour or more. It is clinically characterized by loud snoring at night, either continuous or interrupted by pauses, followed by loud breathing. Sleep is fitful, broken by arousals, and yields little rest.[51] This syndrome has many implications for the anesthetist because patients are exquisitely sensitive to all central depressant drugs, with upper airway obstruction or respiratory arrest occurring even with minimal doses, and because patients with sleep apnea syndrome have a potentially difficult airway to manage. Perioperative risks that patients with sleep apnea syndrome face emphasize the importance of detection and perioperative evaluation and planning.[52] Steroids may be used to decrease the amount of airway swelling. Supplemental oxygen should be used in patients who demonstrate desaturation. Opioids and sedatives should be avoided, as should other drugs that have central and sedating effects. Postoperative pain is effectively controlled with acetaminophen and topical anesthetic sprays. Postoperative monitoring for apnea, desaturation, and arrhythmias is a necessity in sleep apnea patients.[53] Obstructive sleep apnea has been reported in 20 percent to 50 percent of children with DS.[54] The causes, severity, and presentation of upper airway obstruction in children with DS are related to the age of the child and to associated comorbidities. The treatment of comorbidities and secondary ear, nose, and throat disorders is an integral component of the surgical management of upper airway obstruction in such cases.[55]

While the prevalence of obstructive sleep apnea syndrome among children with DS is reported to vary from 30 percent to 50 percent, the nocturnal respiratory pattern of adults with DS is not well known. According to the literature, and in conjunction with the current study's results, it could be hypothesized that the nocturnal respiratory pattern of adults with DS depends on several pathogenetic factors such as age, severity of upper airway abnormalities, body mass index, other pathological conditions, and age-related brainstem dysfunction.[56] The

sleep apnea syndrome in DS patients must be evaluated when using opioids in order to avoid respiratory arrest.

CONCLUSION

DS is a condition characterized by mental retardation and associated with multiple congenital anomalies. Neurotransmission abnormalities involve opioid receptors and pain transmission, with repercussions on pharmacodynamic and clinical aspects. Therefore, in these patients, a clear knowledge of the structure and function of opioid receptors is vital for the use of these drugs in performing safe and adequate procedures.

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ORIGINAL ARTICLE

A comparison of patient-controlled epidural pethidine vs. nurse-administered epidural pethidine for analgesia after caesarean section

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ABSTRACT

Patient-controlled epidural analgesia with pethidine for post-caesarean section patients has been shown to be efficacious. However, no studies to date have compared it with intermittent nurse-administered epidural pethidine. The aim of this study was to compare the analgesia efficacy, pethidine requirement, side effects, and nurses' and patients' satisfaction with these two techniques in post-caesarean section patients. After obtaining informed patient consent, we recruited 34 patients undergoing elective lower-segment caesarean section. A combined spinal epidural technique was used to provide anesthesia for all patients, and 50 mg pethidine was given epidurally at the end of the operation. Patients were assigned to two groups: group P (n = 17) received patient-controlled epidural analgesia with pethidine (25 mg of five mg/ml solution, lockout of 10 minutes and maximum dose of 150 mg/four hours), and group N (n = 17) received nurse-administered epidural pethidine (bolus of 50 mg and maximum dose of 50 mg/two hours) when required. We collected data at six, 12, 24, 36, and 48 hours following initiation of anesthesia. Visual analogue pain scores (median) were lower in group P than in group N, both on movement and at rest, at six, 12, 24, 36, and 48 hours postoperatively ($p < 0.05$). Total pethidine consumption (median) and frequency of side effects were similar in both groups. Patients in group P exhibited a trend toward earlier return to activities of daily living and care for the newborn; however, this did not reach statistical significance, and there was no difference in maternal satisfaction between the two groups. Satisfaction scores of nurses caring for patients in group P were higher than for those in group N (median 100 mm, interquartile range [IQR] 90 to 100, vs. median 90 mm, IQR 80 to 90, $p < 0.05$). Patient-controlled epidural analgesia with pethidine improved patients' pain scores after caesarean section when compared with intermittent nurse-administered epidural pethidine. Regarding the mode of delivery of postoperative analgesia, we noted a higher satisfaction score among nurses caring for group P than among those caring for group N.

Key words: post-caesarean section analgesia, epidural analgesia, patient-controlled analgesia, pethidine

INTRODUCTION

Patient-controlled epidural analgesia (PCEA) with pethidine for post-caesarean analgesia was first described and evaluated in a study in 1992.[1] Since then, several studies have compared its efficacy with PCEA fentanyl, epidural morphine, and patient-controlled intravenous analgesia (PCIA) with morphine.[2-4] However, no study to date has compared its analgesia efficacy with intermittent nurse-administered epidural pethidine in post-caesarean section patients.

In our center, parturients routinely receive intermittent nurse-administered epidural pethidine for post-caesarean analgesia in the first 24 hours. This method has several pitfalls. It presents a major workload for the nursing staff in the ward, and there are occasional delays in the administration of pain relief when the ward staff is busy. Advantages of the PCEA include giving patients greater autonomy over the amount of analgesic they require, potential improvement in pain scores and patient satisfaction, and potential improvement in nurses' satisfaction with patient care due to a decrease in workload.[1]

The primary aim of our study was to compare maximum pain scores at rest and on movement in the first 48 hours in patients who received either PCEA or nurse-administered epidural pethidine after caesarean section. We also compared side effects, total pethidine consumption, time to return to activities of daily living and care of the newborn, and patients' and nurses' satisfaction.

METHODS

After institutional review board approval, we recruited

Table 1. Patients' demographic profile			
	Group P (n = 17)	**Group N (n = 17)**	**p value**
Age (years)	35 (3.6)	33.3 (3.8)	0.187
Weight (kg)	73.2 (12.1)	81.4 (12.5)	0.061
Height (cm)	166.6 (9.6)	165.2 (3.9)	0.577
Bupivacaine dose (mg)	10.5 (0.5)	10.5 (0.5)	0.187
Fentanyl dose (mcg)	16 (2)	16 (2)	0.385
Lignocaine supplementation (mg)	60 (60)	30 (45)	0.116
Duration LSCS	74.1 (24.2)	66.6 (15.3)	0.279
Previous LSCS	12/17 (70.6)	11/17 (64.7)	0.714
Values are mean (SD) or proportion of patients (percent).			

34 ASA Grade I patients presenting for elective caesarean section under regional anesthesia. Informed written consent was obtained. Patients who did not understand or refused the use of PCEA; who had contraindications to regional anesthesia; or who had an allergy to pethidine, paracetamol, or diclofenac were excluded. Patients were randomized, using sealed opaque envelopes, into two groups; group P received epidural pethidine via a patient-controlled analgesia pump (GemStar® Ambulatory PCA Infusion Pump), and group N received epidural pethidine via nurse-administered bolus when required.

All patients received combined spinal epidural anesthesia for caesarean section with intrathecal heavy bupivacaine 10 mg to 12.5 mg and fentanyl 15 mcg to 25 mcg. A bolus dose of epidural pethidine 50 mg in 10 ml of normal saline was administered to all patients at the end of the surgery, along with paracetamol 1 g and diclofenac 100 mg suppository.

Postoperative analgesia for group P was maintained using PCEA with pethidine. The PCEA pump was set to administer a 5-ml bolus of pethidine 5 mg/ml (25 mg) with each demand, with a 10-minute lockout interval and a four-hour maximum dose of 150 mg. This setting was to ensure that each patient would not receive a dose exceeding the maximum safe dose of 900 mg over 24 hours. Group N received postoperative analgesia via intermittent epidural boluses of pethidine administered by a nurse when required. Pethidine solution of 5 mg/ml concentration was administered in 50-mg boluses each time the patient experienced postoperative pain, with a two-hour maximum dose of 50 mg. This was the standard protocol in our center for patients after caesarean section. All patients received postoperative paracetamol 1 g every six hours for 48 hours and diclofenac suppository 100 mg every 12 hours for the first 24 hours; following this, diclofenac was administered orally 50 mg every eight hours for the next 24 hours.

The investigators assessed the:

1. pain scores at rest and on movement (supine to sitting position) using visual analogue scores (VAS) of 0 to 100 mm, 0 = no pain and 100 = severe pain, at six,12, 24, 36, and 48 hours postoperatively;

2. amount of epidural pethidine (mg) used at 24 hours;

3. number of doses of rescue opioid needed in the first 24 hours;

4. number of doses of opioid required after epidural pethidine was ceased at 48 hours;

Table 2. Pain scores (VAS) at rest 48 hours post-caesarean section			
Time post-caesarean section (hours)	**Group P (n = 16)**	**Group N (n = 17)**	**p value**
6	0 (0 – 10)*	0 mm (0 – 30)	0.433
12	0 (0 – 10)*	20 mm (5 – 40)	0.004
24	0 (0 – 5)	10 mm (2.5 – 30)	0.003
36	0 (0 – 10)	10 mm (10 – 20)	0.001
48	0 (0 – 0)	10 mm (5 – 20)	0.001
Data in median (interquartile range) and VAS in mm; * Patients analyzed, N = 17.			

5. presence of side effects experienced at 24 hours postoperatively;

6. patient's ability to care for herself and the baby at 24 hours and 48 hours postoperatively, using the following criteria:

(i) initiate diaper change without assistance;

(ii) lift and hold baby without assistance;

(iii) initiate breast-feeding without assistance;

(iv) ambulate without assistance; and

(v) shower without assistance;

7. time of removal of epidural catheter;

8. patient's satisfaction with the mode of analgesia using a 100-point scoring system (0 = very dissatisfied, 100 = very satisfied) (the patient satisfaction score was obtained from the patient 24 hours postoperatively by the acute pain team); and

9. nurses' satisfaction with the mode of delivery of postoperative analgesia (information collected by the acute pain relief team at 24 hours from the nurses attending to the patient; using a 100-point scoring system, 0 = very dissatisfied, 100 = very satisfied) (nurses' satisfaction scores were obtained from the three nurses attending to the patient over a 24-hour period; average nurses' satisfaction score was then calculated for each patient).

The investigators were notified when patients experienced inadequate pain relief. The investigators were informed if patients in group N requested analgesia less than two hours after the last pethidine dose or when the pain score remained higher than 40 after two doses of epidural pethidine (50 mg/two hours) had been administered. For group P, investigators were informed when pain scores remained higher than 40 and pethidine used was at doses greater than 100 mg in two hours. After reviewing the patients, rescue analgesia would be given if necessary. Rescue analgesia of intravenous (IV) tramadol 100 mg/six hours PRN for 48 hours was made available for the patients. If the pain score remained higher than 40 despite institution of rescue analgesia, the study protocol was aborted and the patient would be given subcutaneous morphine.

Patients who had moderate or severe respiratory depression (respiratory rate < eight breaths/minute) would be reviewed by the investigator, given supplementary oxygen, treated with IV naloxone 100 mcg, and monitored for the next four hours with a pulse oximeter.

Patients had the epidural catheter removed 24 hours postoperatively. However, if the patients had required two or more doses in the last four hours, the option to keep the catheter for another four hours was available to the patients. IV/PO tramadol 100 mg/six hours and PO oxycodone 5 to 10 mg/four hours were available to provide analgesia for patients after cessation of epidural pethidine.

Table 3. Pain scores (VAS) on movement 48 hours post-caesarean section			
Time post-caesarean section (hours)	**Group P (n = 16)**	**Group N (n = 17)**	**p value**
6	0 (2.5 – 35)*	22.5 (11.3 – 50)	0.127
12	20 (10 – 40)*	40 (20 – 65)	0.014
24	10 (10 – 30)	40 (30 – 50)	0.001
36	20 (10 – 35)	40 (20 – 55)	0.014
48	15 (10 – 20)	40 (20 – 50)	0.001
Data in median (interquartile range) and VAS in mm; * Patients analyzed, N = 17.			

The power of the study was calculated based on a previous study done using PCEA with pethidine for post-caesarean analgesia.[2] A difference of 20 in pain scores at 24 hours between the two groups was assumed to be clinically significant in our project. Thirty-two patients were required to detect this difference, with a power of 80 percent and a significance level of 0.05. Data was entered and analyzed with SPSS version 11.5. Nonparametric data (pain scores, amount of pethidine used, patients' and nurses' satisfaction), parametric data (patients' demographic profiles), and dichotomous data (presence of side effects and ability to care for oneself and the newborn) were analyzed using the Mann-Whitney U test, t-test, and χ^2 test, respectively.

RESULTS

Data were analyzed from 34 patients who completed the study. There were no failed blocks, and all patients had successful regional anesthesia for caesarean section. One patient in group P had disconnection of the epidural catheter from the filter, resulting in early termination of epidural analgesia 14 hours after caesarean section. Data from this patient were included until the time of withdrawal. There were no differences in patients' demographic profiles or amounts of bupivacaine and fentanyl used for regional anesthesia (Table 1). Group P had significantly lower visual analogue pain scores, both at rest and on movement, for the 48-hour period following caesarean section (Tables 2 and 3). The amount of epidural pethidine used in group P was similar to that used in group N (median 250 mg, interquartile range [IQR] 200 to 300 mg, vs. 225mg, IQR 200 to 250mg, $p > 0.05$). The number of doses of oral opioid required after the epidural pethidine was ceased in the first 48 hours was similar in groups P and N (median 3, IQR 2 to 3, vs. 4, IQR 2 to 4, $p > 0.05$). Incidence of side effects was similar in both groups (Table 4).

There was a trend toward earlier ability to care for oneself and the baby at 24 hours postoperatively, but this did not reach statistical significance. All patients were able to care for themselves and their newborns by 48 hours (Table 5). Time to epidural catheter removal was similar (group P: mean 25.7 hours, SD (5.8); group N: mean 25.2 hours, SD (1.8); $p = 0.72$).

Patients' satisfaction with the mode of analgesia at 24 hours post-operation was not significantly different (group P: median 95, IQR 87.5 to 100; group N: median 90, IQR 80 to 100; $p = 0.085$). Satisfaction scores of nurses caring for patients in group P were higher than for those in group N (median 100 mm, IQR 90 to 100, vs. median 90 mm, IQR 80 to 90; $p < 0.019$). The decrease in nursing workload resulting from the use of PCEA with pethidine may have contributed to the higher satisfaction scores among nurses caring for group P.

DISCUSSION

PCEA pethidine has been shown to be superior to intramuscular pethidine and PCIA with pethidine.[4-6] Our study is the first study to compare PCEA to nurse-administered epidural pethidine, and it revealed that PCEA with small boluses of 25 mg of pethidine on demand gave lower visual analogue pain scores, both at rest and on movement, in the first 48-hour period post-caesarean section than intermittent nurse-administered boluses of pethidine.

Table 4. The side effects profile at 24 hours			
	Group P (n = 16)	**Group N (n = 17)**	**p value**
Nausea	5/16 (31.3)	5/17 (29.4)	0.603
Vomiting	1/16 (6.3)	4/17 (23.5)	0.187
Itch	2/16 (12.5)	4/17 (23.5)	0.374
Sedation	3/16 (18.8)	6/17 (35.3)	0.251
Respiratory depression	0/16 (0)	1/17 (5.9)	0.515
Data in proportion of patients (percent).			

Due to the obvious difference in the mode of delivery of epidural pethidine, it was not possible to blind the patient or the assessor for the trial. In a previous study comparing PCEA with PCIA pethidine, the median pain scores in the first 24 hours for the PCEA group were between 10 and 20 mm, comparable with our results.[4] The higher pain scores reported in the nurse-administered epidural pethidine group could be attributed to several factors. Some patients chose to wait until they experienced moderate to severe pain before requesting analgesia from the nurse, citing inconvenience and unwillingness to bother the nurses when they were busy. There could have been delays in pethidine administration, as it requires two registered nurses to sign out the controlled drug. This problem is compounded in wards that are understaffed.

PCEA with pethidine offers several advantages. There was an increase in nurses' satisfaction; they no longer needed to retrieve controlled drugs or administer them intermittently to patients, which may have decreased nursing workloads. While the nurses were trained and had to learn to manage the new PCEA pumps, as well as

Table 5. Ability to return to activities at 24 hours post-caesarean section			
	Group P (n = 16)	**Group N (n = 17)**	**p value**
Initiate nappy change without assistance	13/16 (87.5)	10/17 (58.8)	0.217
Lift and hold baby without assistance	14/16 (87.5)	11/17 (64.7)	0.118
Initiate breast feeding without assistance	15/16 (93.8)	14/17 (82.4)	0.335
Ambulate without assistance	14/16 (87.5)	11/17 (64.7)	0.118
Shower without assistance	14/16 (87.5)	11/17 (64.7)	0.118
Data in proportion of patients (percent).			

monitor the pumps for malfunction, this study revealed that these requirements did not appear to affect nurses' satisfaction adversely. The decrease in nurses handling the epidural filter while administering intermittent epidural pethidine potentially decreases the risk of breach of sterility and contamination. PCEA also gives patients a sense of control over the pain relief requirement and allows them to titrate the analgesia and balance it with the side effects they experience. Our study concurred with a previous study evaluating nurses' and patients' satisfaction with patient-controlled epidural pethidine after caesarean section.[7]

The amount of pethidine used in both groups was comparable and similar to previous studies involving epidural pethidine for post-caesarean section analgesia.[8,9] However, due to the smaller but more frequent dosing of pethidine (25-mg bolus), as opposed to the larger (50 mg) and intermittent boluses administered by the nurses, we saw a trend toward decreasing incidence of side effects, although this did not reach statistical significance. The parturients with PCEA also trended toward earlier return to activities of self-care and care for the new born. However, this was not statistically significant, and our study was not powered to detect this.

Maternal satisfaction is an important endpoint in most research; unfortunately, it is difficult to assess. Although some studies have reported greater satisfaction with PCEA than conventional analgesia, most other studies confirmed that patients generally do not like to criticize their own treatment and rate their satisfaction consistently high.[10-12] PCEA gave patients control over their pain relief and significantly decreased pain scores, but the lack in difference in satisfaction scores showed that other factors such as personal experience, support from caregiver, caregiver-patient relationship, and the inclusion of both parties in decision making affect patients' satisfaction.[13]

In conclusion, PCEA with pethidine, when compared with intermittent nurse-administered pethidine, resulted in improved pain scores both at rest and on movement in the first 48 hours following caesarean section. This was associated with an increase in nurses' satisfaction with the mode of analgesia provided.

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LITERATURE REVIEW

Effect of drug and medical treatment on wide geographic variations in repeated emergency department use by HIV-infected drug users

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ABSTRACT

Repeated (≥ two visits) emergency department (ED) visits by HIV-infected (HIV+) drug users in New York State (NYS) vary widely by region and may reflect regional inequities in receipt of needed drug treatment and medical services. The study's objective was to evaluate receipt of drug treatment and medical care by HIV+ drug users by region and its effect on ED use. For NYS Medicaid-enrolled HIV+ drug users (N = 11,556) in 1996 and 1997, we identified receipt of long-term (≥ six months) drug treatment, HIV care, and a usual source of medical care from claims files. Regions were classified as New York City , downstate suburban, upstate urban, and rural/small city. We examined adjusted associations of these services with ≥ two ED visits in the entire cohort and separately among patients who do and do not receive these three types of services. Repeated ED visits were greatest in rural/small cities (40.7 percent) and least in New York City (24.1 percent; p < 0.001), and receipt of drug treatment was also poorest (p < 0.001) in rural/small cities, whereas receipt of HIV care and usual source of medical care varied less by region. Adjusted odds of ≥ two ED visits was increased for patients in rural/small cities (1.89 [confidence interval, 1.44 to 2.50]) vs. New York City and reduced for patents with long-term drug treatment (0.76 [confidence interval, 0.69 to 0.84]). Among persons receiving long-term drug treatment, observed regional differences in ED use largely disappeared. Regional variations in receipt of long-term drug treatment by HIV+ drug users in one state appear to contribute to large differences in ED utilization.

Key words: HIV-infected drug users, emergency department visits, long-term drug treatment, regional inequities

INTRODUCTION

The National Center for Health Statistics reported that emergency department (ED) use by Americans rose by over 20 percent in the past decade.[1] Individuals who repeatedly visit the ED stress an already overburdened medical care safety net. Because illicit drug users place significantly greater demands on the ED for care than do nondrug users,[2] identifying healthcare services that can reduce ED use by drug users offers important benefits not only for drug users but also for all other patients needing ED care. Among Medicaid-enrolled drug users in New York State (NYS), our group reported that HIV infection was associated with substantially increased demands on the ED for care.[3] In that study, we also observed a marked variation in ED use across NYS regions for HIV-infected (HIV+) and uninfected drug users.

The reasons for observed wide regional variations in ED use may relate to receipt of beneficial healthcare services that can reduce complications from drug-related or medical conditions and thereby reduce urgent care needs. We predicted that (HIV+) drug users with poorer access to drug treatment and medical care services would rely more heavily on the ED for care than would those with good access to these services. We expected that access to these services would be poorest in rural/small cities where availability of drug treatment and HIV services may be more limited and/or less convenient than in New York City and its suburbs. With its wide spectrum of urban, suburban, and rural regions, NYS represents a microcosm of the geographic variations that are likely to be observed in other regions of the country.

METHODS

We conducted a retrospective cohort study of drug users enrolled in the NYS Medicaid program from federal fiscal year 1996 through 1997. This study examined files of longitudinally linked claims for all ambulatory medical

services from physicians and clinics, as well as substance abuse services covered by the Medicaid program. This database contains information on inpatient, pharmacy, home healthcare, case management, and laboratory diagnostic services. We applied validated screens using *ICD-9-CM* codes for specific diagnoses (e.g., drug dependence, unspecified; human immunodeficiency virus [HIV] disease) and services (e.g., drug treatment, antiretroviral therapy) to this comprehensive database to identify drug users and, among these, persons with HIV infection. The operating characteristics of the drug user and HIV case-finding algorithms are very good to excellent.[4] This process identified drug users aged 13 to 60 years old and enrolled in Medicaid at least 10 months in 1996 (n = 78,943). Of these, 59,104 patients were also enrolled in Medicaid for 10 or more months in 1997. We then excluded 861 women who were pregnant in 1997, because pregnancy would influence their healthcare use, and eight persons without demographic data. Of the remaining 58,243 nonpregnant drug users, we identified 11,556 with known HIV infection.

Our dependent variable was two or more ED visits in federal fiscal year 1997. As in our prior research,[5] we considered only repeated ED visits that occurred on different days and excluded visits that resulted in immediate hospitalization. Patient demographics were obtained from Medicaid eligibility files including age, sex, and NYS region of residence, but reliable data on ethnicity were not available. To define NYS regions, we used the county classification used by the NYS Department of Health to define local social service districts (Peter Gallagher, personal communication) that includes New York City, downstate suburban, upstate urban, small cities, and rural. Because of small sample sizes, we combined subjects in the rural and small city regions for analysis.

Identification of comorbid conditions was obtained from *ICD-9-CM* codes on inpatient (one occurrence) and outpatient (two occurrences) claims files in 1996 and included mental health disorders (e.g., depression, non-drug-related psychoses, anxiety), chronic diseases other than HIV (e.g., diabetes), and clinical AIDS. As a proxy for unmeasured health status, we calculated the total hospital days in 1996 and grouped them by quartile for analysis.

To determine whether healthcare factors resulted in sustained reductions in ED use, we defined patterns of drug treatment and medical care in 1996 and assessed demands on ED use in 1997. Long-term drug treatment was defined as treatment from a single methadone or medically supervised drug-free (Title 1035) program for at least six contiguous calendar months in 1996. To focus on the impact of medically supervised outpatient care, we excluded detoxification, residential, and nonmedically supervised ambulatory programs from this analysis. We applied a six-month minimum criterion for the duration of drug treatment based on evidence from studies of methadone treatment.[6] A regular source of medical care was defined as the clinic or physician visited at least twice by a study patient during 1996 and delivering more than 35 percent of all outpatient medical encounters in that year. Eligible providers were clinics, group practices, or individual physicians, but not providers who do not deliver longitudinal care, such as radiologists and ED physicians. For ties, we selected the regular medical provider according to a previously developed hierarchy of specialists.[7] We identified HIV specialty care as at least two visits in 1996 to clinics or private physicians with an agreement with NYS to offer HIV specialty services and expertise in exchange for higher Medicaid payment rates or from a provider specializing in infectious diseases.[8] From National Drug Codes on pharmacy claims, we identified antiretroviral drugs approved by the Food and Drug Administration. Ongoing combination antiretroviral therapy was defined from pharmacy claims based on paid prescriptions for at least two concurrent antiretroviral drugs prescribed for a minimum of two consecutive months.

Using the χ^2 test, we examined bivariate associations of region of residence with patient and healthcare variables including repeated ED use, drug treatment, usual source of medical care, and HIV specialty care. For the entire cohort, we estimated a logistic regression model predicting repeated ED use that included patient demographics, region of residence, clinical characteristics, and healthcare service utilization. We also examined unadjusted and adjusted associations of region of residence with repeated ED use separately for persons who did and did not receive each of the three types of healthcare services in order to examine whether regional variations disappeared among persons who received a particular type of service. Analyses were performed using Statistical Analysis Software 8.0 (SAS Institute, Cary, NC).

RESULTS

Of 11,556 HIV+ drug users in the study cohort, the majority resided in New York City, but in this large sample, at least 200 patients lived in each region (Table 1). Significant geographic differences in patient characteristics are apparent. In general, drug users living outside of New York City were younger, more likely to have a mental health disorder, less likely to be diagnosed with cocaine or heroin abuse or dependence, more likely to abuse alcohol, and less likely to be treated with antiretroviral therapy.

One quarter of the cohort visited the ED repeatedly in 1997, resulting in a total of 14,247 ED visits over the course of the year. Repeated visits to the ED varied widely by region, from to 24 percent in New York City to 41 percent in the rural/small city region (Table 2). Overall, 40 percent of the study cohort received long-term drug treatment but, again, wide regional variations appeared.

Table 1. Demographics by New York State Region for HIV-infected drug user cohort

Characteristic[a]	Total population (N = 11,556)	New York State Region			
		New York City (N = 10,263)	Downstate suburban (N = 547)	Upstate urban (N = 510)	Rural/ small city (N = 236)
	Percent				
Total	100	88.8	4.7	4.4	2.1
Female gender	39.0	38.9	41.3	38.6	42.4
Age (years)					
< 30	7.8	7.5	8.3	11.2	14.8‡
30 to 39	42.8	42.7	40.2	45.9	46.2
40+	49.3	49.8	51.6	42.9	39.0
Comorbidity					
AIDS	15.6	15.8	15.7	12.9	11.4
Other medical condition	35.1	35.4	36.8	28.4	33.5†
Mental health disease	22.5	22.0	27.2	24.3	33.1‡
Illicit drug use					
Cocaine/heroin abuse or dependence	58.8	59.5	52.5	54.5	51.7†
Other specified drug abuse/dependence	5.4	4.8	7.1	13.9	9.8‡
Drug dependence, unspecified	15.5	15.8	10.8	14.9	14.4*
Alcohol use					
No abuse	64.4	66.0	61.8	44.5	47.5‡
Alcohol abuse/dependence	26.7	25.4	28.7	44.5	39.4
Acute alcohol complications	8.9	8.8	9.5	11.0	13.1
Combination antiretroviral therapy ≥ two months	48.0	49.1	38.2	38.4	41.1‡

[a] See text for description of variables; p values for differences among the four regions from the χ^2 test: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

Table 2. Repeated emergency department (ED) use and pattern of healthcare by New York State Region for HIV-infected drug user cohort

Characteristic[a]	Total population (N = 11,556)	New York State Region			
		New York City (N = 10,263)	Downstate suburban (N = 547)	Upstate urban (N = 510)	Rural/ small city (N = 236)
	Percent				
Repeated ED visits	25.0	24.1	27.4	32.9	40.7
Long-term drug treatment	40.6	42.1	46.6	18.0	15.7‡
Usual source of medical care	51.8	51.3	53.9	52.8	62.7†
HIV specialty care	50.8	50.6	47.2	60.8	48.3‡
Hospital use in 1996					
Less than 7 days	53.0	53.3	52.8	48.0	51.3‡
7 to 21 days	22.9	23.1	23.4	18.2	22.0
More than 21 days	24.1	23.6	23.8	33.8	26.7

[a] See text for description of variables; χ^2 test p values for differences among the four regions: † $p < 0.01$; ‡ $p < 0.001$.

Only 16 percent of drug users in the rural/small city region received long-term drug treatment compared with 42 percent in New York City and 47 percent in the downstate suburban region. Other healthcare patterns differed less markedly by region. Approximately half of the study cohort had a usual source of medical care, but two thirds of rural/small city residents received this care compared with less than 55 percent of persons in the other regions. Receipt of HIV specialty care (i.e., ≥ two visits in a year) ranged from 61 percent for persons in the upstate urban region to 47 percent in the downstate suburban region. Drug users in the upstate urban region received more inpatient care than did persons in other regions.

After adjustment for patient demographics, clinical characteristics, and other health services (Table 3), persons with long-term drug treatment had nearly 25 percent lower adjusted odds of repeated ED use than those without this treatment. The protective effect of having a usual source of care on repeated ED use was weaker but still significant. HIV specialty care was not significantly associated with repeated ED use. Significant regional differences persisted in this adjusted model, with persons in the rural/small city region having nearly 90 percent greater adjusted odds of repeated ED visits than New York City residents.

Within each region, we conducted bivariate comparisons of repeated ED use for persons who did and did not use each of the services of interest (i.e., long-term drug treatment, usual source of medical care, and HIV specialty care) (Tables 4 to 6). We also conducted bivariate and multivariate analyses of the association of region with ED use among persons with and without each of these types of services. These analyses allow us to examine whether receipt of these services reduces the regional variation in ED use. With the exception of the downstate suburban region, intraregional comparisons showed that the proportion of persons who used the ED repeatedly was significantly greater for those without long-term drug treatment than for those with this care (Table 4). In the upstate urban region, for example, 36 percent of the subjects without long-term drug treatment used the ED repeatedly versus only 20 percent of persons with this care. Both before and after adjustment for demographic, clinical, and other healthcare characteristics, ED use varied significantly by region only among drug users *without* long-term drug treatment. In this group of drug users who lacked long-term drug treatment, the adjusted odds of multiple ED visits for persons in the rural/small city region was increased two-fold compared to those in New York City. Among persons *with* long-term drug treatment, much smaller differences in the adjusted odds of repeated ED use appeared and are significant only for persons in the downstate suburban region vs. those in New York City.

Intraregional bivariate comparisons of ED use for drug users with and without a usual source of medical care revealed no significant differences (Table 5). However,

Table 3. Adjusted associations with repeated emergency department visits	
Variable	**Adjusted odds [95 percent CI][a]**
Long-term drug treatment	0.76 [0.69, 0.84]‡
Usual source of medical care	0.87 [0.80, 0.95]†
HIV specialty care	0.97 [0.88, 1.06]
Region	
Rural/small city	1.89 [1.44, 2.50]‡
Upstate urban	1.35 [1.11, 1.65]†
Downstate suburban	1.18 [0.97, 1.45]

[a] Reference groups: no long-term drug treatment, no usual source of medical care, no HIV specialty care, New York City; also adjusted for: age, gender, comorbidity, drug abuse, alcohol use, hospitalized days in 1996, combination antiretroviral therapy; † $p < 0.01$; ‡ $p < 0.001$.

significant interregional differences appear both before and after adjustment in separate analyses in drug users *without* a usual source of care as well as in drug users with a usual source of care. Both models show that persons in the rural/small city and upstate urban regions had significantly increased adjusted odds of ED use vs. New York City residents.

Similarly, analyses dividing the cohort into those with and without HIV specialty care (Table 6) fail to reveal any intraregional differences. Separate analyses among those with and without HIV specialty care also show significant variations in ED use across regions. Among persons with HIV specialty care, persons in rural/small cities and in upstate urban regions have significantly higher adjusted odds of repeatedly using the ED vs. those in New York City. Among persons without HIV specialty care, a twofold increase in the adjusted odds of repeated ED visits appeared for those in the rural/small cities region, but residents of the other two regions had no significant differences in ED use compared with New York City residents.

DISCUSSION

Drug abuse,[9] HIV infection,[10] and Medicaid enrollment[11] are all recognized correlates of increased demand for ED services. Because our study cohort has all three characteristics, these patients are likely to be among the heaviest users of ED services in NYS. Our cohort's 11,556 HIV+ drug users made over 14,000 separate ED visits in one year, and one quarter of the patient sample visited the ED two or more times. This frequency of visits translates into roughly 125 visits per 100 persons in comparison with an estimated national rate of 28 ED visits per 100 persons.[12] Therefore, our data offer further evidence regarding drug users' heavy reliance on ED care.

Yet this demand for ED services was far from uniform across NYS regions. Of HIV+ drug users in the 38 counties classified as rural or having only small cities, approximately 40 percent visited the ED repeatedly compared with only 24 percent of those in New York City. However, regional differences in ED use were virtually eliminated for HIV+ drug users who received long-term drug treatment. Only approximately 20 percent or less of persons with long-term drug treatment used the ED repeatedly compared with 28 to 45 percent (depending on region) of persons without long-term drug treatment. These data provide compelling evidence that receipt of long-term drug treatment is associated with a significant reduction in ED use by HIV+ drug users in NYS and can largely eliminate regional variations in repeated ED visits.

Unfortunately, we found that receipt of long-term drug treatment was very poor outside of the New York City region, with less than 20 percent of study residents of the upstate urban and rural/small city regions receiving this care vs. over 40 percent of study residents in the New York City region. This low rate likely reflects known gaps between need for substance abuse treatment and availability of these facilities.[13] Although 24 percent of methadone programs are located outside of the New York City area, the average capacity of these programs is much smaller (average 240 vs. 359 in New York City, respectively) (source: New York State Office of Alcoholism and Substance Abuse Services). A larger proportion of medically supervised drug-free programs are outside

Table 4. Adjusted associations with repeated emergency department use from separate logistic regression models for HIV-infected drug users with and without long-term drug treatment

Region of residence	No long-term drug treatment			Long-term drug treatment		
	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)
Total	6,861	29.2‡[a,b]		4,695	18.9[a,c]	
Rural	199	44.7†	2.05 [1.52, 2.76]‡	37	18.9	0.91 [0.39, 2.13]
Upstate urban	418	35.9†	1.38 [1.12, 1.72]†	92	19.6	1.05 [0.61, 1.80]
Downstate suburban	292	30.5	1.04 [0.80, 1.35]	255	23.9	1.38 [1.02, 1.88]*
New York City	5,952	28.1‡	1.0	4,311	18.6	1.0

[a] p value from χ^2 test for intraregional comparisons of ED use by persons without and with long-term drug treatment: † $p < 0.01$, ‡ $p < 0.001$; [b] p value (not shown) from χ^2 test < 0.001 for interregional comparison of ED use; [c] p value (not shown) > 0.05 for interregional comparison of ED use; [d] Adjusted for gender, age, AIDS, other chronic medical condition, mental health disease, type of illicit drug abuse, alcohol abuse or complications, combination antiretroviral treatment, usual source of medical care, HIV specialty care, hospitalized days in 1996; * p value < 0.05.

Table 5. Adjusted associations with repeated emergency department use from separate logistic regression models for HIV-infected drug users with and without a usual source of medical care

Region of residence	No usual source of medical care			Usual source of medical care		
	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)
Total	5,576	25.6[a,b]		5,980	24.5[a,c]	
Rural	88	47.7	2.14 [1.37, 3.34]‡	148	36.5	1.75 [1.22, 2.49]
Upstate urban	241	33.6	1.34 [1.01, 1.80]*	269	32.3	1.37 [1.04, 1.81]
Downstate suburban	252	29.0	1.19 [0.89, 1.60]	295	26.1	1.15 [0.87, 1.52]
New York City	4,995	24.6	1.0	5,268	23.6	1.0

[a] p value from χ^2 test $p > 0.05$ for all four intraregional comparisons of ED use by persons with and without a usual source of medical care; [b] p value from χ^2 test < 0.001 for interregional comparison of ED use; [c] p value from χ^2 test < 0.001 for interregional comparison of ED use; [d] Adjusted for gender, age, AIDS, other chronic medical condition, mental health disease, type of illicit drug abuse, alcohol abuse or complications, combination antiretroviral treatment, long-term drug treatment, HIV specialty care, and hospitalized days in 1996; p value * < 0.05; ‡ $p < 0.001$.

Table 6. Adjusted associations with repeated emergency department use from separate logistic regression models for HIV-infected drug users with and without HIV specialty care

Region of residence	No HIV specialty care			HIV specialty care		
	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)	N	Repeated ED use (percent)	Adjusted odds[d] (95 percent CI)
Total	5,683	25.6[a,b]		5,873	24.4[a,c]	
Rural	122	45.1	2.02 [1.38, 2.96]‡	114	36.0	1.66 [1.10, 2.50]*
Upstate urban	200	33.0	1.27 [0.93, 1.75]	310	32.9	1.35 [1.04, 1.75]*
Downstate suburban	289	28.0	1.21 [0.92, 1.60]	258	26.7	1.14 [0.85, 1.53]
New York City	5,072	24.7	1.0	5,191	23.5	1.0

[a] p value from χ^2 test $p > 0.05$ for all four intraregional comparisons of ED use by persons with and without a usual source of medical care; [b] p value from χ^2 test $p < 0.001$ for interregional comparison of ED use; [c] p value from χ^2 test < 0.001 for interregional comparison of ED use; [d] Adjusted for gender, age, AIDS, other chronic medical condition, acute infection, mental health disease, type of illicit drug abuse, alcohol abuse or complications, combination antiretroviral therapy, long-term drug treatment, usual source of medical care, and hospitalized days in 1996; p value * < 0.05; ‡ < 0.001.

of New York City (38 percent), but again programs are smaller (average 86 vs. 106 clients in New York City programs). Thus, limited treatment slots may contribute to observed variations in receipt of long-term drug treatment across regions.

Even if adequate treatment slots were available, factors such as limited transportation, large distances, and the stigma of drug treatment may disproportionately affect persons living outside of New York City. Poor transportation and large distances were both cited as reasons for a dismal 10 percent of substance abusers in nonmetropolitan and rural areas with mental health problems receiving care for these conditions, based on data from the National Household Survey on Drug Abuse.[14] Problems with transportation are even more daunting for clients of methadone treatment programs who need to come to the facility almost on a daily basis. The stigma of drug abuse presents a major obstacle to expansion of drug treatment facilities.[15,16] To avoid this stigma, drug users try to "pass as normal."[17] Maintaining anonymity is easier in large metropolitan areas. Our data suggest that communities may suffer indirect consequences related to these barriers to drug treatment such as dysfunctionally high demand for ED care by drug users.

Of all the regions, access to a usual source of medical care was greatest for these residents of the rural/small cities. Unfortunately, even among persons receiving this care, we still observed significantly increased adjusted odds of ED use compared to New York City residents after adjustment for long-term drug treatment, HIV care, and other patient characteristics. Residents of New York City suburbs were significantly more likely to receive HIV specialty services than those of the other regions, but this care did not protect against higher ED use. In prior research conducted by our group, HIV+ persons whose usual source of care was a generalist were less likely to use the ED than were those with an HIV specialist in this role.[18] Generalists may be better equipped to handle emergencies than HIV specialty clinics. But a large proportion of urgent care needs of HIV+ drug users relate to drug abuse. We previously reported that roughly one third of hospitalizations for HIV+ drug users were for drug abuse–related problems.[4] Options to involve medical care providers in treating drug abuse have expanded in recent years. Buprenorphine has been approved by the Food and Drug Administration for the treatment of narcotic dependence.[19] Creative solutions such as this are necessary to improve access to treatment for addiction but need to be accompanied by adequate support for medical providers because few are taking advantage of this opportunity.[20]

We should acknowledge that NYS is a region of the United States where gaps between need for drug treatment for HIV+ persons and availability are smallest.[21] In other states, regional variations in receipt of drug treatment and, consequently, in repeated ED use may be much smaller because statewide access to drug treatment programs is universally poor. In addition, we lacked information on other predictors of ED use such as unstable housing[22] or frequency of drug use.[10] We did not evaluate

availability of case management for drug users, which was reported to produce greater stability of health status and reduced ED use in a small intervention study in Canada.[23]

This study has important implications not only for the care of drug users with HIV infection but also for the public in general. Failure to address drug treatment needs can lead to significant urgent care needs of these patients that, in turn, result in the ED being used to manage these conditions. Solutions can include expanding availability and accessibility of drug treatment programs and involving other types of providers such as generalists and HIV specialists in the management of substance abuse. All these solutions require resources, and the general public needs to recognize that they also benefit from these initiatives.

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