Journal of Opioid Management™

A medical journal for proper and adequate use

Volume 1, Number 1 | MARCH/APRIL 2005 | ISSN 1551-7489

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Published bimonthly by Prime National Publishing Corporation
470 Boston Post Rd., Weston, MA 02493 • 781-899-2702, Fax: 781-899-4900
www.opioidmanagement.com
E-mail: jom@pnpco.com

Subscription Rates: (All rates in US dollars)

Individual: US $298; Canada $323; Foreign $363
Libraries/Institution: US $398; Canada $423; Foreign $463
Single issues: US $70; Canada $75; Foreign $80

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Postmaster: Send address changes and form 3579 to: ***Journal of Opioid Management***, 470 Boston Post Road, Weston, MA 02493.

12576 2/4/05 Rev. A

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12552 2/7/05 Rev. I

EDITORIAL

Opioid management: Addressing the gap in understanding, education, and practice

Robert E. Enck, MD

As Editor-in-Chief, I'd like to welcome readers to this first issue of *Journal of Opioid Management*. The mission of the Journal is to promote the adequate and safe use of opioids in the treatment of pain as well as to educate readers on the legal and regulatory issues surrounding abuse, addiction, and prescription practices.

There is a clear need for education in the use and abuse of opioids in clinical practice. Since I practice in a large academic environment, I see this need on a daily basis. House staff are often confused on the starting doses of opioids, management of side effects, and pain management in general. Although medical students have taken a course in pharmacology, they have difficulty applying what they've learned at the bedside, and the subject is far too broad to cover adequately in the classroom.

The same can be said of the nursing students and staff. There is a wide chasm between physician and nurse understanding of opioid use and pain management in general. Hopefully, *Journal of Opioid Management* can close this gap.

Pain often is inadequately treated because of reluctance to prescribe opioid analgesics and fear that they will be abused. Many physicians have the perception that patients want more pain medication than they're comfortable prescribing. The difference between tolerance, physical dependence, and addiction is frequently misunderstood.

The belief that the use of opioids for pain relief causes addiction is a common clinical misconception; in reality, the most common cause of escalating pain is worsening disease, not an increased tolerance to pain medication. Pseudo-addiction (drug-seeking behavior) is caused by inadequate analgesic prescribing. In pseudo-addiction, the drug-seeking behavior stops when adequate medication dosages are given. Conversely, in true addiction, drug-seeking behavior continues to escalate.

Patient fears of opioid dependence are an additional hindrance to adequate pain management. Many patients are concerned about becoming addicted to opioids. In fact, compared with the abuse of other drugs, illicit drugs in particular, the abuse of opioid analgesics appears to be relatively low.[1]

The key challenges surrounding opioid management that will be addressed in the Journal are:

- recognizing and managing drug-seeking behavior and drug diversion;
- ethical issues, such as the double effect and its meaning in pain control;
- new technologies, such as implantable opioid devices for continuous intraspinal delivery;
- the perspective of patients and their expectations for pain control;
- recent efforts to liberalize opioid use for treatment of chronic nonmalignant pain;
- common prescribing errors and how to avoid them;
- legal issues and the ongoing regulatory environment; and
- addressing addiction issues in healthcare providers.

Recent research promises new treatment approaches, including opioid analgesics acting outside the central nervous system, targeting of opioid peptide-containing immune cells to peripheral damaged tissue, and gene transfer to enhance opioid production at sites of injury. Although these advances are exciting, there is still a ways to go.

Original articles, case studies, literature reviews, editorials, and letters concerning all aspects of opioid management will be considered. Articles selected for publication are vetted by a distinguished editorial board, who bring a broad range of knowledge and experience to the publication. Together, we look forward to making *Journal of Opioid Management* an invaluable resource in furthering pain management through adequate opioid research and practice.

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MPA AS EFFECTIVE AS LEUPROLIDE IN TREATING ENDOMETRIOSIS PAIN

Depot-medroxyprogesterone acetate (MPA) and depot-leuprolide acetate are equally effective for managing pain associated with endometriosis but have different adverse side effects, according to a study presented at the 2004 Global Congress of Gynecologic Endoscopy in San Francisco, California. In this comparative study of therapeutic options, investigators randomized 274 women (age range: 18 to 49 years) with endometriosis pain to receive an injection of 140 mg MPA subcutaneously or 11.25 mg leuprolide intramuscularly every three months for a six-month period, with a subsequent one-year follow-up.

Results at six months showed MPA to be statistically equivalent to leuprolide in relieving four of five endometriosis symptoms, including dysmenorrhea, dyspareunia, pelvic pain, and pelvic tenderness. The therapies were equivalent in relief of all symptoms at 18 months.

The most significant differences between the two drugs were the side effects. Specifically, MPA was associated with significantly lower Kupperman Index scores and decreased bone mineral density compared with leuprolide. MPA recipients also experienced more frequent hot flashes, menopausal symptoms, and vaginal dryness compared with those taking leuprolide. (Source: Medscape Medical News, November 18, 2004.)

NEW EPIDURAL INJECTION PROVIDES TWO DAYS OF POSTSURGICAL PAIN RELIEF

Endo Pharmaceuticals Inc. recently initiated commercial shipments of the first single-dose epidural injection for patients undergoing major surgery in the United States. The injection, or DepoDur™, provides up to 48 hours of pain relief.

Most postoperative pain relief methods used today require catheters or intravenous lines. In contrast, DepoDur™—which is a morphine sulfate extended-release liposome injection—is delivered as a single epidural shot, thereby reducing the need for external tubes or pumps and possibly accelerating patients' recovery.

Unlike common morphine treatments that are administered epidurally, DepoDur™ does not require an indwelling catheter for continuous pain relief. Such catheters can make it difficult for patients to move around after surgery and can increase the risk of infection. A recent analysis reported in the *Journal of the American Medical Association*, encompassing three decades of research, indicates that epidural analgesia provides significantly better post-operative pain control compared to parenteral opioids. Research also shows that patients with properly managed postsurgery pain may have less complicated rehabilitation periods and fewer chronic pain problems than patients whose pain is mismanaged.

The primary side effect of DepoDur™ is respiratory depression, particularly in elderly, debilitated patients and those with compromised respiratory function. Patients must be monitored for at least 48 hours after administration, and the facility must be equipped to resuscitate patients.

For more information about this new product, go to *www.depodur.com*. (Source: *Pain.com*, December 7, 2004.)

PATIENT–CONTROLLED TRANSDERMAL FENTANYL ANALGESIC CONVENIENT, EFFECTIVE AFTER HYSTERECTOMY

For hysterectomy patients, patient-controlled transdermal fentanyl (IONSYS) analgesia is as effective and more convenient than traditional intravenous patient-controlled analgesia (IV PCA) with morphine, according to research presented in November 2004 at the American Society of Regional Anesthesia and Pain Medicine's annual meeting in Phoenix, Arizona.

Because both pain management systems provide equivalent pain control, researchers wanted to determine how they compare when used after a common surgical procedure. The study included only women who had undergone a hysterectomy.

Specifically, 138 patients were assigned to the IONSYS system and 137 to the IV PCA system. The primary endpoint was patient global assessment of analgesia at 24 hours. Results showed that 84.8 percent of patients in the IONSYS group and 83.9 percent in the IV PCA group rated pain control as excellent or good.

Presenters said the greatest advantages of IONSYS are convenience and the avoidance of drug dispensing and programming errors. (Source: Reuters Health News, November 17, 2004.)

SUSTAINED–RELEASE MORPHINE MAY ALLEVIATE PAIN IN REFRACTORY PATIENTS

Morphine sulfate sustained-release (SR) capsules appear safe and effective for the treatment of moderate to severe, chronic, nonmalignant pain in patients unresponsive to other therapies, according to a study presented in October 2004 at the 17th World Conference of Family Doctors in Orlando, Florida.

Morphine SR is designed with a polymer-coated pellet technology that avoids the initial release of morphine at the start of the dose. This feature may reduce the "high" patients experience with other oral pain management therapies.

Known as the *Kadian: Response of Non-malignant, Undertreated Subjects with Moderate/Severe Pain* (KRONUS-MSP) study, the trial is the largest to date to examine the tolerability of a sustained-release opioid for the treatment of chronic, nonmalignant pain, according to the researchers.

KRONUS-MSP was performed as a community-based prospective, randomized, open-label, blinded end-point study to investigate the effect of morphine SR on quality of life, pain, sleep, treatment satisfaction, and tolerability in patients with chronic, nonmalignant pain that had been previously unsuccessfully managed.

The study population included 1,418 patients, aged 18 to 85 years, with moderate to severe, chronic, nonmalignant pain and a baseline visual numeric scale pain score of 4 or higher. Patients presented with chronic pain in various locations, such as the back, neck, and limbs.

Patients were randomized to a four-week morning or evening dose of morphine SR, starting at 20 to 200 mg/day once daily, based on their previous regimen. Adjustments to the dosing were made after the first week or second week for dose titration, and patients were allowed to switch to a twice-daily regimen, if required. No additional opioids were allowed. Adverse events were recorded on case report forms for evaluation.

There were no significant differences observed in outcomes between patients receiving a morning or an evening dose. Overall, 39.7 percent of patients reported at least one adverse event, of which 71.9 percent were considered mild or moderate. The most frequent adverse events were constipation (12 percent) and nausea (10 percent).

A total of 136 patients discontinued the study because of adverse events. The events that most commonly lead to withdrawal were nausea (27.9 percent), vomiting (15.4 percent), and constipation (10.3 percent).

According to the researchers, results of the KRONUS-MSP trial demonstrated that patients were successfully switched from prior, ineffective pain management regimens to morphine sulfate SR capsules. (Source: Medscape Medical News, October 22, 2004.)

MORPHINE RISKY FOR HEART PATIENTS, RESEARCHERS SAY

The routine practice of prescribing morphine for heart patients with chest pain carries a 50 percent higher risk of death, according to Duke University researchers. They presented their findings at the American Heart Association's annual scientific sessions in New Orleans last year. In their outcomes analysis of more than 57,000 high-risk heart attack patients, 29.8 percent received morphine within the first 24 hours of hospitalization. These patients had a 6.8 percent death rate, compared to a 3.8 percent death rate for those receiving nitroglycerin.

Researchers said these results raise serious concerns about the safety of routine morphine use in this group of heart patients. They said that morphine doesn't treat what actually causes pain—it just masks pain. As a result, it may make the underlying disease worse. (Source: MedlinePlus News, November 11, 2004.)

Make your thoughts known!

Write *Journal of Opioid Management*!

The *Journal* welcomes letters on subjects related to all aspects of opioid management. Letters in response to articles in specific issues of the *Journal* are especially welcome, but, to ensure timely publication, they should be sent soon after distribution of the issue in question.

You may send your letter by mail, fax, or e-mail.

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CALENDAR

Society for Pain Practice Management (SPPM)
18th Annual Pain Management Symposium
March 12-18, 2005
Doubletree La Posada
Scottsdale, Arizona

For registration information, contact:
SPPM
5101 College Boulevard, Suite 100
Leawood, KS 66211
Tel: 913-387-3155 • Fax: 913-387-3156
Web site: *www.sppm.org*

International Harm Reduction Association (IHRA)
16th International Conference on the Reduction of Drug Related Harm
March 20-24, 2005
The Waterfront Hall
Belfast, Northern Ireland

For registration information, contact:
Project Planning International
Montalto Estate
31 Spa Road
Ballynahinch, Co. Down
Northern Ireland BT24 8PT
Tel: 44-0-28-9756-1993 • Fax: 44-0-28-9756-5073
E-mail: *dawn@project-planning.com*
Web site: *www.ihrcbelfast.com*

American Pain Society (APS)
24th Annual Meeting
March 30-April 2, 2005
Hynes Convention Center
Boston, Massachusetts

For conference information, contact:
APS
4700 West Lake Avenue
Glenview, IL 60025
Tel: 847-375-4715 • Fax: 877-734-8758
E-mail: *info@ampainsoc.org*
Web site: *www.ampainsoc.org*

American Society for Pain Management Nursing (ASPMN)
Annual Meeting
March 30-April 3, 2005
Hyatt Regency
Albuquerque, New Mexico

For conference information, contact:
ASPMN
7794 Grow Drive
Pensacola, FL 32514
Tel: 850-473-0233 • Fax: 850-484-8762
E-mail: *aspmn@puetzamc.com*
Web site: *www.aspmn.org/html/AnnualMtg.htm*

American Society of Addiction Medicine (ASAM)
Pain and Addiction: Common Threads IV
April 14, 2005
Hyatt Regency Hotel
Dallas, Texas

For registration information, contact:
ASAM
4601 North Park Ave, Arcade Suite 101
Chevy Chase, MD 20815
Tel: 301-656-3920 • Fax: 301-656-3815
E-mail: *email@asam.org*
Web site: *www.asam.org/conf/conf_gf.htm*

Harvard Medical School and Beth Israel Deaconess Medical Center
Principles and Practice of Pain Medicine
June 22-26, 2005
Fairmont Copley Plaza Hotel
Boston, Massachusetts

For registration information, contact:
Harvard Medical School
Department of Continuing Education
P.O. Box 825, Boston, MA 02117-0825
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International Association for the Study of Pain (IASP)
11th World Congress on Pain
August 21-26, 2005
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Sydney, Australia

For registration information, contact:
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GUEST EDITORIAL

Progress in pain management: Where are we?

Frederick J. Goldstein, PhD, FCP

INTRODUCTION

With the death of Dr. Elisabeth Kübler-Ross on August 24, 2004, the field of pain management lost one of its most important proponents. Her initial desire and professional actions over 30 years ago to advance the care of dying patients have spilled over into discussions of how we take care of patients presenting with pain, especially those who are terminal. However, the loss of this outstanding colleague does not signify reduced attention to pain management issues. In fact, many clear indications of continuing and expanded concern exist in this area.

Over the past few years, legislative actions at state and federal levels were taken because of current recognition that both acute and chronic pain remain undertreated, and that improvement in the delivery of proper analgesia—especially opioids—is necessary. A few examples are as follows.

"DECADE OF PAIN CONTROL AND RESEARCH" BILL

Recognizing that pain management does not have a major voice at the federal level and has a low level of support for research, education, and treatment, the 106th US Congress passed H.R. 3244—the "Decade of Pain Control and Research" bill (Title VI, Sec. 1603)—which President Clinton signed into law. It took effect on January 1, 2001.[1] It was hoped that this legislative accomplishment would increase attention on pain in both the public and private sectors and would lead to greater progress in research, education, and clinical management. Major credit for this federal statement was given to the Pain Care Coalition, a national coalition advocating responsible pain care policies at the federal level formed in 1998 by the American Academy of Pain Medicine, American Headache Society, and American Pain Society.

FSMB MODEL POLICY

In May of 2004, the Federation of State Medical Boards (FSMB) House of Delegates adopted its *Model Policy for the Use of Controlled Substances for the Treatment of Pain*, which was developed to "provide state medical boards with an updated template regarding appropriate management of pain in compliance with applicable state and federal laws and regulations."[2] Of significance is that this approach also considers *inadequate* treatment of pain to be below the standard of medical practice. Although this FSMB policy was not designed to advocate rigid policies for physicians, concern was expressed therein that inadequate pain management can result from the following:

- lack of knowledge of medical standards, current research, and clinical guidelines for appropriate pain treatment;
- the perception that prescribing adequate amounts of controlled substances will result in unnecessary scrutiny by regulatory authorities;
- misunderstanding of addiction and dependence; and
- lack of understanding of regulatory policies and processes.

Therefore, the FSMB model policy was developed to foster consistency in "promotion of adequate pain management and education of the medical community about treating pain within the bounds of professional practice and without fear of regulatory scrutiny." It includes the following points:

- state medical boards view pain management as important and integral to the practice of medicine;
- opioid analgesics may be necessary for the relief of pain;
- prescribing opioids for other than legitimate medical purposes poses a threat to the individual and society;
- physicians have a responsibility to minimize the potential for the abuse and diversion of controlled substances; and
- physicians will not be sanctioned solely for prescribing opioid analgesics for legitimate medical purposes.

CALIFORNIA LEGISLATION

With major involvement of the California Medical Association, new state legislation was created to assist physicians in their efforts to properly manage pain and to lessen the fear of being investigated by legal authorities following an unwarranted arrest. It ensures that a medical review takes place before any charges of unlawful prescribing are filed. As of January 1, 2006, medical and law enforcement organizations are to develop interagency protocols designed to ensure that patients receive adequate analgesia under existing law.[3] After approving this bill without opposition, the California Legislature sent it to Governor Arnold Schwarzenegger on August 20, 2004.

One of the most devastating potential outcomes of undertreating pain is that, for some patients, the situation becomes a *suicidogen*,[4] which subsequently leads to the emergence of *Kevorkianism*.[4] It is hoped that recent actions undertaken at federal and state levels will lessen these possibilities.

Frederick J. Goldstein, PhD, FCP, Professor of Clinical Pharmacology, Department of Neuroscience, Physiology and Pharmacology, Philadelphia College of Osteopathic Medicine; Clinical Research Associate, Department of Anesthesiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

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LEGAL COLUMN

Who should regulate the practice of medicine?

Erin A. Egan, MD, JD

Treating pain and suffering is a fundamental duty in the practice of medicine. Mechanisms and strategies for pain management are part of the art of medicine, and substantial clinical skill, experience, and judgment are essential to proper pain management. Unfortunately, the policy issues of pain management are intertwined with the debate on physician-assisted suicide (PAS), to the detriment of patients in pain. The debate around PAS is passionate on both sides, but people directly involved in providing care to patients need to remain focused on keeping the issue of pain management separate.

Adequate pain control remains an important issue for patients in the United States, and evidence indicates that pain is still under-recognized and undertreated.[1] Attempts by the federal government to minimize illegal use of legitimate pain medications and to make PAS under the Oregon Death with Dignity Act (DWDA) illegal have an important impact on pain management practices. Most physicians have no personal involvement with the DWDA, but all physicians are affected by possible (real or perceived) limitations on the prescription of pain medications. Although it is unnecessary for pain management issues to be enmeshed in the debate about the legality of PAS, trying to prohibit use of a medication for one purpose without raising questions about its use for other purposes is a tricky proposition.

The federal government, through the Drug Enforcement Agency (DEA), has taken steps to crack down on physicians prescribing large amounts of OxyContin®, a long-acting morphine derivative.[2] Attorney General John Ashcroft has also asked the Supreme Court to review *Oregon v. Ashcroft,* a case dealing with the DWDA.[3] For physicians to feel safe prescribing adequate pain medication to control pain, even in refractory cases, two issues need to be resolved: 1) Who is the proper regulator of medical practice—the federal government or the states? and 2) Can states or the federal government decide what a legitimate medical practice is?

The US Supreme Court has the opportunity to review the case of *Oregon v. Ashcroft*[4] at the request of Attorney General John Ashcroft.[3] When the Supreme Court has considered cases involving PAS in the past, the Court has expressly endorsed adequate pain control and has emphasized that pain control considerations are separate from PAS considerations. The Supreme Court has considered the issue of assisted suicide in two previous cases, *Washington v. Glucksberg*[5] and *Vacco v. Quill*.[6] While neither of these cases directly dealt with issues of pain control, they do affect the practice of pain control indirectly. *Glucksberg* and *Vacco* include language that expressly approves the use of adequate pain control, even when it might have the effect of hastening death.[7]

Oregon v. Ashcroft deals with the "Ashcroft Directive," which directs the DEA to enforce the Attorney General's determination that prescribing controlled substances for the purpose of assisting suicide is not a "legitimate medical purpose." Therefore, any physician who writes such a prescription violates the Controlled Substances Act (CSA) and is subject to prosecution.[8] This challenge to the legitimacy of the DWDA through the enforcement powers of the DEA presumes that the CSA[9] empowers the federal government to regulate medicine. Traditionally, regulation of medical practice has been left to the state governments.[10] States license physicians, describe the acceptable scope of their practice, and set up regulatory strategies for review and discipline. If the DEA is allowed to discipline physicians for practicing medicine in compliance with state law, such as a physician prescribing a lethal dose of medication in compliance with the DWDA, then the DEA is regulating the practice of medicine. Determining which practices constitute "legitimate medical purpose[s]" is the type of determination typically left to state regulatory and disciplinary boards. Historically, when physicians were involved in DEA prosecutions, it was for diverting drugs or prescribing drugs that are trafficked on the street and are not used to treat an actual medical condition. The actions promoted by the Ashcroft Directive cross the line into regulating the practice of medicine.

This issue has another important application in pain management. Some states protect physicians who aggressively control pain from criminal sanctions if they are acting in good faith. Such protections would be suspect if the DWDA could be overridden by federal enforcement agencies.

Many people believe that the Supreme Court will refuse to review *Oregon v. Ashcroft.* The decisions in *Glucksberg* and *Vacco* allowed states to prohibit PAS, finding that the issue of whether to PAS may be prohibited is one that the states have the authority to decide for themselves. Presumably, this leaves the states open to decide to permit it as well, although the Court has not expressly decided this. Refusing to hear the *Oregon v. Ashcroft* case would have the effect of affirming this position. Refusing to hear the case will also protect state sovereignty in the regulation of medical practice.

What constitutes the safe and effective practice of medicine has been typically left to the medical profession to determine. In his directive to the DEA, "Dispensing of Controlled Substances to Assist Suicide,"[11] Attorney General Ashcroft made the determination that assisting suicide is not a "legitimate medical purpose" under the CSA. The CSA allows the DEA to regulate controlled substances when they are not used for a "legitimate medical purpose."[12] States have been empowered to allow or disallow certain practices, but generally, the medical profession has determined the validity of a treatment or procedure.

This language in the Ashcroft Directive, as well as the increasing practice of targeting physicians who prescribe high doses of narcotics to manage refractory pain,[13] makes physicians concerned that their attempts to aggressively treat pain will have legal consequences. The doctrine of double effect holds that an act is proper and ethical if the intent is proper and ethical, despite the fact that the act may have more than one effect.[14] Therefore, it is appropriate to aggressively treat pain, even if that means death may occur sooner, as long as the intent is to treat pain. This was approved by Supreme Court Justice O'Connor in her concurring opinion in *Vacco* and *Glucksberg*.[15] The majority opinion in *Vacco* makes exactly this point, endorsing aggressive pain control and affirming that the decisive issue is the physician's intent to control pain.[16]

The Attorney General attempts to divorce the PAS issue from the issue of pain control, titling a paragraph of the memo "Use of Controlled Substances to Manage Pain Promoted."[17] However, the DEA has specifically targeted OxyContin as a drug of abuse and warns that the higher strength versions of the drug should only be used in opioid-tolerant patients.[18] While it is true that only opioid-tolerant patients should be on high doses of the drug, or any opioid, many patients with chronic severe pain become tolerant and require high doses. The concerning issue is that a physician's judgment on the amount of opioid medication needed to control a patient's pain is subject to the federal government's interpretation of what is a "legitimate medical purpose." The Attorney General and DEA are creating a precedent for medical decision making by federal agencies and taking this power out of the hand of physicians. *Oregon v. Ashcroft* may not be heard in the Supreme Court, and the DEA has a multipronged initiative for dealing with OxyContin abuse, but the effects on physicians responsible for managing pain are significant. One-quarter of physicians say that fear of discipline by a medical board or prosecutor has caused them to alter their treatment strategies.[19]

Ultimately, practitioners need to honor the duty to help patients and find the moral courage to treat pain adequately in spite of concerns of legal consequences. Fear of pain when dying is a substantial concern for many people, and many patients are in pain at the end of their lives.[20] Acting in the patient's best interest requires that physicians treat pain. Physicians can protect themselves by documenting their decision making and intent to treat pain. Specifically, physicians must document that they have prescribed high doses of pain medication because the degree of pain the patient was experiencing justified the dose, and the need to treat the pain outweighed the risks. Ultimately, physicians need to advocate on behalf of their patients and their colleagues. Pain control is, and always will be, important to patients. Physicians who aggressively treat pain and undertake to help those patients whose pain is most severe deserve respect and admiration. Physicians need to advocate keeping the determination of what constitutes valid medical practice firmly within the hands of practitioners. Even as the sensational issue of *Oregon v. Ashcroft* fades, these problems will persist and continue to impair the quality of people's lives.

Erin A. Egan, MD, JD, Assistant Professor of Medicine, Department of Medicine and Neiswanger Institute for Bioethics and Health Policy, Loyola University Medical Center, Maywood, Illinois.

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With the withdrawal of COX-2 inhibitors, opioids are an obvious alternative choice for pain

Rob Hutchison, PharmD

INTRODUCTION

Opioids are often used in combination with other analgesics in multimodal approach. Pharmacotherapy in alleviating pain may require, in addition to an opioid, nonsteroidal anti-inflammatory agents. This article will help the clinician determine when to use nonsteroidal anti-inflammatory agents and which nonsteroidal anti-inflammatory agents may be better options to use in conjunction with opioid management.

The cyclooxygenase 2 (COX-2) selective nonsteroidal anti-inflammatory drug (NSAID) rofecoxib (Vioxx®) was voluntarily removed from the worldwide market in September 2004. Its manufacturer (Merck) announced that the decision was based on new data from a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial called APPROVe (Adenomatous Polyp Prevention on Vioxx). The APPROVe trial revealed a twofold increase in the risk of developing cardiovascular (CV) embolic events, such as stroke and myocardial infarction, in patients receiving rofecoxib 25 mg daily for 18 months or more.[1] More recently, the news of a CV signal with celecoxib (Celebrex®, Pfizer) has raised concerns that the problem of an increased CV risk may be a class effect shared by all the selective COX-2 inhibitors.

In light of these apparent risks to patients, physicians and other practitioners should become familiar with the mechanisms of NSAID action, the differences among COX-2 selective NSAIDs, and alternative NSAID options.

BACKGROUND

The US Food and Drug Administration's (FDA) approval of rofecoxib and celecoxib (Celebrex) in 1999 led to a steady surge in the use of COX-2 selective drugs for inflammatory-mediated pain. Another COX-2 selective NSAID, valdecoxib (Bextra®), was released in November 2001, and others are currently under investigation. Lower gastrointestinal (GI) toxicity and no effect on bleeding time were cited as the advantages of these drugs over the nonselective NSAIDs such as ibuprofen (Advil®, Motrin®) and naproxen (Aleve®, Naprosyn®). These characteristics are important considerations, particularly in surgical patients and individuals receiving long-term NSAID therapy for chronic pain. Direct-to-consumer advertising fueled a rapid rise in the use of COX-2 selective NSAIDs. Television advertising budgets for COX-2 selective agents skyrocketed over the last five years, and these analgesics rapidly dominated the prescription NSAID market. It was estimated that 80 million individuals had taken rofecoxib by the time it was withdrawn in September 2004.[2] Pfizer agreed in December to an FDA request to suspend all direct-to-consumer marketing of Celebrex after the news of a CV signal.

An increased risk of CV events was first seen in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.[3] As a result of this study, the FDA adopted labeling changes for rofecoxib in April 2002 that included information about the increased risk of CV events compared with naproxen. Originally, the difference in CV risk was attributed to a cardioprotective effect of naproxen—which was later proven to be false[4]—rather than specifically to rofecoxib. This cardioprotective interpretation was reiterated in a 2001 meta-analysis of randomized trials of rofecoxib and three meta-analyses of naproxen and myocardial infarction published in 2002.[5] However, in August 2004, the FDA initiated and funded a retrospective database analysis that showed that rofecoxib, when taken at more than 25 mg per day, was associated with a greater risk of acute myocardial infarction and sudden cardiac death than other NSAIDs such as Celebrex.[4] This increased risk led Merck to voluntarily withdraw rofecoxib.

MECHANISMS OF NSAID ACTION

The COX enzyme is crucial to the formation of prostaglandins and exists in two isoforms: a constitutive (i.e., always present) isoform called COX-1, and an inducible isoform called COX-2 that is expressed at inflammation sites. The COX-2 selective NSAIDs (rofecoxib, celecoxib, valdecoxib) selectively inhibit COX-2 and thereby inhibit prostaglandin E_2 (PGE_2). Inhibition of

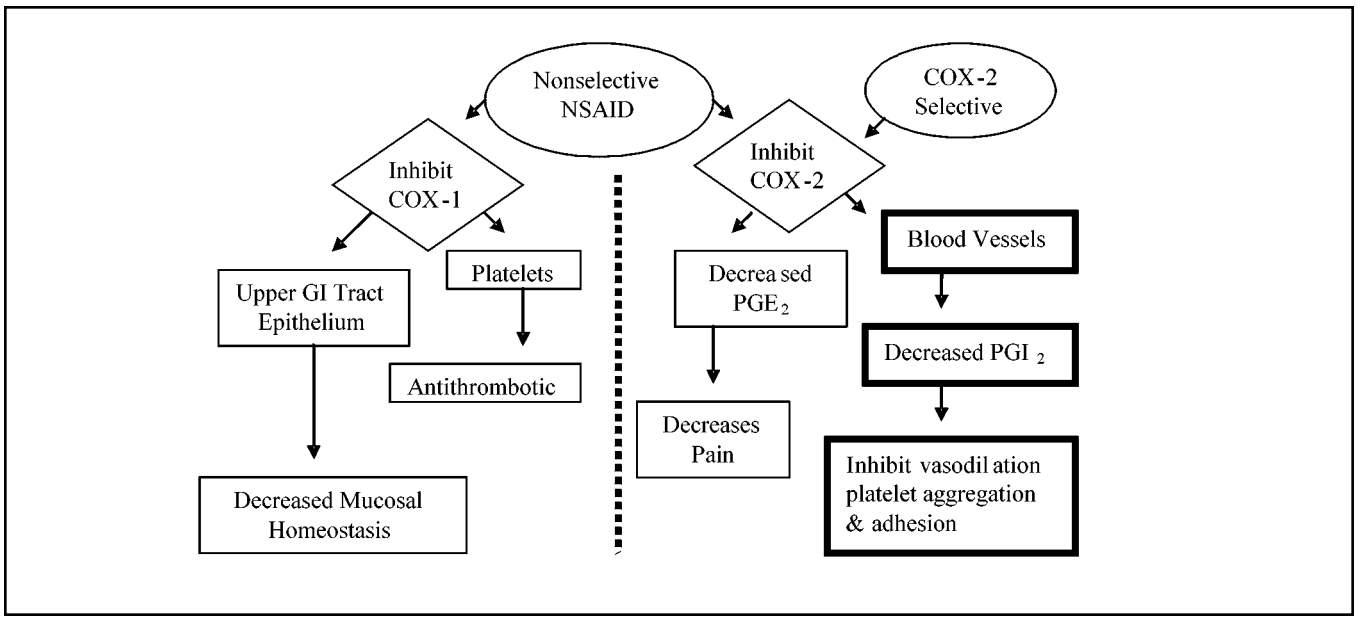

Figure 1. Schematic pathways of some of the functional effects of inhibition of COX-1 and COX-2. Copyright 2004 by Sarah E. Hutchison. Used with permission.

PGE_2 results in a decrease in inflammatory-mediated pain (Figure 1). However, the COX-2 selective NSAIDs also inhibit prostaglandin I_2 (PGI_2), another type of prostaglandin found in blood vessels, which is a vasodilator.[6] The decrease in PGI_2 in the blood vessel diminishes vasodilation and promotes platelet aggregation and adhesion.[7] This is thought to be, at least in part, the mechanism for the increased CV events observed in the patients who took rofecoxib.

Nonselective NSAIDs, such as aspirin, ibuprofen, naproxen, and ketorolac (Toradol®), inhibit both COX-1 and COX-2. This inhibition produces both a decrease in inflammatory-mediated pain and an antithrombotic effect on platelets.

DIFFERENCES AMONG THE COX–2 SELECTIVE NSAIDS

The reason why rofecoxib has been associated with a higher risk for CV events compared to other drugs in its class is still under investigation. It may lie in the differences in duration of effect or degree of COX-2 selectivity among the various NSAIDs. A drug's duration of effect can be predicted by its half-life (i.e., the time it takes for the amount of drug in the body to be reduced by 50 percent). Figure 2 demonstrates that rofecoxib has a longer duration of effect (half-life of 17 hours), and Figure 3 shows that both rofecoxib and valdecoxib have a higher degree of COX-2 selectivity compared to other NSAIDs. Aspirin has much more selectivity for the COX-1 and a very long effect on platelet inhibition (antithrombotic effect).

ALTERNATIVE NSAID OPTIONS

There are many pain-relieving alternatives to rofecoxib (Table 1) for people who suffer from inflammatory-mediated pain (e.g., arthritis). It's important for the healthcare professional to conduct a complete evaluation

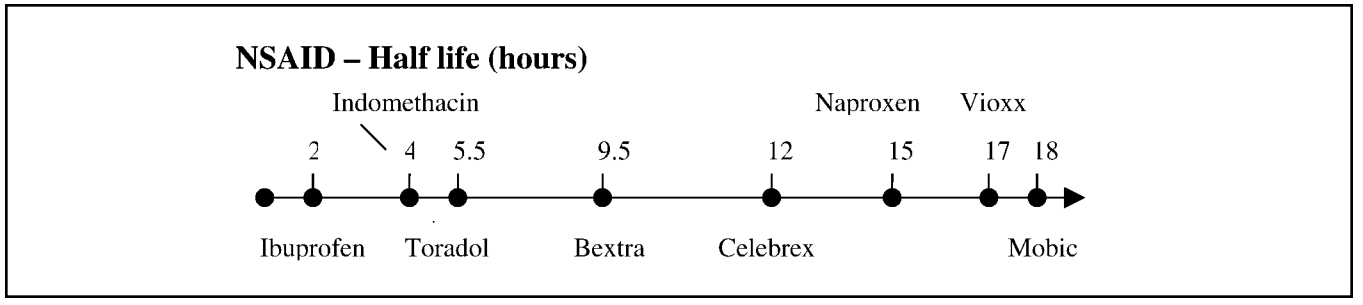

Figure 2. NSAID—half life (hours). Note: Duration of effect is dependent on individual hepatic metabolism and renal function and may vary. Copyright 2004 by Rob Hutchison. Used with permission.

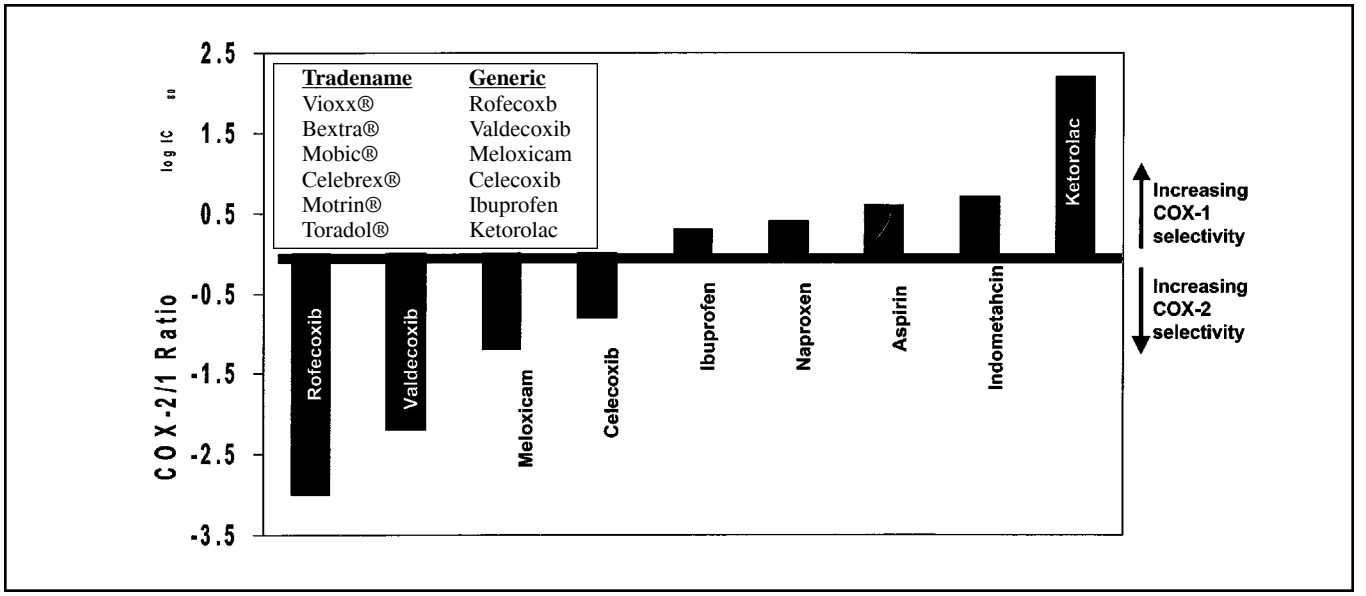

Figure 3. COX-2 selectivity. Adapted from Warner TD, Mitchell JA: Cyclooxygenase: New forms, new inhibitors, and lessons from the clinic. *FASEB J*. 2004; 18(7): 790-804.

of the patient's risk factors when considering the use of an NSAID, particularly when long-term treatment is anticipated.

At this time, the FDA has issued an advisory statement to not use nonselective NSAIDs longer than 10 days without physician consultation. The advisory statement also cautioned use of COX-2 selective agents in high-risk settings (immediately after heart surgery).[4] Valdecoxib (Bextra), as reported by Pfizer Inc., has undergone a label change to warn about an increased risk of CV events (about 1 percent of patients) immediately following coronary artery bypass graft surgery—a very specific medical setting.[8] Other NSAID options with a low GI adverse-effect profile include the nonaspirin salsalate products, such as salsalate (Disalcid®). The nonselective NSAIDs, such as ibuprofen, are appropriate for individuals with adequate renal function and no GI or CV risk factors for short-term use (< 10 days).[4]

It's important to remember that aspirin appears to eliminate any GI protection offered by a COX-2 selective NSAID. Therefore, using a COX-2 selective agent while taking aspirin as an analgesic may not be cost-effective. However, be sure to remind individuals not to discontinue their cardioprotective aspirin when taking a COX-2 selective NSAID.

A patient's renal function and the existence of underlining hypertension are other considerations when selecting an NSAID. Studies are lacking on the safe use of NSAIDs in individuals with renal disease. The COX-2 selective NSAIDs offer no additional renal protection

Table 1. COX-2 selective considerations

Risk	May consider COX-2	Avoid Cox-2*
Less ↓ More	Short-term use; risk for GI bleed	Daily aspirin use[10]
	No cardiovascular disease (CVD)	Risk factors for CVD[11]
	Long-term use; risk for GI bleed	Long-term use; CVD
	Renal impairment (RI), 3 to 7-day use	Long-term use; RI and CVD

* More studies are needed to determine safety. FDA Public Health Advisory, December 23, 2004.[4]

compared with the nonselective NSAIDs. Short-term NSAID use for precise indications, such as a three- to seven-day treatment of painful gout, may be appropriate in patients with end-stage renal disease.[9]

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ORIGINAL ARTICLE

A comparison of rapid (opioid) detoxification with clonidine-assisted detoxification for heroin-dependent persons

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ABSTRACT

This study compares two methods of detoxification available to heroin users in Western Australia: clonidine-assisted detoxification (CD) or clonidine-naloxone precipitated withdrawal under sedation (rapid opioid detoxification [ROD]). Oral naltrexone was made available to all participants following detoxification. Eighty heroin-dependent persons were randomly assigned to either ROD or CD. Most undertaking ROD commenced and completed this treatment. Less than one-third undertaking CD completed this treatment. There was no significant difference in those treated by CD or ROD in subjective assessment of degree or duration of pain, severity of withdrawal and craving, nor was there an increase in the withdrawal sequelae after treatment. Induction of oral naltrexone following ROD was greater, but oral naltrexone compliance levels and abstinence from heroin four weeks following detoxification were similar between ROD and CD groups. The level of patient satisfaction between the two treatments was also similar. The authors discuss why ROD is considered more effective than CD.

Key words: rapid opioid detoxification, naloxone/naltrexone, clonidine-assisted withdrawal

INTRODUCTION

The heroin withdrawal syndrome is well-documented, with symptoms including insomnia, irritability, restlessness, malaise, pain, fatigue, and gastrointestinal hypermotility, which extend over a seven- to 10-day withdrawal period. The objective of managed withdrawal or detoxification is to suppress withdrawal symptoms. Clonidine-assisted detoxification (CD) has commonly involved the use of andrenergic agonists and adjunctive medication to mitigate withdrawal symptoms. For example, the use of clonidine, a centrally active α-2 agonist, can reduce some of the autonomic symptoms but not craving or anxiety. Regardless of the type of withdrawal approach used, patients still experience a significant degree of withdrawal symptomatology over the seven- to 10-day withdrawal period.[1]

Unfortunately, a high proportion of patients fail to complete CD procedures—25 to 50 percent for inpatients and up to 80 percent for outpatient programs.[2] The primary reasons for failing to complete CD include difficulty tolerating the duration and severity of withdrawal symptoms. Cravings in patients undergoing protracted managed withdrawal are also considered to be a significant factor in relapse.[3]

One response to these difficulties has been to accelerate the process of detoxification using opioid antagonists, while sedating (or anesthetizing) the patient to minimize discomfort. This procedure is most commonly known as rapid opioid detoxification (ROD). The ROD procedure is designed to significantly reduce the time required for detoxification through the use of opioid antagonists such as naloxone and naltrexone to precipitate withdrawal, thus shortening the duration of patient discomfort.[1,4,5] During the ROD procedure, sedation or general anesthesia, along with antiemetics, antidiarrheals, and centrally acting sympathetic antagonists are employed to mitigate withdrawal symptoms.[6] Immediate induction of naltrexone, which more often than not follows ROD, may also distinguish ROD from CD in reducing craving.[7] However, in the current study, the majority of subjects desired detoxification so as to initiate naltrexone maintenance.

The current study was commissioned by the Department of Health (Western Australia) to evaluate the effectiveness of two detoxification programs available in Perth, Western Australia: one using CD (inpatient and outpatient) and the other ROD with induction of oral naltrexone.

METHODS

Subject selection

Heroin-using adults with a desire to enter a detoxification program were recruited over the period of July 2000 to October 2001 in Perth, Western Australia. The study was advertised through selected general practitioners, hospital emergency departments, psychologists, the Perth Needle Exchange Programme, community and private alcohol,

Table 1. Inclusion and exclusion criteria for the study
Inclusion criteria:
resident within the Perth metropolitan area
willing and able to provide written informed consent
current heroin user and dependent on heroin as defined by DSM-IV criteria
have a stated goal of abstinence from opiates
considered willing and able to participate in either of the randomly allocated detoxification procedures
completion of prestudy clinical screening to the satisfaction of the study investigators
Exclusion criteria:
previous enrollment in the study
current enrollment in any other research project relating to the treatment of opiate dependence
pregnancy or unable to complete the study protocol, e.g., four-week period due to, for example, pending incarceration
contraindications due to naltrexone, e.g., chronic hepatitis with associated liver damage or pain that requires narcotic treatment
history of adverse reactions to medication likely to be used in the study
suffering from medical conditions potentially exacerbated by opiates
suffering from a major psychiatric condition that would prevent giving informed consent
Subject study withdrawal criteria:
a subject could withdraw from the study at any time or for any reason without being obliged to divulge their reason for doing so to the investigators or clinic staff
noncooperation with clinic staff and/or noncompliance with study clinic regulations
unacceptable adverse events including distress due to effects of any study procedure or medication

drug, and other advisory services, the West Australian Alcohol and Drug Information Service, newspapers, television reports, and pharmacies.

All subjects were assessed for dependence using the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria. Potential subjects underwent screening to determine study eligibility (Table 1) and, upon initial contact, were given general information as to the nature of the study. Within 24 hours of initial contact during weekdays, all subjects were interviewed in person at the study center. Subjects were fully informed of the study and given the opportunity to ask questions and discuss their participation. Eligible subjects were randomly assigned to one of two detoxification treatment groups. One group was assigned to undergo ROD during day surgery at a private, community-based treatment facility. A second group was assigned to undergo CD as an inpatient or as an outpatient, as determined following clinical assessment at a community-based public facility. Subjects were also provided with a summary of the possible risks and discomforts of using naltrexone if randomized to ROD. All subjects were offered the chance to undergo oral naltrexone maintenance. Both treatments were cost-neutral to the participants.

Clinical assessment of whether the subject was considered suitable for the assigned treatment was determined by the clinician at the treatment service. No treatment arm considered a patient to be unsuitable for treatment. Persons who were interested in participating and fulfilled study inclusion criteria were required to provide informed consent in accordance with the University of Western Australia Human Ethics Research Committee guidelines.

Study participants

A total of 80 subjects entered the study. Of these, 41 were randomized to ROD and 39 were randomized to CD.

Detoxification regimens

Patients undergoing ROD received clonidine-naloxone precipitated withdrawal and were inducted onto oral naltrexone during day surgery. The exact treatment regimen depended on the length of time since last opioid use. Generally, patients were given premedication with subcutaneous octreotide (≈ 0.1 mg) for abdominal pain and intravenous (IV) ondansetron (≈ 2 mg) for nausea 30 to 45 minutes prior to commencement of detoxification and an IV line inserted into the peripheral vein of the arm. Depending on the level of opioid use in the days before treatment, an oral flunitrazepam also was administered immediately prior to detoxification. Then patients were administered IV naloxone (≈ 800 µg) over a period of five to eight minutes in titred IV doses interspersed with IV doses of clonidine hydrochloride (150 µg in 10 ml saline) and a sedative hypnotic (midazolam hydrochloride), depending on the level of arousal and discomfort experienced by the patient. When no significant withdrawal signs appeared, patients were allowed to rest for 20 to 30 minutes before oral doses of 4, 8, 15, and 23 mg naltrexone were gradually dispensed at 30-minute intervals.

Patients undergoing detoxification underwent CD over five to seven days (inpatient) or seven to 10 days (outpatient), as described by Palmer.[8] CD involved a two-step procedure. First, a medical assessment was conducted. Second, prescribed pharmaceuticals were dispensed from the clinic pharmacy for use on an outpatient basis at home over the seven- to 10-day withdrawal period. Patients were considered to have commenced CD only after accessing prescribed pharmaceuticals. Prescribed pharmaceuticals involved the use of 75 to 150 µg oral clonidine reviewed daily, daily dispensing of 10 to 20 mg temazepam, and additional medications (e.g., hyosine butylbromide, quinine bisulphate, and metaclopramide hydrochloride) at doses indicated for symptomatic relief.

The study did not provide or require any alteration to the standard detoxification procedures offered by the clinical services.

Study plan

The following data were collected:

Post-screening. Information on general drug use, medical (including treatment history), and general demographics were collected using the Opioid Treatment Index.[9,10]

Immediately prior to detoxification. Self-reports of withdrawal history, preference for withdrawal procedures, and expectations of treatment and physical withdrawal (Part 1, Severity of Dependence Questionnaire [SODQ])[11] and craving[12] were made.

Immediately post-detoxification. Self-reports of the duration of detoxification procedure and level of discomfort, together with physical withdrawal (Part 1, SODQ[11]) and craving[12] were made.

Four weekly follow-ups. Over a four-week post-detoxification follow-up period, subjects were contacted weekly either in person or by telephone to verify whether they were taking daily oral naltrexone or had used heroin.

Statistical analysis. Subjects were classified for analysis on whether detoxification treatment was completed. The categorization is more detailed in the results section (Table 2) but to summarize: Subjects were compared on whether detoxification was commenced and completed (i.e., detoxification completed) or not commenced or not completed (i.e., unsuccessful detoxification).

Generalized mixed liner models were used to test significance where repeated measures were made for the same group of study subjects (e.g., for comparing discrete time point measures within the same detoxification group when comparing before-and-after outcomes). Mann Whitney U-tests were used for comparisons between detoxification treatments. In all instances, significance was ascribed at the 5 percent level.

RESULTS

Study population

Eighty heroin users were assigned to either CD or ROD. There was no significant difference in the population randomized to the respective treatment services in relation to age, gender, socioeconomic status, or total length of heroin use.

General demographics

The general age range of the study population was 16 to 50 years, with the average (± SE) age of 30.6 ± 1.04 years. Sixty-four percent of the population was male, and 36 percent was female.

Ninety-nine percent of the population were nonaboriginal, and 82.5 percent were born in Australia. All received a secondary education to at least year 10, 49 percent received a tertiary education qualification, and 57.5 percent were known to be unemployed. Of those who were born in a country other than Australia, all had been residing in Australia for at least 14 years. Fifty-five percent of the population was classified in the high-medium disadvantage or lower category, as determined by their residential postcode from the Socio-Economic Indices for Areas 96 Disadvantage Index (Australian Bureau of Statistics).

There were no significant differences in the age, gender, place of birth, aboriginality, and levels of education and employment between the two treatment populations.

Heroin and other drug use

Only 6.2 percent of the study population reported using opioids other than heroin in addition to heroin.

Sixty-six percent of the study population had used heroin for more than five years, with 47 percent using heroin on a regular basis (i.e., daily) for more than five years. Nearly 57 percent of the study population had spent more than 75 percent of their total heroin use period as regular heroin users.

In the month prior to deciding to seek treatment, 95 percent (n = 76) of the study population used heroin daily or more than once a day.

In the month prior to seeking treatment, tobacco (91 percent), cannabis (64 percent), alcohol (51 percent), tranquilizers (45 percent), and amphetamines (26 percent) were the other most frequently used drugs reported among the study population. Cannabis was reported to have

Table 2. Status of study subjects by clinic				
Treatment	**Status**	**Percent frequency**	**Classification**	**Percent frequency**
ROD	Commenced and completed	87.8 (n = 36)	Successful completion	87.8 (n = 36)
	Attended clinic but did not commence detoxification	7.32 (n = 3)	Unsuccessful completion	10.53 (n = 5)
	Did not attend clinic at all	2.4 (n = 1)		
	Self-detoxified (prison)	2.4 (n = 1)		
	Total	100 (n = 41)		100 (n = 41)
CD	Commenced and completed	28.2 (n = 11)	Successful completion	28.2 (n = 11)
	Commenced but did not complete	23.1 (n = 9)	Unsuccessful completion	71.8 (n = 28)
	Crossover to ROD	5.1 (n = 2)		
	Self-detoxified	5.1 (n = 2)		
	Attended clinic but did not commence detoxification	33.3 (n = 13)		
	Did not attend clinic at all	11.0 (n = 2)		
	Total	100 (n = 39)		100 (n = 39)

ROD = Rapid opiate detoxification; CD = Clonidine-assisted detoxification; actual numbers of patients are shown in parentheses.

been used most frequently—more than once a day, while alcohol, tranquilizers, and amphetamines were reported to have been used most frequently—more than once a week. Only one person reported using cocaine, and three persons reported using hallucinogens once a week or less often. Of the 91 percent who reported tobacco use, the average (± SE) number of cigarettes smoked per day was 19 ± 4.

Previous treatments

Sixty-seven percent (n = 54) of the study population had previously undergone treatment for addiction (predominantly heroin addiction). Forty-nine percent (n = 39) of those who had previously undergone treatment had been in receipt of more than one type.

Incentive to be treated

During the pretreatment interview, 96 percent (n = 77) of the study population stated that it was their choice to enter treatment, while 4 percent (n = 3) stated it was suggested to them. All subjects stated that their reason for seeking treatment was to cease heroin use. Forty-four percent (n = 45) of the study population had reduced heroin intake prior to entering detoxification. Ninety-six percent (n = 77) of the population stated that they were considering entering naltrexone maintenance after detoxification, 2.5 percent (n = 2) stated that they did not want naltrexone maintenance, and one participant was unsure.

Treatment assessment

Number of subjects commencing treatment. Table 2 shows the classification used for the analyses based on the study subjects' detoxification status. Of the 41 subjects assigned to ROD, 88 percent (n = 36) commenced and completed treatment, while 46 percent (n = 18) of the 39 subjects assigned to CD commenced, but only 28.2 percent (n = 11) completed treatment. Of the 39 patients assigned to CD, 10 patients attended as inpatients. Of these 10 patients, three did not complete detoxification, and one crossed over to ROD. Of those who never started treatment, a higher proportion of those assigned to CD (33.3 percent, n = 13 vs. 7.32 percent, n = 3) attended the clinic but failed to commence detoxification. Two subjects commenced CD but did not complete and crossed over to ROD. For the purpose of assessing detoxification,

Table 3. Oral naltrexone and absence of heroin use in the four weeks post-detoxification

		Oral naltrexone compliance			Absence of heroin use
		Over entire four weeks	At some time in four weeks	Not at all over four weeks	
ROD	Of the 36 persons who commenced	56% (20)	86% (31)	14% (5)	39% (14)
	Of the 36 persons who completed	56% (20)	86% (31)	14% (5)	39% (14)
CD	Of the 20 who commenced	40% (8)	50% (10)	50% (10)	30% (6)
	Of the 11 who completed	73% (8)	90% (10)	9% (1)	55% (6)

ROD = Rapid opiate detoxification; CD = Clonidine-assisted detoxification; actual numbers of patients are shown in parentheses.

procedure assessment has been restricted to the 47 subjects who completed detoxification.

Assessment of detoxification. Of the 47 subjects who started and completed detoxification, information on detoxification assessment was collected from only 92 percent of those who underwent ROD and 82 percent of those who underwent CD. The remainder was lost to follow-up. Of those who were questioned, 22 percent (n = 2/9) of those who underwent CD felt the procedure was too long compared to 15 percent (n = 5/33) of those who underwent ROD. There was no significant difference in the proportion of subjects undergoing ROD (30 percent, n = 10/33) and those undergoing CD (22 percent, n = 2/9) who felt the degree of pain experienced was too great. Similarly, there was no significant difference between subjects' perception of pain duration associated with the two procedures (ROD: 21.9 percent, n = 7/32; CD: 22 percent, n = 2/9). Fifty-four percent (n = 18/33) and 78 percent (n = 7/9) of those questioned who were undergoing ROD and CD, respectively, stated that they would undergo the treatment again. Of those questioned following ROD, 81 percent (n = 26/32) stated that the presence of support in the form of a "salient other" had been helpful during detoxification.

Assessment of physical withdrawal. It should be noted that average (± SE) physical withdrawal scores, as measured by Part 1 of the SODQ[11] immediately before CD commenced, were not significantly different in those who completed detoxification compared to those who were unsuccessful in completing detoxification (3.4 ± 0.76 vs. 5 ± 1.97, respectively).

The change in physical withdrawal scores (± SE) before and after detoxification was not significantly different for ROD (13.09 ± 1.24, n = 35 before vs. 12.39 ± 1.16, n = 33 after) or CD (3.4 ± 0.76, n = 10 before vs. 5.63 ± 1.47, n = 8 after).

Assessment of craving. Craving levels before detoxification were the same for both groups whether assigned to ROD or CD. There was no significant difference in craving scores (± SE) before and after detoxification, regardless of whether it was through ROD (3.25 ± 0.23, n = 35 before vs. 2.71 ± 0.3, n = 33 after) or CD (3.23 ± 0.59, n = 35 before vs. 2.21 ± 0.46, n = 9 after). Neither was there any significant difference in craving levels after detoxification between the two groups. Craving was not different in those who commenced but did not complete CD, compared to those who commenced and completed detoxification.

Assessment of oral naltrexone maintenance and absence of heroin use four weeks post-detoxification. Results of assessment through self-report of oral naltrexone compliance and absence of heroin use are presented in Table 3.

DISCUSSION

Managed withdrawal can and should be assessed on three major criteria: first, the percentage of those seeking treatment compared to those who commence withdrawal; second, the percentage of those who commence treatment compared to those completing managed withdrawal; and third, the severity of withdrawal sequelae and

patient satisfaction associated with the procedure. It could also be argued that a fourth criterion should be post-withdrawal abstinence from heroin.

Of the 41 patients assigned to ROD, only five failed to complete compared with 28 of the 39 assigned to CD. This occurred despite the majority of patients stating that they wished to undertake opioid detoxification in order to enter oral naltrexone maintenance (96 percent) and/or to cease heroin use (100 percent), and that the risk of attrition was similar between treatments, as the majority of patients attended both treatments on an outpatient basis.

Clearly, some feature of ROD facilitated a significantly greater proportion of patients who attended for withdrawal assessment to undertake treatment, as only three of the 41 patients attended the clinic but failed to commence ROD compared with 13 of the 39 patients randomized to CD. One likely possibility is the nature of ROD, which involved the prompt administration of an opioid antagonist as a medically supervised nonambulatory day procedure and provided little avenue for treatment avoidance. In contrast, patients undergoing CD were expected to self-supervise detoxification over a seven- to 10-day period through pharmacy-dispensed medications. It is also possible that despite subjects' initial agreement to be randomized to either ROD or CD, many patients had an undisclosed preference for ROD, which influenced their motivation to collect medications and ultimately commence conventional withdrawal.

ROD was also associated with a higher rate of detoxification completion than CD (89 percent commenced and completed ROD vs. 30 percent completing CD). This outcome is not surprising since ROD was initiated and completed as a medically supervised nonambulatory day procedure, while CD was completed over a seven- to 10-day period, largely on an outpatient basis. However, even three of the 10 CD patients managed as inpatients failed to complete their inpatient withdrawal regimen. Similar proportions have been reported previously for those completing CD[13] or ROD under sedation and receiving their first dose of naltrexone.[14] The above finding shows, as it has in previous studies,[1] that accelerating the process of detoxification, while sedating/anesthetizing the patient to minimize discomfort, overcomes some of the problems of patient adherence to treatment. In fact, studies have shown that rapid withdrawal proves successful in instances where protracted withdrawal has been unsuccessful[15] and may even increase the uptake of abstinence-based maintenance programs.[16]

The current study's findings suggest that there was no more of an increase in patient discomfort before and after treatment due to withdrawal symptoms associated with ROD than there was with CD. Current study results are contrary to previous reports in which patients undergoing ROD under sedation[4,5,17] or anesthesia[18] reported increased levels of discomfort compared to more conventional withdrawal methods.

The difference between our results and those of other published ROD procedures more than likely lies in the amount and duration of action of the opioid antagonist used. In studies that report significant withdrawal sequelae over ROD, the use of repeated 1.2 mg naloxone IV every 30 minutes until no or little withdrawal sequelae were observed[5] or the single administration of 50 mg oral naltrexone[4,17] would have caused chronic high-level antagonism to opioids and accounted for the reported symptoms. This contrasts dramatically with the current protocol in which naloxone was used in titred doses, with recuperation times between doses, before small, but increasing doses of oral naltrexone were administered over 120 minutes. Given that naloxone has a half-life of one hour[19] and is metabolized rapidly on its first passage through the liver so it retains only one-fiftieth of its potency,[20] it is likely that this low-dose naloxone delivery produced significant withdrawal for only minutes. This low-level precipitation of withdrawal, alleviation of withdrawal symptoms with clonidine and sedative hypnotics, and recuperation time prior to the administration of the competitive antagonist naltrexone in a low oral dose may be an important component in the current study, providing a safe and relatively comfortable ROD. In fact, Gerra et al.[21] provided support for this in a comparison of patients detoxified with clonidine over five days, with patients undergoing ROD over two days. It was reported that there were fewer withdrawal symptoms, cravings, and mood problems in the ROD group than in the clonidine-only group.

The authors suggest that ROD is more effective than CD on a number of grounds. First, the majority of patients randomized to ROD were successfully withdrawn, while only the highly self-motivated few completed CD. It is evidenced in the high dropout rate between commencement and completion of CD. Second, ROD is a better method of inducting patients onto naltrexone maintenance, in that a higher proportion of patients who undertook ROD entered oral naltrexone immediately and sometime over a four-week post-withdrawal follow-up period, than those who undertook CD. However, this disparity in uptake was not translated into compliance with oral naltrexone or a reduction in relapse to heroin use over the four-week follow-up. This suggests that while ROD has the ability to induct persons onto oral naltrexone, there still remains a deficit in the ability to maintain oral naltrexone compliance. The shorter periods of detoxification associated with ROD would infer that should a relapse to dependent opioid use occur, ROD may provide the ability to quickly and effectively again withdraw patients with minimal loss during the withdrawal process. Given that heroin dependence is a chronic relapsing condition, this feature of ROD to opportunistically take a

relapse-dependent patient at the commencement of the day and successfully withdrawn him or her by the evening should not be overlooked.

We have already suggested that given the longer duration of CD, completion of this procedure probably was achieved by only a highly motivated few. Given the transient nature of motivation, it is therefore not unreasonable that these latter few would be more compliant, even though all participants said it was their desire to enter naltrexone maintenance. The authors argue that rather than reflecting a deficit in ROD, which clearly has the ability to induct persons onto naltrexone maintenance, more needs to be done to improve methods of naltrexone delivery to increase compliance.

CONCLUSION

In conclusion, this study dispels some of the commonly held views within the heroin treatment arena. The disparity in results between the current and previous ROD studies raises questions about the use of large doses of opioid antagonist during ROD and whether this practice should be avoided. Clearly, further studies that directly compare the two approaches are required. The study shows that ROD is more effective in detoxifying a greater number of clients than CD, and, more importantly, 96 percent of all randomized subjects indicated that they wished to withdraw in order to enter naltrexone maintenance. As the ROD detoxification procedure included induction of oral naltrexone, it follows that in terms of naltrexone maintenance uptake, this ROD procedure is more likely to show greater success than CD. Comparison of our results with other studies also suggests that not all ROD procedures produce equitable results, and that a best practice for ROD needs to be established.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Dr. Sean Murray and Ms. Eveline Durkin with data collection and the willing helpfulness of medical, nursing, and ancillary staff at the treatment clinics. This research was supported by funds from the Department of Health (Western Australia) and was carried out with approval from the University of Western Australia Human Research Ethics Committee.

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12565 12/27/04 Rev A

ORIGINAL ARTICLE

Morphine prescription to terminally ill patients with lung cancer and dyspnea: French physicians' attitudes

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ABSTRACT

This study aimed to investigate factors associated with analgesic use of morphine in end-of-life care. French general practitioners (GPs) and oncologists (N = 719) were asked whether they would prescribe morphine as first-line therapy to patients with terminal lung cancer suffering from dyspnea associated with cough and great anxiety. Overall, 54 percent of oncologists and 40 percent of GPs stated that they would prescribe morphine in the presented case. This prescriptive attitude correlated with physicians' age, professional background, communication skills, and attitude toward terminally ill patients. The findings of this study indicate that improving analgesic use of opioids in end-of-life care is not only a matter of enhancing technical skills acquired through training or experience but also a matter of improving communication and empathy between physicians and patients.

Key words: morphine, dyspnea, end-of-life care, lung cancer, France

INTRODUCTION

Dyspnea, or breathlessness, defined as a subjective sensation of difficult or uncomfortable breathing, is a common symptom among patients with terminal lung cancer.[1-4] It can result from both the progression of disease and aggressive treatments such as radiotherapy and chemotherapy.[5-7] Dyspnea and the sensation of smothering may cause terrible suffering in patients with advanced lung disease, and it is perceived as one of the most devastating symptoms by patients and their families.[8] Previous studies have found that dyspnea was associated with a sharp decrease in quality of life and will to live—i.e., many patients would rather die than suffer from dyspnea.[9,10]

Strong opioid analgesics, especially morphine, have been proved both safe and efficient as a first-line therapy for managing dyspnea in advanced disease in general, and terminal cancer in particular.[11-15] Nevertheless, dyspnea is usually poorly managed, first because of inadequate assessment and secondly because healthcare providers are frequently reluctant to use opioids to treat dyspnea, as they are concerned about the risk of respiratory depression, especially in patients with advanced lung disease.[2,15,16]

In this study, we investigated personal, professional, and attitudinal factors associated with the first-line prescription of morphine to terminal lung cancer patients suffering from dyspnea among a representative sample of French general practitioners (GPs) and oncologists. We analyzed data from the first French national survey on physicians' knowledge, attitudes, beliefs, and practices toward palliative care, conducted in 2002 by the Regional Centre for Disease Control of South-Eastern France and the National Institute for Health and Medical Research, Unit 379.

METHODS

Sampling and data collection

The survey was carried out among a random sample of French GPs and oncologists. The latter specialists are more likely than GPs to be involved in end-of-life care for patients with lung cancer. Because the corresponding populations differ greatly in size (about 68,000 GPs and 700 oncologists in France), we built a stratified sample with a sufficient number of specialists from the complete French physicians database of the European society CEGEDIM™. Eligible respondents were randomly selected at the following sampling rates: three of every 200 GPs and two of every five oncologists. Only specialties that

Table 1. Factors associated with morphine prescription for a terminally ill patient with lung cancer and dyspnea, univariate analysis (French national survey on physicians' knowledge, attitudes, beliefs, and practices towards palliative care [n = 719, 2002])					
Would you prescribe morphine first line to a terminally ill patient with lung cancer, suffering from dyspnea associated with cough and great anxiety?		**Yes (1) n = 320 (%)**	**No (2) n = 399 (%)**	**1 vs. 2**	
				Univariate OR [CI 95%]	**p**
Personal characteristics					
Gender	female (n = 247)	107 (33.4)	140 (35.0)	1	> 0.05
	male (n = 472)	213 (66.6)	259 (65.0)	1.1 [0.8 – 1.5]	
Age	< 45 (n = 355)	148 (46.3)	207 (51.9)	1	> 0.05
	≥ 45 (n = 364)	172 (53.7)	192 (48.1)	1.2 [0.9 – 1.7]	
Professional characteristics					
Medical specialty	GPs (n = 502)	202 (63.1)	300 (75.2)	1	< 0.001
	oncologist (n = 217)	118 (36.9)	99 (24.8)	1.8 [1.3 – 2.5]	
Number of patients followed up to death during the prior 12 months	≤ 12 (n = 525)	186 (58.1)	275 (68.9)	1	< 0.01
	>12 (n = 194)	134 (41.9)	124 (31.1)	1.6 [1.2 – 2.2]	
University degree in palliative care or pain management	No (n = 635)	270 (84.4)	365 (91.5)	1	< 0.01
	Yes (n = 84)	50 (15.6)	34 (8.5)	2.0 [1.2 – 3.2]	
Strictly private practice	No (n = 372)	194 (60.6)	178 (44.6)	1	< 0.001
	Yes (n = 347)	126 (39.4)	221 (55.4)	0.5 [0.4 – 0.7]	
Member of a team specializing in pain management	No (n = 640)	273 (85.3)	367 (92.0)	1	< 0.01
	Yes (n = 79)	47 (14.7)	32 (8.0)	2.0 [1.2 – 3.2]	
Systematic disclosure of information to competent dying patients					
Diagnosis	No (n = 637)	272 (85.0)	365 (91.5)	1	< 0.01
	Yes (n = 82)	48 (15.0)	34 (8.5)	1.9 [1.2 – 3.0]	
Prognosis	No (n = 685)	300 (93.8)	385 (96.5)	1	> 0.05
	Yes (n = 34)	20 (6.3)	14 (3.5)	1.9 [0.9 – 3.7]	
Therapeutic objectives	No (n = 289)	112 (35.0)	177 (44.4)	1	< 0.05
	Yes (n = 430)	208 (65.0)	222 (55.6)	1.5 [1.1 – 2.0]	
Attitude toward dying patients					
Feeling comfortable with dying patients	No (n = 358)	142 (44.4)	216 (54.1)	1	< 0.05
	Yes (n = 361)	178 (55.6)	183 (45.9)	1.5 [1.1 – 2.0]	
Opinions towards morphine use					
Prescribing high-dose morphine to a dying patient is euthanasia	No (n = 620)	287 (89.7)	333 (83.5)	1	< 0.05
	Yes (n = 99)	33 (10.3)	66 (16.5)	0.6 [0.4 – 0.9]	

would probably be in contact with terminal lung cancer patients with dyspnea were selected for analysis, so we did not select neurologists who were also involved in the national survey.

This random selection resulted in a sample of addresses corresponding to 1,120 GPs and 295 oncologists. These physicians received a letter through the mail that introduced the survey and promised anonymity. The telephone survey (using the Computer Assisted Telephone Interview system) began three weeks later and lasted from February 12 to March 13, 2002. Physicians were contacted Monday through Friday between 8:00 AM and 8:00 PM. Investigators proposed a later appointment if physicians were not free to respond at once.

Questionnaire and statistical analysis

An expert group that included GPs and specialists developed the questionnaire. Early versions of this questionnaire were tested in two pilot surveys. The final version included 202 closed-ended questions, but the present study only used a subset of them. The questionnaire included a clinical case describing a terminally ill patient with lung cancer suffering from dyspnea associated with cough and great anxiety. Respondents were asked whether they would prescribe morphine as a first-line therapy to such a patient.

Other questions assessed personal characteristics (e.g., age, gender, etc.), professional background (e.g., medical specialty, university degree in palliative care or pain management, experience in end-of-life care during the prior 12 months, part of a team specializing in pain management, practicing in only a private setting), attitudes toward terminally ill patients (e.g., systematic disclosure of diagnosis, prognosis, or therapeutic objectives to competent terminally ill patients; feeling comfortable with dying patients), and opinions regarding morphine use in end-of-life care (e.g., whether prescribing high-dose morphine to a dying patient should be considered euthanasia). See the appendix for the exact wording of the questions addressing attitudes.

We computed successively univariate and multivariate logistic regressions to investigate which personal, professional, and attitudinal factors were significantly associated with morphine first-line prescription in the case described above. The multivariate model was performed with a stepwise selection method (entry threshold: $p < 0.05$).

RESULTS

Data collected

In total, 19 of the 1,415 letters sent to GPs and oncologists were returned—these particular physicians had retired or moved to an unknown address. The remaining 1,415 physicians were contacted successfully, of which 719 agreed to participate. The response rate was higher for oncologists (74 percent) than for GPs (45 percent). Physicians most frequently cited lack of time as their reason for refusal. Nonrespondents did not differ from respondents in terms of gender, age, and town size. Completed interviews lasted a half-hour on average.

Factors associated with prescription of morphine

In our sample, 54.4 percent of oncologists (118 out of 217) and 40.2 percent of GPs (202 out of 502) stated that they would prescribe morphine as a first-line therapy to a terminally ill patient with lung cancer suffering from dyspnea (Table 1). In univariate analysis, gender and age were not correlated to prescriptive attitude toward morphine. Professional characteristics were far more predictive of willingness to prescribe morphine. For example, oncologists and physicians with more experience in end-of-life care during the prior 12 months were more likely to endorse such a prescription, as were physicians trained in palliative care or pain management and those working in a specialized team. By contrast, this prescriptive attitude was significantly less prevalent among physicians who practiced only in a private setting. With regard to communication and attitude toward terminally ill patients, physicians who reported systematic disclosure of diagnosis and therapeutic objectives to competent patients and those who felt comfortable with dying patients were more prone to prescribe morphine in the proposed short clinical case. Lastly, physicians who considered prescribing high-dose morphine to a dying patient as euthanasia were less likely to uphold morphine prescription.

In multivariate analysis, five different factors remained statistically significant (Table 2). Older physicians and those with a university degree in palliative care or pain management were more likely to uphold morphine prescription, while those with a strictly private practice were less likely to do so. Concerning attitudinal factors in end-of-life care, physicians who reported systematic disclosure of diagnosis and those who felt comfortable with terminally ill patients were more prone to endorse prescription of morphine to a dying patient with lung cancer and dyspnea.

DISCUSSION

Before discussing our results, we must acknowledge several limitations of the present study. First, we lack information about nonrespondents, even if they were not different from respondents according to the few characteristics that could be controlled from the initial file (age, gender, and size of town). Secondly, a closed-ended questionnaire prevents physicians from qualifying or justifying

Table 2. Factors associated with morphine prescription for a terminally ill patient with lung cancer and dyspnea, stepwise logistic regression (French national survey on physicians' knowledge, attitudes, beliefs, and practices towards palliative care [N = 719, 2002])

Would you prescribe morphine in first line to a terminally ill patient with lung cancer, suffering from dyspnea associated with cough and great anxiety?		**1 vs. 2 multivariate OR [CI 95%]**
Personal characteristics		
Age	< 45 (n = 355)	1
	≥ 45 (n = 364)	1.3 [1.0 – 1.7]
Professional characteristics		
University degree in palliative care or pain management	No (n = 635)	1
	Yes (n = 84)	1.6 [1.1 – 2.4]
Strictly private practice	No (n = 372)	1
	Yes (n = 347)	0.5 [0.4 – 0.7]
Systematic disclosure of information to competent dying patients		
Diagnosis	No (n = 637)	1
	Yes (n = 82)	1.9 [1.2 – 2.9]
Attitude toward dying patients		
Feeling comfortable with dying patients	No (n = 358)	1
	Yes (n = 361)	1.4 [1.1 – 1.9]

their responses, so we don't know respondents' motives to oppose morphine prescription in the proposed case. Thirdly, we investigated prescriptive attitudes with a short clinical case, not real practices. Nevertheless, in a previous analysis conducted with the same data set and dealing with doctor-patient communication in end-of-life care, we found that physicians' practices were quite consistent with their reported attitudes.[17] Lastly, our study used only one short clinical case with an undifferentiated patient, so we did not address another key issue in inadequate pain management—reluctance toward the analgesic use of morphine may also vary according to the sociodemographic characteristics of patients (especially age and gender).[18]

This case described a terminally ill patient with lung cancer suffering from dyspnea, cough, and great anxiety. Cough and anxiety have been added to dyspnea because they are other common symptoms observed among patients with terminal lung cancer, and because dyspnea may cause anxiety and, reciprocally, anxiety may worsen dyspnea.[2,15,19-21] Moreover, opioids are

effective cough suppressants and anxiety reducers, so in this clinical case morphine could be considered a very appropriate treatment.[22,23] Nevertheless, only half of oncologists and four GPs out of 10 reported that they would prescribe morphine as a first-line treatment for such a case.

Previous studies already have highlighted the persistent reluctance to prescribe morphine among French physicians, especially among GPs, despite significant improvements in physicians' attitudes regarding pain management.[24,25] Many physicians are still unwilling to prescribe opioids because they are worried about potential addiction and other adverse effects, or because they anticipate patients' refusal due to similar fears.[26] More specifically, the pharmacological management of dyspnea may be hampered by lack of knowledge of the effectiveness of opioids for dyspnea relief, lack of clinical experience using opioids to treat dyspnea, and persistent myths about opioids' effects in respiratory disease.[2,15,16]

Our results are consistent with such a diagnosis: Specialized training in palliative care or pain management is a good indicator of knowledge of the analgesic use of opioids, while younger physicians and those who practiced only in private settings probably were less experienced in treating dyspnea with opioids. (The "age effect" was not significant in univariate analysis because younger physicians were more likely to be trained in palliative care or pain management. Therefore, the "age effect" only appeared once controlled for the "training effect.")

With regard to attitudinal factors, once controlled for other variables, considering high-dose morphine prescription to terminally ill patients as euthanasia was not significantly associated with the propensity to prescribe morphine. A previous analysis of the same data set showed that both attitudes were shaped by professional background.[27] However, we also found that the propensity to prescribe morphine for treating dyspnea in terminal lung cancer was positively correlated with systematic communication of diagnosis to competent patients and feeling comfortable with terminally ill patients. The findings of this study indicate that improving analgesic use of opioids in end-of-life care is not only a matter of enhancing technical skills acquired through training or experience but also a matter of improving communication and empathy between physicians and patients.

ACKNOWLEDGMENTS

This study was supported by a grant for improving ambulatory care from the Departmental Center of Private Health, by the Assistance Publique-Hôpitaux de Marseille (within the hospital program for clinical research), and by the Cancer Research Foundation. We also thank Brigitte Planchet-Barraud, MD; Olivier Priolo, MD; Frédéric RaVallec, MD; Helène Granier, MD; and Michel Rotily, PhD.

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APPENDIX. EXACT WORDING OF QUESTIONS ADDRESSING FRENCH PHYSICIANS' ATTITUDES

Some people say that prescribing high-dose morphine to a dying patient should be considered euthanasia. Do you:

- strongly agree;
- agree;
- neither agree nor disagree;
- disagree; or
- strongly disagree.

(strongly agree and agree were encoded as "yes," other items were encoded as "no")

When providing care for terminally ill patients, do you feel:

- very comfortable;
- comfortable;
- neither comfortable nor uncomfortable;
- uncomfortable; or
- very uncomfortable.

(very comfortable and comfortable were encoded as "yes," other items were encoded as "no")

Do you communicate the prognosis (*resp.* diagnosis, therapeutic objectives) to competent terminally ill patients?

- yes, systematically even if the patient doesn't explicitly ask for;
- yes, if necessary, even if the patient doesn't explicitly ask for;
- yes, if necessary, and if the patient explicitly asks for;
- yes, systematically, but only if the patient explicitly asks for; or
- no, never.

("systematic disclosure" corresponded only to "yes, systematically, even if the patient doesn't explicitly ask for")

ORIGINAL ARTICLE

A randomized trial of one-day vs. three-day buprenorphine inpatient detoxification protocols for heroin dependence

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ABSTRACT

Detoxification from opioids remains an important first step in the treatment of many patients with opioid dependence. Several pharmacologic regimens have been used for opioid detoxification. In the United States, the partial μ-opioid agonist, buprenorphine (BUP) is the most recently approved pharmacotherapy for opioid detoxification and replacement. The literature in recent years has described detoxification protocols using a single high dose of BUP and a three-day BUP regimen. In many settings, such as drug-free programs, a single-dose detoxification protocol would be of significant benefit. There have been no prior studies comparing one-day and three-day BUP-assisted opioid withdrawal.

In this pilot study, we conducted an open-label, randomized trial of one-day vs. three-day BUP/naloxone sublingual tablet-assisted opioid withdrawal. Twenty patients from a therapeutic community treatment program were randomly assigned to receive either 32 mg sublingual BUP over one hour (one-day group), or 32 mg sublingual BUP over three days (three-day group). Nine of 10 subjects (90 percent) in each group completed seven days in the detoxification protocol. There was no statistically significant difference between the two groups in all other outcome variables, including retention in the treatment program, intensity of withdrawal signs and symptoms, amounts of adjunct medications used, and ability to produce opiate-free urine. This study further validates the feasibility of the single high dose of BUP as a rapid detoxification method.

Key words: buprenorphine, detoxification, withdrawal, opioid, heroin

INTRODUCTION

Heroin addiction continues to be a serious problem in the United States. The 2002 National Survey on Drug Use and Health (NSDUH) reports that since the mid-1990s, the prevalence of lifetime heroin use has increased in both youths and young adults.[1] Furthermore, in the past year, 3.7 million Americans reported using heroin at least once in their lives.[1] Detoxification, or "medically supervised withdrawal," is one component of a comprehensive program to treat opioid addiction. Several pharmacological modalities have been used for such a purpose, with buprenorphine (BUP) being the latest agent approved in the United States. BUP is a partial μ-opioid agonist and κ-antagonist. Its unique properties offer several advantages over other detoxification agents, including milder withdrawal symptoms at cessation, lower risk of overdose, and a longer duration of action.[2]

Several studies have reported the effectiveness of a three-day detoxification schedule using a liquid formulation of BUP given sublingually. One study compared the efficacy of a three-day regimen of sublingual (SL) BUP to a five-day course of clonidine for acute detoxification from opioids. BUP was found to be more effective in early relief of withdrawal symptoms.[3] O'Connor[4] compared three methods of opioid detoxification: clonidine, combined clonidine and naltrexone, and BUP given for three days followed by naltrexone. This study demonstrated that the BUP group reported significantly lower mean overall withdrawal symptom scores than the other two groups. Although the detoxification completion and program retention rates among the three groups did not achieve statistical significance, there was a trend toward better retention in the BUP-treated group.[4] Another study conducted by DiPaula[5] using a three-day BUP detoxification regimen again showed high retention in treatment, decreases in withdrawal score, lack of reported adverse events, and a high degree of patient satisfaction. A three-day ambulatory detoxification regimen using intramuscular or tablet BUP formulations with six-month follow-up was described by Gandhi, et al.[6] Almost all patients completed the three-day detoxification regimen, but there was no follow-up between day three and one month after detoxification.[6]

As an alternative to the three-day regimen, a single, high-dose BUP detoxification protocol has also been described in the literature. In Israel, Kutz and Reznik[7,8] tested this regimen in two studies with a total of 30 heroin addicts who were given one dose of a liquid formulation of 32 mg SL BUP. All but one subject completed the seven-day trials with negligible withdrawal symptoms and a smooth transition to naltrexone.[7,8] Recently, Assadi[9] in Iran designed a study comparing patients who received 12 mg BUP intramuscularly over 24 hours to those who received 10.5 mg BUP intramuscularly over five days. The two groups did not significantly differ on treatment retention, successful detoxification, overall symptoms of opioid withdrawal, craving, or drug-induced side effects.[9]

Abstinence-oriented treatment programs, such as those in the therapeutic community, provide an ideal setting for the use of short opiate detoxification programs. Successful withdrawal treatments will allow rapid engagement in counseling and therapy. Although both one-day and three-day BUP-assisted opiate withdrawal protocols have been developed, prior studies have not compared the two methods. In addition, previous studies have used liquid formulations of BUP, rather than the newer, commercially available tablet formulation. Our pilot study compared subjects who received 32 mg SL BUP on the first day of treatment to those who received 32 mg BUP over three days. We speculated that the two groups would exhibit similar treatment retention rates and comparable severity of withdrawal symptoms.

METHODS

Site of study

The study took place at a residential substance abuse treatment program in Detroit, Michigan. Self-Help Addiction Recovery Inc. (SHAR) is a therapeutic community for men and women seeking substance abuse treatment.

Participants

Subjects were eligible for the study if they were enrolled in the SHAR residential treatment program, met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for opiate dependence, were able to provide informed consent, and were 18 years of age or older. Exclusion criteria included pregnant or lactating women, known allergy to BUP, and use of BUP in the last 30 days. Participants had been determined to be medically and psychiatrically stable by the program physician at SHAR.

Detoxification protocols

The BUP formulation used was the combined BUP HCl (8 mg)/naloxone HCl (2mg) SL tablet (Suboxone®, Reckitt Benckiser Healthcare, Berkshire, UK). A total of 20 patients were randomly assigned in an open-label fashion to one of the treatment protocols, with 10 patients in each group. On day one, the one-day group received a total of 32 mg of BUP (8 mg initially, and 24 mg 30 minutes later, if patient tolerated 8 mg); patients did not receive any more BUP thereafter. The three-day group received a total of 32 mg of BUP over three days: 8 mg on day one, 16 mg on day two, and 8 mg on day three. The following adjunct medications were available to all participants on an as-needed basis: clonidine for sympathetically mediated withdrawal symptoms; ibuprofen and/or acetaminophen for bone pain, arthralgia, and headache; trimethobenzamide for nausea; loperamide for diarrhea; and diphenhydramine HCl or trazadone HCl for insomnia. Adjunct medications were given at the discretion of the medical staff of SHAR; SHAR staff members were not aware of the subject's group assignment. Total duration of the study was 17 days. Screening and baseline assessments were performed on day one, detoxification and monitoring took place over the next seven days, and follow-up evaluations were conducted on days 14 through 17.

Assessments

At baseline, all subjects were assessed for drug dependence using DSM-IV criteria. During the detoxification and monitoring period, all participants were assessed each morning for withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS). SHAR medical staff also documented vital signs, ancillary medications, and adverse events. Urine drug screens (UDSs) were collected on day one, day three or four, day six or seven, and one last time during follow-up evaluation (days 14 through 17).

Method of study conduct

The Human Investigation Committee of Wayne State University approved the study. Written informed consent was obtained from all patients who participated in the study. A test of individual understanding of the procedures was also given prior to enrollment. Participation in the study was voluntary, confidential, and anonymous.

Outcomes

The primary outcome of this study was the number of treatment responders in each group. A treatment responder was defined as a participant who completed the detoxification protocol and remained in the treatment program at the end of seven days. The secondary outcomes were treatment retention at the end of 14 days,

Table 1. Demographics			
	One-Day Group (n = 10)	**Three-Day Group (n = 10)**	**p**
Age (years)	46.5 ± 7.38	47.6 ± 6.08	0.720*
Male (%)	80	50	0.160**
African-American (%)	90	80	0.589**
Married (%)	20	10	0.408**
Employed in the past 30 days (%)	20	20	0.494**
Education (%) (1 to 12 years/some college)	80/20	60/40	0.427**
Route of heroin use (%) (nasal/injection)	60/40	70/30	0.639**
Average amount of heroin used per day (in dollars)	48.25 ± 29.58	60.5 ± 28.42	0.358*
* p value by t-test; ** p value by χ-square.			

intensity of withdrawal signs and symptoms, amounts of ancillary medications necessary to control them, and ability to produce opiate-free urine on day six or seven.

Statistical analysis methods

All analyses were performed using SPSS for Macintosh (Version 11.0) computer statistical package (SPSS, Inc., Chicago, IL). Univariate comparisons between groups were made using independent *t* test for continuous measures and χ-square analysis for categorical variables. Two-tailed probabilities were used for all *t* tests.

RESULTS

Subject characteristics

Twenty eligible SHAR residential treatment program participants enrolled in the study, 10 of which were assigned to each detoxification protocol. The features of the two groups were comparable with no statistically significant differences in demographic or heroin use characteristics (Table 1). At baseline, six subjects in each group met DSM-IV criteria for cocaine dependence. There were no individuals who met criteria for BUP dependence. One subject in the one-day group was alcohol-dependent by DSM-IV criteria, without physiologic dependence.

Treatment responders and treatment retention

All 20 participants received all of the scheduled doses of BUP during the first three days of the protocol. Eighteen of 20 subjects completed seven days in the detoxification protocol. One subject in the one-day group left the program on day five, and one subject in the three-day group left the program on day three. Fourteen-day retention was 70 percent (n = 7) for subjects in the One-Day Group and 50 percent (n = 5) for those in the Three-Day Group, without statistically significant difference (χ-square; p = 0.361).

Severity of withdrawal symptoms

Both groups reported moderate withdrawal symptoms on day one and mild symptoms on days two through seven. Throughout the study, there was no statistically significant difference between groups on the total daily COWS score. The mean total COWS score at baseline for the one-day group was 13.20 ± 3.615, and the mean score for the three-day group was 14.20 ± 2.658 (p = 0.533). The day after the first administration of BUP, the mean total COWS scores for the one-day and three-day groups were 2.50 ± 2.224 and 3.00 ± 2.160, respectively (p = 0.616). COWS scores remained at or below this level for the remainder of the study.

Ancillary medications usage

The two groups required similar amounts of adjunct medications to control their withdrawal symptoms (Table 2). No correlation was detected between the amounts of ancillary medications and daily mean COWS scores.

Table 2. Adjunct medication usage on days 1 through 7				
	Clonidine or clonidine plus other adjunct medications Number of subjects (%)	**No clonidine Number of subjects (%)**	**No adjunct medications given Number of subjects (%)**	**p**
Day 1				
One-Day Group (n = 10)	0	0	10 (100)	0.329*
Three-Day Group (n =10)	1 (10)	1 (10)	8 (80)	
Day 2				
One-Day Group (n = 9)**	7 (77.8)	1 (11.1)	1 (11.1)	0.445*
Three-Day Group (n = 10)	5 (50)	3 (30)	2 (20)	
Day 3				
One-Day Group (n = 9)**	7 (77.8)	0	2 (22.2)	0.319*
Three-Day Group (n = 10)	7 (70)	2 (20)	1 (10)	
Day 4				
One-Day Group (n = 9)**	7 (77.8)	0	2 (22.2)	0.300*
Three-Day Group (n = 9)	6 (66.7)	2 (22.2)	1 (11.1)	
Day 5				
One-Day Group (n = 9)**	6 (66.7)	2 (22.2)	1 (11.1)	0.319*
Three-Day Group (n = 9)	8 (88.9)	0	1 (11.1)	
Day 6				
One-Day Group (n = 8)**	4 (50)	3 (37.5)	1 (12.5)	0.755*
Three-Day Group (n = 9)	3 (33.3)	4 (44.4)	2 (22.2)	
Day 7				
One-Day Group (n = 8)**	3 (37.5)	5 (62.5)	0	0.138*
Three-Day Group (n = 9)	1 (11.1)	5 (55.6)	3 (33.3)	
* p value by χ-square; ** missing data for one subject.				

Almost all subjects received some ancillary medications each day, but the types of medication used in each group were similar. The majority of subjects received clonidine on study days two through five. By day seven, only four of 17 remaining subjects received clonidine.

Abstinence from opiates measured by UDS

All participants had opiate-positive urine specimens at the beginning of the study. Only one subject who was in the one-day group remained opiate-positive during a repeat UDS at day six/seven. At baseline, 80 percent (n = 8) of the one-day group and 70 percent (n = 7) of the three-day group subjects were cocaine-positive on UDS. At day six/seven, one subject remained cocaine-positive on UDS.

DISCUSSION

This is the first study to compare one- and three-day sublingual BUP-assisted opioid withdrawal protocols. Our results confirmed the original hypothesis that high-dose BUP given only on the first day of detoxification would not differ significantly from the three-day regimen on all outcome variables. It is also consistent with study results by Kutz and Reznik[7,8] and Assadi,[9] who demonstrated that a single high-dose BUP was an effective detoxification method. This study conducted urine drug testing during the protocol, which has not been done in many prior detoxification studies.

This study uses commercially available BUP tablets for both detoxification regimens. Previous studies of one- and three-day detoxification regimens have used liquid

formulations for either injection or SL administration. Liquid formulations of BUP have been shown to result in higher plasma levels of drug when compared to equivalent tablet doses, particularly at the 8 mg dose.[10] This study is the first to demonstrate the effectiveness of the tablet formulations of BUP in both three- and one-day detoxification protocols.

The results of this study may be largely dependent on subject characteristics and the supportive environment of the therapeutic community. The inpatient treatment setting may be critical in helping subjects remain engaged in treatment. Although both studies by Kutz and Reznick[7,8] took place with outpatients, this population in Israel seems to have been a highly selected subject group. All of our subjects were heroin-dependent and using similar amounts of drug. Persons with a high level of physiologic dependence and those using long-acting opiates may not respond as well to the single-dose detoxification. Similarly, patients with chronic pain who are maintained on opioids and need detoxification treatment might not respond well to single-dose therapy.

The limitations of this study include the small sample size, lack of control group, and the open-label design. A much larger group of participants may be necessary to detect a significant difference between the two protocols. A control group would be difficult to implement in a study of treatment-seeking individuals. Although a double-blinded study is more desirable, we do not anticipate results from such a design would differ greatly from ours.

The high treatment retention rate at seven days and high dropout rate at 14 days were expected. BUP-assisted opioid detoxification led to much greater initial program retention in the therapeutic community than did historical controls. The overall 14-day retention rate of 60 percent was viewed as a positive improvement at the therapeutic community. At least four patients who left before 14 days had enrolled near the end of the protocol recruitment period and admitted that they sought treatment with the intent of leaving after detoxification.

This study shows similar levels of ancillary medication use by both groups of subjects over the duration of the study. Both groups showed reductions in the use of clonidine, as well as other supportive medications, over the course of the detoxification period. In contrast with some other detoxification regimens,[4,9] benzodiazepines were not needed for this population. In the setting of the therapeutic community, many patients will request supplementary medications during the open dispensary hours. It is not clear whether subjects "required" supplementary medications or if it was simply requested due to availability. The very low COWS scores for all subjects suggest that medication was taken due to availability. Further work in controlled settings is warranted.

In conclusion, one- and three-day BUP detoxification protocols can be equally effective in managing opioid withdrawal in an inpatient setting. The effectiveness and simplicity of the one-day regimen demonstrates that this is a feasible method for opioid detoxification. Further study with a larger number of subjects is warranted.

ACKNOWLEDGMENTS

Funding for this study was provided by a grant from the State of Michigan (Joe Young, Sr.). Funding for Dr. Pierre was provided by a grant from the National Institute of Drug Abuse (DA013710). The authors are responsible for all elements of this research. There are no conflicts of interest to report in the development or completion of this project.

The authors would like to acknowledge the assistance of Gregory Washington, MD, and Charles R. Schuster, PhD, in the development of this study.

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ORIGINAL ARTICLE

Oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients: An overview of its pharmacological and clinical characteristics

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ABSTRACT

Breakthrough pain is a transitory flare of pain occurring in most cancer patients against a background of otherwise controlled persistent pain. Treatment of breakthrough pain is a challenging phenomenon. Oral transmucosal fentanyl citrate (OTFC; brand name Actiq®, Chephalon Inc., West Chester, PA), a new opioid formulation with a unique delivery system, reflects the characteristics of breakthrough pain (rapid onset of action and short duration), making it an effective treatment for cancer patients who already receive opioids and experience flares of pain. This review article aims to present the role of oral transmucosal fentanyl citrate in the management of breakthrough pain in cancer patients. In particular, it is going to discuss the synthesis, clinical pharmacology, pharmacokinetic and pharmacodynamic properties, toxicity, and clinical efficacy of this novel agent.

Key words: oral transmucosal fentanyl citrate, breakthrough pain, cancer

INTRODUCTION

The vast majority of patients with advanced cancer report pain, which is usually controlled sufficiently with a fixed-schedule, around-the-clock opioid regimen. In addition to this chronic and persistent pain, up to two-thirds of cancer patients also experience transient exacerbations of severe pain that occur against a background of otherwise controlled, tolerable pain.[1,2] This transitory exacerbation is commonly described as "breakthrough pain" and characterized by rapid onset (median interval from onset to peak: three minutes; range: one second to 30 minutes), moderate to severe intensity, and relatively short duration (median duration: 30 minutes).[3-5]

Immediate-release, short-acting oral opioids taken as needed are commonly used to treat breakthrough pain. In cancer patients, morphine sulfate, oxycodone, and hydromorphone are commonly used for this purpose. Oral transmucosal fentanyl citrate (OTFC; brand name Actiq®, Chephalon Inc., West Chester, PA) is the first medication developed specifically for the treatment of breakthrough pain. It provides fentanyl, its active ingredient, via a unique oral transmucosal delivery system and offers personal pain control to cancer patients.

PHARMACOLOGICAL CHARACTERISTICS

Synthesis

OTFC is a solid formulation of fentanyl citrate, a potent (50 to 100 times as potent as morphine), short-acting, rapid-onset, lipophilic, synthetic opioid with selective activity for μ-receptors expressed in the brain, spinal cord, and other tissues. OTFC is formulated as a solid drug matrix on a handle, allowing the unit to rotate in the mouth for optimal absorption and the removal of the unit if signs of excessive opioid effects occur during administration. OTFC is available in six strengths equivalent to 200, 400, 600, 800, 1,200, or 1,600 mcg fentanyl base.

Clinical pharmacology

Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid μ-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS).[5] The most clinically useful pharmacologic effects of fentanyl's interaction with μ-receptors are analgesia and sedation. Other opioid effects—at clinically relevant doses—may

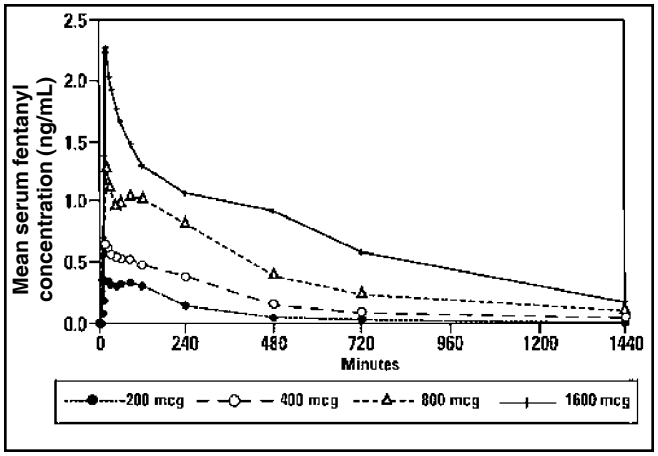

Figure 1. Mean serum fentanyl levels following administration of the four strengths of OTFC (200, 400, 800, and 1,600 mcg units) in adult subjects (*Actiq® Summary of Product Characteristics*).

include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria, and confusion or difficulty in concentrating.

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a three- to five-minute half-life). In individuals who are not opioid-tolerant, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/ml to surgical anesthesia and profound respiratory depression at levels of 10 to 20 ng/ml.[6]

In the clinical setting, pharmacological and pharmacokinetic differences have been observed among patients who have been administered fentanyl. The variable binding of serum fentanyl to plasma proteins may be a factor in these observed differences. Approximately 80 percent of fentanyl is bound to plasma proteins,[7] such as the acute phase protein α1-acid glycoprotein,[8] with only free fentanyl able to cross the blood-brain barrier. Variability in endogenous opioid concentrations in cerebrospinal fluid may also contribute to these observed differences.[9,10] The requirement for higher-than-estimated blood concentrations typically sufficient to elicit clinically significant analgesia (~1 ng/ml) may result in ventilatory depression (at > 2 ng/ml).[11] This need for additional supportive analgesia without severe respiratory depression led to the development of the oral transmucosal fentanyl delivery system.

Pharmacokinetics

The absorption pharmacokinetics of fentanyl in the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the gastrointestinal tract.[12] Both the blood fentanyl profile and the bioavailability of fentanyl will vary, depending on the fraction of the dose absorbed through the oral mucosa and the fraction swallowed.

Under normal conditions, approximately 25 percent of the total OTFC dose are rapidly absorbed from the buccal mucosa and become systemically available. The remaining 75 percent of the total dose are swallowed with the saliva and then slowly absorbed from the gastrointestinal tract. About one-third of this amount (25 percent of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50 percent bioavailability of OTFC is divided equally between rapid transmucosal absorption and slower gastrointestinal absorption.

Dose proportionality among four of the available strengths of OTFC (200, 400, 800, and 1,600 mcg) has been demonstrated in a balanced crossover design in adult subjects.[13] Figure 1 shows the mean serum fentanyl levels following these four doses of OTFC. The curves for each dose level are similar in shape to increasing dose levels that produce increasing serum fentanyl levels.

The pharmacokinetic parameters of the four strengths of OTFC tested in the dose proportionality study are shown in Table 1. The mean C_{max} ranged from 0.39 to 2.51 ng/ml.[13] The median time of maximum plasma concentration (T_{max}) across these four doses of OTFC varied from 20 to 40 minutes (a range of 20 to 480 minutes) as measured after the start of administration. Moreover, studies in healthy donors showed that two smaller doses of OTFC (400 mcg) administered simultaneously are pharmacokinetically equivalent to an identical dose administered as a single unit (800 mcg).[14]

Metabolism and elimination

Fentanyl is principally (more than 90 percent) metabolized into norfentanyl and other inactive metabolites in the liver and intestinal mucosa by the cytochrome P450 3A4 isoenzyme system and oxidative μ-dealkylation. Less than 7 percent of the dose is excreted unchanged in the urine, and only about 1 percent is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl is 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about seven hours.[6]

Dosage and administration

OTFC is presented as a sweetened lozenge with an integral oromucosal applicator (unit) intended for oral administration by sucking. Each dosage unit contains 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, or 1,600

Table 1. The pharmacokinetic parameters of the four strengths of OTFC (200, 400, 800, and 1,600 mcg units) tested in the dose-proportionality study (*Actiq® Summary of Product Characteristics*)

	Pharmacokinetic parameter			
	T_{max}, minute median (range)	C_{max}, ng/ml mean (% CV)	AUC_{0-1440}, ng/ml minute mean (% CV)	$t_{½}$, minute mean (% CV)
200 mcg	40 (20 – 120)	0.39 (23)	102 (65)	193 (48)
400 mcg	25 (20 – 240)	0.75 (33)	243 (67)	386 (115)
800 mcg	25 (20 – 120)	1.55 (30)	573 (64)	381 (55)
1,600 mcg	20 (20 – 480)	2.51 (23)	1,026 (67)	358 (45)

mcg fentanyl citrate. To minimize opioid-related side effects, it is necessary to identify a "successful" dose via closely supervised titration. Titration is considered necessary, as clinical trials could not establish a predictable relationship between a daily dose of around-the-clock medication and an OTFC dose. Before titration with OTFC, persistent background pain should be controlled with opioid therapy, and patients should typically experience no more than four episodes of breakthrough pain per day. The initial dose of OTFC should be 200 mcg, titrating upwards as necessary.

During titration, if adequate analgesia is not obtained within 15 minutes after the complete consumption of a single lozenge, a second lozenge of the same strength may be consumed. No more than two lozenges should be used to treat an individual pain episode. If treatment of several consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase to the next available strength should be considered. Patients should be carefully monitored until a successful dose is determined. Once a successful dose has been established, patients should be maintained on this dose and should limit consumption to a maximum of four units per day.[2] If more than four units per day are needed, the dose of fixed-schedule analgesics should be increased or the overall pain management strategy reconsidered.

Adverse events and drug interactions

Adverse events seen with OTFC are typically opioid-related and include somnolence, dizziness, nausea, constipation, asthenia, and confusion. The therapeutic range of fentanyl is between 1 and 3 ng/ml.[16] Overdose may result in hypoventilation and possible respiratory failure. Inappropriate use, either accidental or intentional, may induce fentanyl intoxication. Therefore, all patients must be followed for respiratory depression symptoms.

Because fentanyl is metabolized by the cytochrome P450 3A4 isoform, inhibitors of this enzyme may produce increased or prolonged opioid side effects. The concomitant use of other CNS depressants may produce additive sedative effects. OTFC should not be administered to patients who have received monoamine oxidase inhibitors within the previous 14 days.

CLINICAL CHARACTERISTICS

To date, OTFC for the management of breakthrough pain has been evaluated via small, short-term studies in adult patients with cancer-related pain. In these studies, patients were either taking an oral opioid (usually morphine) or transdermal fentanyl as their around-the-clock medication to control persistent pain.

Two randomized, double-blind dose titration studies of OTFC have been published (n = 65, 62).[2,17] The results demonstrated that 74 percent and 76 percent of patients, respectively, were able to identify a safe and effective dose of OTFC. The mean successful dose of OTFC in these studies was approximately 600 mcg. No relationship was found between the successful dose of OTFC and the total daily dose of around-the-clock opioid in either study, indicating that the optimal dose of OTFC cannot be predicted by the total daily dose of fixed-schedule opioid.

These titration studies also included open-label comparisons of OTFC and the patients' usual oral opioids used for breakthrough pain. Although neither study was designed to validly compare the analgesic efficacy of OTFC to the usual rescue drug, OTFC was reported to produce a greater analgesic effect, better global satisfaction, and a more rapid onset of action than the usual breakthrough medication.[2,17]

The efficacy of OTFC has been evaluated in one randomized, placebo-controlled trial and one randomized, comparative study[18] with immediate release morphine sulphate (MSIR).[19] The placebo-controlled study was a multicenter, crossover study that evaluated the efficacy of individualized doses of OTFC. A total of 130 patients who met the eligibility criteria underwent open-label dose titration to identify their successful dose. Ninety-two patients successfully completed the dose titration phase and consented to participate in the randomized, double-blind phase, during which each patient acted as his/her own control.

Each patient was given 10 units. Seven were OTFC at the same dose found to be effective for the particular patient in the titration phase, and three were identically formulated placebos. All 10 doses were to be taken within a 14-day period. Patients were allowed to take a dose of their usual rescue medication if adequate pain relief was not achieved after 30 minutes. Patients completed a medication diary at 0, 15, 30, 45, and 60 minutes following consumption of a unit.

In the primary efficacy analysis (excluding protocol violations; n = 86), analgesic effect in terms of pain-intensity difference (i.e., the difference in pain intensity immediately before consumption of trial medication and at 15, 30, 45, and 60 minutes post-consumption) and pain relief were significantly greater with OTFC than with placebo for all time points ($p < 0.0001$). The mean global performance evaluation values also significantly favored OTFC ($p < 0.0001$). Patients required significantly more additional rescue medication for breakthrough pain episodes treated with placebo than for episodes treated with OTFC—34 percent vs. 15 percent; RR = 2.27 (95 percent CI: 1.51 to 3.26), $p < 0.0001$.[18]

The comparative study was a randomized, double-blind, crossover study assessing the efficacy of successful doses of OTFC with MSIR. Initially, 134 patients who met the eligibility criteria and were using a successful dose of 15 mg, 30 mg, 45 mg, or 60 mg MSIR were entered into an open-label dose titration phase to identify a successful dose of OTFC. Ninety-three of these patients successfully completed the titration phase and entered the randomized, double-blind phase, during which each patient acted as his/her own control. Each patient was given 10 sets of medication (five contained OTFC + placebo capsules; five contained placebo units + MSIR capsules). The patient consumed a full set of study medication at each episode of breakthrough pain, with all 10 doses to be taken within a 14-day period.

In the primary efficacy analysis (for patients who had at least one evaluable episode for each study drug; n = 75), OTFC was statistically significantly superior to MSIR in terms of pain intensity difference ($p < 0.008$) and pain relief ($p < 0.009$) at each time point and global performance rating ($p < 0.001$). In addition, significantly ($p < 0.001$) more pain episodes treated with OTFC had a greater than 33 percent change in pain intensity at 15 minutes than MSIR, implying a faster onset of action with OTFC.[19]

Another open-label study evaluated the long-term safety and tolerability of OTFC in ambulatory cancer patients with breakthrough pain.[20] Participants were patients who had participated in a previous short-term titration trial of OTFC, were experiencing at least one episode per day of breakthrough pain, and had achieved relief of their breakthrough pain with an opioid. In total, 41,766 units of OTFC were used to treat 38,595 episodes of breakthrough pain in 155 patients. Patients averaged 2.9 breakthrough pain episodes per day. About 92 percent of episodes were successfully treated with OTFC, and there was no trend toward decreased effectiveness over time. Most patients (61 percent) did not require dose escalation during treatment. Global satisfaction ratings were consistently above 3 (0 = poor, 4 = excellent), indicating very good to excellent relief. Common adverse events associated with OTFC were somnolence (9 percent), constipation (8 percent), nausea (8 percent), dizziness (8 percent), and vomiting (5 percent). Six patients (4 percent) discontinued therapy due to an OTFC-related adverse event. There were no reports of abuse, and patients and their families raised no concerns about the drug's safety. OTFC was used safely and effectively during long-term treatment of breakthrough pain in cancer patients at home.

Finally, a recent retrospective study evaluated the efficacy of OTFC in the outpatient management of severe cancer patient crises.[21] Prior to OTFC treatment, all patients reported a mean pain intensity of 9.0 (SD = 1.2). After OTFC treatment, patients reported a mean intensity of 3.0 (SD = 1.4), a significant reduction in pain intensity ($p < 0.001$). In most cases, OTFC averted the need for an emergency center visit, parenteral opioids, and hospital admission, which suggests that OTFC could be an effective alternative over intravenous opioids to rapidly titrate analgesia in selected opioid-tolerant cancer patients experiencing severe pain.

CONCLUSION

OTFC is an opioid agonist available in a unique delivery system and is the first opioid analgesic formulation specifically developed and approved for the control of breakthrough pain. The safety profile and pharmacokinetic characteristics (i.e., rapid onset of action and relatively short duration) of this new opioid formulation make it ideal for the management of breakthrough pain in cancer patients already receiving around-the-clock opioid medication for pain.

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ORIGINAL ARTICLE

Establishing the safety and efficacy of an opioid titration protocol

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ABSTRACT

The primary goal of this single-group study was to determine the safety of a standard opioid titration order sheet to manage pain in ambulatory cancer patients. Secondary goals were to examine opioid toxicity and efficacy of this pain protocol.

Twenty-seven patients who required fixed-dose opioids and who had uncontrolled pain were enrolled. All patients had their initial opioid dose titrated by the study physician using the opioid titration order sheet. Data were obtained by the study nurse during a weekly telephone interview and used to determine if pain was controlled. After initial titration, a trained study nurse titrated opioid doses based upon the standing order sheet. At each contact, patients were assessed for adverse effects, pain intensity, and analgesics used.

Patients who completed the four-week trial (n = 17) did not differ from patients who did not complete the trial. No adverse effects were observed in 39 opioid titrations completed by the study nurse. Opioid toxicities, worst pain, usual pain, and pain-related distress declined from baseline to week four. Patients who were adherent to their prescribed medications reported significantly lower pain intensity and distress (ps ≤ 0.06).

The opioid titration order sheet, used by a trained nurse, is safe to use in ambulatory cancer patients who have moderate to severe pain. Common opioid toxicities were reduced. The protocol also demonstrated initial efficacy in improving worst and usual pain and pain-related distress. Further research to establish efficacy of the protocol is recommended.

Key words: cancer pain, standing orders, opioid titration

INTRODUCTION

Cancer-related pain has been reported in 50 percent of all patients[1] and more than 85 percent of patients with terminal disease.[2] Given current pharmacological and intervention strategies, the majority of patients should be able to achieve controlled pain. Nonetheless, uncontrolled cancer pain remains a major symptom control issue. Extensive studies have been conducted to identify barriers to uncontrolled pain in order to develop and test interventions. Multiple factors have been identified that contribute to the undertreatment of cancer pain. One commonly cited cause is lack of knowledge by medical staff and patients about cancer pain and its treatment. Erroneous beliefs, particularly about the danger of opioid use, also prevent optimal pain control. One obvious solution to these barriers is pain education. Educational interventions aimed at both medical staff and patients have been tested. While education interventions can improve knowledge and beliefs, they have failed to result in consistent, clinically meaningful improvements in pain outcomes.[3] A more powerful and robust intervention strategy is necessary to effectively reduce cancer-related pain.

Achieving controlled pain is a complex process that requires interaction between healthcare providers (typically physicians and nurses) and the patient-family unit. We developed a conceptual model describing an ideal interaction between healthcare providers and patients that would result in optimal pain control. The ideal interaction involves five steps: 1) the patient effectively communicates pain issues to the provider; 2) the provider assesses current pain, the treatment plan, and reasons for poor pain control; 3) the provider modifies the treatment plan to provide more effective relief; 4) the provider reviews the revised plan with the patient and family; and 5) the patient follows the treatment plan. The first and the last steps in the process are patient driven, while the middle three steps are initiated by the provider (Figure 1). A great deal of work has been done to address the role of patient education to enhance patient adherence and communication with providers about pain control issues. As noted above, these interventions have failed to consistently improve pain control.[3] We chose to develop an intervention that addressed the provider role in pain control.

Based on our conceptual framework, the provider is

Step 1. Patient: Patient report of pain

Step 2. Provider: Assessment of pain

Step 3. Provider: Medication modifications

Step 4. Provider: Review of plan with patient

Step 5. Patient: Patient follows treatment plan

Figure 1. Critical steps for adequate pain outcome.

responsible for three specific tasks: 1) assessing pain control and related issues (such as side effects and adherence), 2) generating a treatment plan, and 3) communicating the plan to the patient. If the provider complies with these steps in the care process, we hypothesize that pain control will be enhanced (i.e., decreased pain intensity and side effects). Furthermore, we posit that the occurrence of a positive pain outcome, which is dependent upon the degree to which the patient follows the treatment plan, will increase the patient's willingness to report pain at the next healthcare encounter. Conversely, the process can break down if the provider does not follow the steps of the care process. In this instance, the feedback is negative, and patients may be less likely to communicate pain control problems to the provider during the next encounter.

Within our conceptual framework, there are two critical components that determine the healthcare provider's ability to actualize their pain control tasks: 1) the knowledge base and expertise to allow for adequate assessment and treatment of pain, and 2) the time to obtain pertinent data (pain characteristics, barriers, and side effects) and communicate changes in the treatment plan to the patient. Unfortunately, it is evident that many physicians and nurses lack the skills needed to assess and treat pain.[4-6] Thus, providers enter practice lacking basic knowledge about how to assess and manage cancer pain. Providers, therefore, learn to manage pain through trial and error, consultation with more seasoned providers, or continuing education. This type of educational process is suboptimal and leads to large gaps in knowledge. One strategy used to reduce knowledge deficits is provider education. Many educational programs for physicians and nurses have demonstrated short-term improvements in knowledge and attitudes.[7-9] However, this increased knowledge has not resulted in long-term change in assessment and prescribing behaviors[10] or demonstrated a beneficial impact on pain outcomes.[11]

In addition to knowledge deficits, the medical delivery system used by most practicing oncologists prohibits timely and adequate response to cancer-related pain. A high volume of patient care problems and little time to address palliative issues burdens physicians. Lack of time has been identified as a critical barrier to good pain control.[12] In order to save time, most oncologists use nursing staff to assist in symptom control. The use of nurses with advanced training and skills may be an acceptable and appropriate way to ensure timely and adequate control of symptoms. Unfortunately, nurses are usually poorly trained in symptom management and learn these skills on the job. Furthermore, there are few tested guidelines to aid them in this task.

The literature suggests that specific, evidence-based recommendations in the form of pathways, protocols, and algorithms may result in improved clinical outcomes through reducing variation in clinical care. The more specific and accessible the recommendations are, the more likely that providers will adopt new clinical practices. In most instances, successful guideline implementation has incorporated a multifaceted approach with some mix of education, feedback, or monitoring, and patient-provider reminders.[13] We postulated that a well-developed protocol might enhance pain outcomes in the ambulatory cancer patient. We therefore undertook the development of a protocol specifically to address opioid titration. The protocol gives step-by-step instructions to providers, thus allowing providers with a limited knowledge base to use it effectively. In addition, it was designed to be nurse-managed, thus reducing the time required by physicians. The primary goal of this single-group design study was to test the safety of the opioid titration order sheet by examining the occurrence of severe adverse events. In addition, the study examined the efficacy of the protocol in reducing opioid toxicities and selected pain outcomes.

PATIENTS AND METHODS

Sample eligibility

Patients were recruited from a comprehensive cancer center located in a medical center in the southeastern United States. Eligible patients had: 1) histologically proven cancer, 2) uncontrolled cancer pain requiring opioids on a regular (fixed-dose) schedule, 3) the ability to read and understand English, 4) cognitive ability (Mini-Mental Status Examination [MMSE]) > 24, 5) a life expectancy of more than 12 weeks, and 6) an age of 18 years or older. Patients were excluded from the study if they: 1) had pure neuropathic pain; 2) presented in a pain crisis, which is defined as severe pain unresponsive to traditional opioid therapies; or 3) required immediate anesthesia or neurosurgical measures for pain control. Patients were removed from the study if they required hospitalization during the opioid titration trial, if they were transferred to hospice, or if they presented to the clinic or emergency department in a pain crisis. This study was approved by the Institutional Review Board, and all patients provided written informed consent prior to beginning the study.

Intervention

Patients who met eligibility criteria and expressed interest in study participation were screened using the MMSE[14] to ensure adequate mental capacity to complete self-report measures. Patients with adequate MMSE scores (> 24) were then enrolled in the study. Baseline evaluation included an assessment by a physician in order to adjust medications and to sign the titration order sheet. Patients then completed pain intensity and interference items of the Brief Pain Inventory (BPI),[15,16] a single-item distress scale,[17,18] and the Medication Side Effect Checklist (MSEC).[19] Patients and family (when available) underwent a baseline educational program that included a review of medication doses and schedule, written and oral explanation about toxicities, and an assessment of barriers. They were instructed in how to complete the daily diary, which included a daily measure of worst and usual pain and all medications taken to manage pain and side effects. Patients also were instructed to contact the study nurse for any pain related issues. Emergent problems that occurred at night or on weekends were referred to the on-call team.

All follow up was conducted by one study nurse using telephone interviews. Patients were contacted a minimum of once each week for follow-up assessment. Follow-up assessments included an assessment of pain (results of the daily diary were reviewed and recorded), evaluation of adherence and barriers, and an evaluation of toxicity. The physician trained the study nurse in the use of the titration order sheet. The physician reviewed the study nurse dose calculations for the first month to ensure accuracy.

The opioid titration order sheet provides standing orders for opioid dose adjustment based on the level of pain and the use of breakthrough medications. The study nurse used the data obtained from the patient interview to calculate an appropriate dose modification. Once the dose modification was calculated, the patient was told how to take their medications. If adherence barriers were identified (e.g., fear of addiction), the study nurse addressed the barriers and encouraged the patient to take medications as prescribed. If opioid toxicities were identified, standing orders for side-effect management were implemented. Patients who had a dose modification for moderate pain or dose reductions were contacted within 48 to 72 hours after dose titration. Patients who had a dose modification for severe pain were contacted within 24 hours or the next working day. Patients experiencing a pain crisis or who developed new pain of unclear etiology were referred for evaluation by the primary oncologist.

The criteria for dose adjustment were based on pain level and the use of breakthrough medications. The pain level was categorized as mild (1 to 4), moderate (5 to 6), and severe (≥ 7).[20] For the purposes of this study, controlled pain was defined as a usual pain level of 4 or less, with four or fewer rescue doses per 24 hours. To eliminate dose titration based upon transient or isolated activity-dependent pain, the patient must meet the criteria for three consecutive days before titration would be initiated. Patients with severe escalating pain could be titrated more rapidly after consultation with the physician.

Patients who did not meet these criteria for controlled pain were instructed to modify their opioid dose. Patients with mild usual pain (1 to 4) taking more than four rescue doses per day were instructed to adjust their fixed dose by an amount equal to the daily rescue dose in an effort to decrease the frequency of need for breakthrough medications. Patients with moderate pain (5 to 6) were instructed to increase their 24-hour opioid total (fixed dose plus rescue doses taken) by 25 percent. Patients with severe pain (≥ 7) were instructed to increase the 24-hour opioid total by 50 percent. Rescue doses were then recalculated to equal 10 to 15 percent of the new daily fixed-dose opioid total. If a patient met the criteria for controlled pain (usual pain < 4 and use of more than four rescue doses in 24 hours) and desired a decrease in opioid dose, a 25 percent reduction in 24-hour opioid total was prescribed.

Outcome measures

The primary outcome measure for this study was adverse events due to opioid overdose. Adverse events were assessed at each follow-up telephone interview. Since toxicities secondary to opioids are common, we clearly defined the parameters that were considered adverse events. These included severe lethargy, obtund sensation, and respiratory depression with a rate less than 8 per minute.

Opioid toxicity was assessed at baseline and during each follow-up interview using the MSEC.[19] Side effects included on the six-item MSEC are those typically associated with opioid use, including constipation, drowsiness, nausea, vomiting, confusion, and dry mouth. The severity of each side effect that had been experienced in the past week was rated on an 11-point Numerical Rating Scale (NRS). Items were averaged to provide a mean weekly side effect score.

Adherence was assessed at each follow-up interview. Adherence to fixed-dose medications and the use of breakthrough dosing for moderate or severe pain was assessed. Patients were categorized as adherent if they: 1) took their fixed-dose opioids as prescribed, and 2) took rescue medications when usual pain was > 4.

Patients completed a daily diary from baseline through week four of the trial.[21,22] Usual and worst pain, fixed-dose opioid use, rescue medications taken, and other coanalgesics used were recorded in the daily diary. At baseline, week one, and week four, patients completed the interference items from the BPI[15,16,20] and the pain-related distress item.[17,18] Worst and usual pain intensity

Table 1. Sample description				
Variable	**Did not complete study**		**Completed study**	
	Number of Ss	**Percent in group**	**Number of Ss**	**Percent in group**
Gender				
Male	8	80	8	47
Female	2	20	9	53
Ethnic background				
White	10	100	13	76.5
African-American	0		4	23.5
Marital status				
Married	3	60	12	75
Single/divorced	2	40	4	25
	Mean	**SD**	**Mean**	**SD**
Age in years	57.1	11.38	54.59	9.67
Cancer dx in months	11.3	12.35	32.0	52.45
Pain duration months	8.96	13.49	16.6	17.15
Mental status	29	1.63	28.2	2.41
Worst pain (0-10)	7.3	1.64	6.24	2.95
Usual pain (0-10)	5.8	1.03	4.47	2.92
Side effects (0-10)	1.96	1.63	2.45	1.50
Distress (0-10)	5.9	2.85	5.0	2.88
Interference (0-10)	4.38	2.70	3.78	2.57

and pain-related distress were obtained using 0 to 10 NRSs. Interference because of pain is a seven-item scale, which includes interference with ability to walk, general activity, usual work, mood, sleep, relations with others, and enjoyment in life. Each item was rated on an 11-point NRS, and responses were averaged for a total interference score. All instruments have established reliability and validity.

Data analysis

The sample size was based upon the ability to detect a 10 percent rate of adverse events. Demographic and clinical variables were examined using descriptive statistics. A weekly average of worst and usual pain was computed from the daily diary. The average number of rescue doses per day was computed. Average scores were computed for the interference and side effects scales. Differences in demographic, clinical, and baseline variables between patients who completed and did not complete the study were examined using χ-square for categorical and independent t-test for continuous variables. Toxicities were examined in two ways: 1) the proportion of patients with no toxicities was compared to patients with toxicities using χ-square, and 2) the change in mean severity of toxicities was tested using repeated measures analysis of variance (ANOVA). Efficacy of the intervention was examined using a two-factor repeated measure ANOVA. In each analysis, time was the factor within subjects and adherence was the factor between subjects. Dependent variables included worst pain, usual pain (5 data points), pain-related distress, and interference because of pain (3 data points). This type of analysis allowed us to examine main effects for time and adherence and to determine if there were interactions between time and adherence for the selected pain outcomes. Level of significance was $p \leq .10$ for this pilot study. This level of significance was selected to increase our ability to detect differences over time, which may be clinically significant.

RESULTS

Patient characteristics

Out of a total of 27 patients who enrolled in the study, 17 completed the four-week trial (63 percent retention).

Table 2. Use of rescue medications over time						
	Rescue doses per day			Rescue doses per week		
	Mean	Median	Range	Mean	Median	Range
Week 1	1.79	1.20	0 – 6	12.25	7.0	0 – 42
Week 2	1.82	1.79	0 – 5.29	11.86	11.0	0 – 37
Week 3	2.08	2.07	0 – 5.29	13.0	12.5	0 – 37
Week 4	1.84	1.85	0 – 4.14	12.29	8.0	0 – 29

Reasons for discontinuing the study were hospitalization (n = 3), referral to hospice (n = 1), death unrelated to disease progression (n = 1), and loss to follow up (n = 5). There were no significant differences between patients who did and did not complete the study on any baseline variable (Table 1). The final sample (n = 17) was predominantly white and married, with a mean age of 57 years. They had been diagnosed with cancer for 11 months and had experienced pain related to the cancer for nine months. Fifty-nine percent were undergoing active treatment at the time of enrollment.

Adverse events associated with opioid titration

Patients were prescribed a long-acting opioid on a fixed schedule and a rescue medication when entered into the study. The dose range of long-acting opioids was as follows: Duragesic (25 to 400 mcg q 72 h), sustained release morphine (30 to 450 mg qd), and sustained release oxycontin (40 to 271 mg qd). Morphine sulfate immediate release tablets or liquid was the most frequently prescribed opioid for rescue dosing. Over the four-week trial, patients averaged approximately two rescue doses per day, however, there was a high degree of variation across patients in use of rescue medications (Table 2).

All patients had a dose adjustment upon entry into the study. Over the four-week study period, 15 patients (88 percent) had dose escalations: eight patients had one additional dose escalation, and seven patients had between two and five dose escalations. One patient tolerated two dose decreases. One patient required no additional dose modification. Each patient had initial opioids titrated by the physician (27 titrations). The study nurse successfully managed an additional 39 titrations. No patient experienced any adverse effect (severe lethargy, obtund sensation, or respiratory depression) over the course of the trial.

Opioid toxicities

At baseline, less than 20 percent of patients reported no toxicities associated with opioid use (Table 3). Drowsiness and dry mouth were most frequently reported and remained the most frequent toxicities experienced after opioid titration. The proportion of patients with no toxicities gradually rose from week one to week four. Chi-square analyses indicated the proportion with toxicities differed significantly from expected at baseline ($p = 0.008$), but no significant differences were found after opioid titration ($ps > 0.10$). The mean score on the MSEC was 1.96 at baseline, with a significant reduction in mean toxicity over time ($p = 0.07$).

Adherence

Nine patients (53 percent) were adherent to both fixed- and rescue-dose analgesic regimens. The majority of patients took their fixed-dose opioids as prescribed. Nonadherence was primarily related to failure to take rescue doses when usual pain rose above four-tenths on the NRS. When queried about failure to adhere to the breakthrough regimen, most patients replied "the pain wasn't that bad," and "they did not need the medication."

Effect of titration on pain outcomes

The opioid titration order sheet had a beneficial effect on pain outcomes. Repeated measures ANOVA indicated a significant main effect for time on worst pain ($p = 0.10$), usual pain ($p = 0.02$), and pain-related distress ($p = 0.03$). All outcomes showed a decline over time. Interference because of pain did show a slight decline over time, but the change was not statistically significant. A main effect for adherence also was significant for worst pain ($p = 0.05$), usual pain ($p = 0.006$), and distress ($p = 0.05$). As expected, patients who took their medications as prescribed reported lower pain and distress than those who did not. No significant differences were found between patients who were and were not adherent for interference because of pain. No significant interaction between time and adherence was found for any pain outcome.

Table 3. Toxicities during trial					
Toxicity	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Constipation*	46.7	21.1	16.7	18.2	7.7
Drowsiness*	66.6	38.5	59.3	60.0	30.8
Nausea*	46.7	21.1	33.3	27.3	23.1
Vomiting*	20.0	21.1	8.3	18.2	15.4
Confusion*	33.3	21.1	16.7	36.4	23.1
Dry mouth*	80.0	53.8	75.0	81.8	43.8
Number of toxicities					
0	17.6	52.9	41.2	40.0	58.8
1	11.8	0	17.6	6.4	17.6
2 – 6	70.6	47.1	42.1	53.3	23.5
Severity**					
Mean	1.96	0.83	0.94	0.99	0.64
SD	1.63	1.23	1.15	1.10	0.98
Range	0 – 5.67	0 – 3.33	0 – 3.67	0 – 3.0	0 – 3.17
* Percent with toxicity; ** Possible range 0 – 10.					

DISCUSSION

The results of this study confirm the safety of an opioid titration order sheet that is managed by a trained nurse with appropriate physician oversight. The primary outcome measure for this study was adverse events. No adverse events were observed in the 66 titrations completed in this trial. Interestingly, despite the large number of dose titrations during the study period, opioid toxicity decreased over time. This may be related to the aggressive assessment of toxicity coupled with the timely institution of standard therapy to manage opioid side effects.

To capture the effect of the intervention on pain control, it is critical to select appropriate outcome measures. The most commonly used outcome measure for cancer pain is pain intensity. A standard measure of pain intensity in the cancer population is the BPI.[15,16,20] Usual pain is considered a measure of basal pain, while worst pain reflects breakthrough pain. Results from this pilot trial indicate that opioid titration using the opioid titration order sheet resulted in improvement in usual and worst pain.

Pain, like other symptoms, is characterized by multiple dimensions.[23] Distress, which is defined as the amount of anguish or bother caused by the symptom,[23,24] also may have a significant impact on intensity, duration, and secondary outcomes.[23-25] In previous work, pain-related distress explained a greater proportion of unique variance in interference than pain intensity (worst or usual), mood disturbance, or analgesics used.[26] Use of the opioid titration order sheet resulted in a significant reduction in distress once the patient had been placed on the protocol and had medications titrated. These findings suggest that distress may be a particularly salient outcome in analgesic trials and merits further study. The lack of effect of the opioid titration protocol on interference because of pain is consistent with previous work,[27] which is an outcome that may be influenced by a number of factors in addition to adequate pain control. Another explanation is that this scale may not be as sensitive to change as the single item pain intensity and distress items.

In our study, only half of the patients adhered to the prescribed regimen. While most patients took their fixed-dose regimen, adherence to the breakthrough regimen was poor. These results confirm the findings of other investigators. In a study by Miaskowski et al.,[28] the lack of adherence to medications prescribed to control metastatic cancer pain was substantial. Adherence rates, over a five-week period, were high (90.0 percent) for medications prescribed on a fixed schedule and notably lower for rescue-dose analgesics (24.7 percent). This study

highlights the problem of medication adherence in patients with cancer pain and provides a reasonable explanation for undertreatment.

Furthermore, we demonstrated that patients who adhere to their regimen are more likely to have improved pain outcomes. Our findings also support the work of Du Pen and colleagues,[27] who tested a pain algorithm in a randomized clinical trial. Use of the pain algorithm resulted in a significant reduction in usual pain for all patients in treatment and a significant reduction in usual and worst pain for patients who adhered to the prescribed regimen. In their sample, the pain algorithm did not affect symptoms experienced, interference because of pain, or quality of life. Thus, Du Pen and colleagues demonstrated the importance of adherence in achieving improvement in pain intensity when patients are managed with a pain algorithm. Both the pain algorithm and the opioid titration order sheet represent strategies that may produce successful implementation of existing pain guidelines.[29,30]

Limitations

Several limitations of this study must be noted. Because of the single-group design, we cannot compare the impact of this protocol with standing titration orders to usual care. The ability to generalize the results of this study are limited by the small sample size and attrition of patients from the study. Thus, future research using a randomized design with a usual care comparison group is recommended.

CONCLUSION

The opioid titration order sheet is a clinical tool that addresses the provider-driven steps of our conceptual model. The order sheet specifies the timing and content of pain assessment, the criteria indicating need for opioid dose adjustment, a standing order for dose titration, and an outline for provider communication of the treatment plan to the patient. After initial assessment by the physician, the standing orders can be used by trained nurses, thus reducing the barriers to effective pain management, knowledge deficits, and time constraints. Our pilot study suggests that this type of clinical tool is safe and effective in improving several critical pain outcomes for ambulatory patients with cancer. The protocol with standing orders also addresses barriers to clinical guideline implementation. Because of their level of specificity, algorithms and protocols may be more easily adopted in clinical settings, thus reducing one of the implementation problems inherent in guidelines. To extend this line of research, we need to determine the applicability of a pain protocol with standing orders for dose titration for community-based providers.

ACKNOWLEDGMENTS

This study was supported by funds from the Vanderbilt-Ingram Cancer Center Pilot Study award.

Preliminary findings from the first 17 subjects were presented at the 2001 ASCO scientific meeting. Wells N, Murphy B, Siet D: Standardized opioid titration order Sheet (SOTOS) for cancer pain. Proc Amer Soc Clin Oncol. 2001; 20: 2983, abstract #2943. The complete study was presented in poster form at the Pain in Europe conference, September 2003.

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ORIGINAL ARTICLE

Evaluation of cognitive functioning in 101 patients before opiate detoxification: Implications in setting up therapeutic strategies

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ABSTRACT

Many studies have brought to light the facts that repeated use of drugs significantly influences one's cognitive functions, and that cognitive problems could interfere directly with one's capacity to participate in a rehabilitation program. In this research, we used the Global Deterioration Scale (GDS) to assess the cognitive status of 101 hospitalized patients in an opiate detoxification program. The results reveal that a majority of the tested patients present cognitive abnormalities to varying degrees of severity. Furthermore, these cognitive deficits are correlated with four Addiction Severity Index (ASI) scales (medical, alcohol use, drug use, and psychiatry, respectively). Considering the results, because cognition is a major issue in detoxification and rehabilitation programs, simple cognitive screening (as with the GDS) coupled with a particular interest in some aspects of a patient's anamnesis could lead to better management of opiate-dependent patients.

Key words: detoxification, rehabilitation, cognitive function, addiction

INTRODUCTION

Many studies have highlighted cognitive abnormalities in the behavior of patients presenting with various psychological or psychiatric disorders such as schizophrenia,[1-3] mood disorders (e.g., depression),[4-6] mania,[4] bipolar disorders,[7-10] nonemotional disorders (e.g., anxiety),[11,12] somatic disorders,[12] dissociative disorders,[12] sexual identity disorders,[12] and even eating disorders.[12] Studies also have demonstrated that repeated use of drugs significantly influences cognitive function.[13-22] In addition, other authors have implicated cognitive mechanisms in the emergence of symptoms during a phase of hysteria.[23] However, in psychiatry, neuropsychological aspects are taken into account very little. This lack of consideration is detrimental to the diagnosis, treatment, and rehabilitation of patients.[24] The length of time necessary to carry out the tests, as well as the difficulty sometimes encountered in transmitting practical information to clinical staff, make systematic neuropsychological evaluation a fairly unattractive prospect in the psychiatric routine.

Concentrating particularly on the influence of drugs on cognitive functions, studies have demonstrated that cocaine,[14,15,22] cannabis,[16,20] crack,[15,21] heroin,[18,19] alcohol,[18,25] and, of course, polytoxicomania[17] were likely to interfere with the cognitive functions. Since a history of polytoxicomania is encountered frequently among patients admitted to opiate detoxification, it appears that focusing particular attention on cognitive functions could be beneficial to patients. Consequently, far from the complexity of certain cognitive models described in the neuropsychological literature, we set up a simple and pragmatic procedure of cognitive evaluation of patients admitted to opiate detoxification. This procedure allowed us to easily identify the cognitive interference in patients admitted to detoxification and to inform the clinical staff who would be able, if necessary, to take adequate measures.

The aim of this paper is to find out what percentage of opiate-dependent patients seeking treatment present cognitive deficits. It also attempts to discover which factors are associated with these deficits. We hypothesized that some of the patients admitted for detoxification had a cognitive deficit likely to interfere with their treatment, and we assumed that these deficits have various etiologies and cannot exclusively be attributed to drug use or abuse.

MATERIAL AND METHODS

Subjects and treatment setting

One hundred and one inpatient admissions for a therapeutic program participated in this investigation (Table 1).

Table 1. Age and educational levels of subjects

Sex	Age	Educational level				
		I	II	III	IV	V
Men (n = 76)	32.58 (SD = 5.98) Range 17 – 57	68% (n = 52)	16% (n = 12)	7% (n = 5)	4% (n = 3)	5% (n = 4)
Women (n = 25)	34.52 (SD = 8.89) Range 19 – 55	44% (n = 11)	36% (n = 9)	12% (n = 3)	8% (n = 2)	

Note: Table 1 shows demographic data, namely age and educational levels (I = primary school; II = secondary school; III = high school; IV = college; V = university), according to the sex (men or women) of the 101 subjects included in the study. Age is expressed in mean with standard deviation (SD) and range. Educational levels are expressed in percentage.

To be admitted into this program, patients had to meet opiate abuse or dependence criteria according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) and be under methadone maintenance. Abuse of or dependence on other drugs at the time of admission was an exclusion criterion. All the patients were admitted for methadone detoxification with no other substance abuse. After admission, the patients received their regular dose of methadone until the beginning of the detoxification procedure. Within 24 hours, a trained psychiatrist assigned them to a detoxification protocol, and a trained psychologist administered the Addiction Severity Index (ASI). A trained neuropsychologist administered the Global Deterioration Scale (GDS) the second day of hospitalization before the beginning of the detoxification procedure. Opiate detoxification treatment included rapid antagonist induction under general anesthesia or methadone tapering combined with clonidine.

Test material and procedure

All patients were subjected to the following two tests: the ASI and the GDS.

The ASI is a semistructured interview designed to address seven potential problem areas in substance-abusing patients: medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status.[27] Severity scores range from 0 to 9, and their interpretations are as follows:

- 0 to 1: no problem, treatment not necessary;
- 2 to 3: slight problem, treatment probably not necessary;
- 4 to 5: moderate problem, treatment probably necessary;
- 6 to 7: considerable problem, treatment necessary; and
- 8 to 9: extreme problem, treatment absolutely necessary.

The ASI provides an overview of all the problems related to substance abuse, rather than focusing on a single area. It was administered to all subjects within the first 24 hours of hospitalization. Three trained members of the clinical team (psychologists) administered the ASI.

The GDS[28] is used to assess the cognitive status of patients. It was administered to all subjects on the second day of hospitalization. This period was chosen to allow an initial evaluation of each patient's mental state before the initiation of the detoxification procedure. A trained neuropsychologist—who was not a member of the treatment team and did not participate in other diagnosis work—administered all GDS tests. The GDS is an instrument that assesses the cognitive state and classifies it in one of seven stages, from a normal cognitive state to a very severe cognitive deficiency. This instrument provides a 7-point rating scale designed to evaluate the cognitive and functional capacity of patients from normal aging through dementia.[26] Because opiate-addicted patients are not in such an important state of cognitive deterioration, we adapted this scale and took into account only the first four evolutionary stages of the cognitive state. Indeed, the last three stages of this scale correspond to very severe deficits that do not concern the patients of this study. The patients answering to the criteria of these last three stages are generally seriously impaired and require a separate and specific therapeutic evaluation. According to Salmon,[26] *Stage 1* corresponds to normal cognition and function, *Stage 2* is commonly associated with complaints of cognitive deficits without clinical manifestations, *Stage 3* is associated with subtle

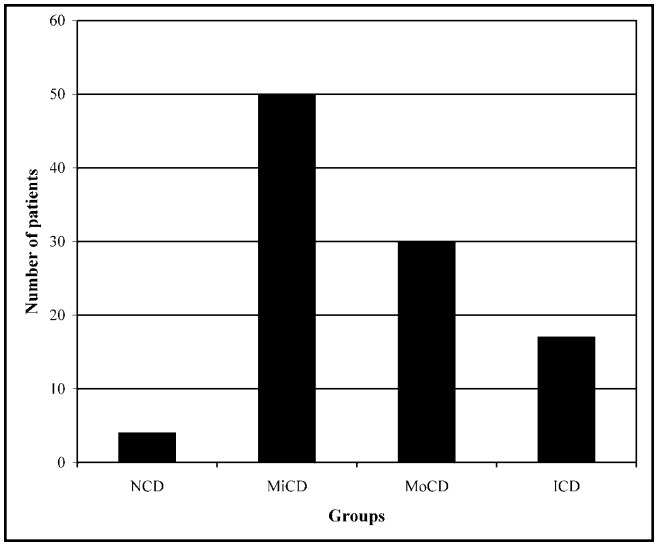

Figure 1. Repartition of patients according to the level of cognitive deficit. Shows patients' repartition in different groups according to the GDS results. Patients can be subdivided into four categories: "NCD" group (no cognitive deficit, n = 4), "MiCD" group (mild cognitive deficit, n = 50), "MoCD" group (moderate cognitive deficit, n = 30), and "ICD" group (important cognitive deficit, n = 17).

cognitive deficits commonly associated with decreased function in demanding work or social settings, while *Stage 4* is associated with obvious cognitive deficits that generally interfere with activities of daily living.

RESULTS

Using the GDS scores, patients were classified as follows:

- Level 1: no cognitive deficit (NCD);
- Level 2: mild cognitive deficit (MiCD);
- Level 3: moderate cognitive deficit (MoCD); and
- Level 4: important cognitive deficit (ICD).

Different groups of patients then were compared with the ASI composite results (i.e., medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status).

Do the patients present cognitive deficits?

According to the GDS results, patients can be subdivided as follows:

- Four patients in the NCD group;
- 50 patients in the MiCD group;
- 30 patients in the MoCD group; and
- 17 patients in the ICD group.

These results indicate that patients showing no cognitive deficit represent a minority. A majority of patients (96 percent of the tested population) present cognitive deficits to varying levels of severity (Figure 1).

Which variables are associated with cognitive deficits?

We performed a regression analysis between groups (NCD, MiCD, MoCD, and ICD) and ASI categories (medical, employment, alcohol use, drug use, legal, family/social, and psychiatric). The results show that a significant linear relationship exists between the first category of ASI (medical) and cognitive deficit ($f = 14.959$, $p = 0.001$); between the third category of ASI (drug use) and cognitive deficit ($f = 12.486$, $p = 0.001$); between the fourth category of ASI (alcohol use) and cognitive deficit ($f = 4.975$, $p = 0.028$); and between the seventh category of ASI (psychiatric status) and cognitive deficit ($f = 8.337$, $p = 0.005$). Together, these results show that our sample of opiate-dependent patients admitted for a detoxification program presents various degrees of cognitive deficit. These deficits are correlated with the severity of four ASI scales: medical status, alcohol use, drug use, and psychiatric status (Figure 2).

DISCUSSION

The results indicate that an overwhelming majority of the patients participating in this study (96 percent) present cognitive deficits to varying degrees of severity, and that these deficits are related to the index of severity for some of the ASI categories (medical status, alcohol consumption, drug use, and psychiatric status). The use of drugs and/or having psychiatric problems could be deteriorating to the cognitive state, but are not inevitably determining. Meanwhile, alcohol abuse and associated medical problems could be partly responsible for cognitive deficits observed among opiate-addicted patients admitted for detoxification. Our results are in accordance with those of other studies. Darke et al.[30] showed that methadone-maintained patients have cognitive deficits, and that a lifetime diagnosis of alcohol dependence and the amount of nonfatal heroin overdoses were independent significant predictors of poorer cognitive performance. In their study, Darke et al.[30] did not rule out the possibility of other contributing factors, such as psychiatric status or previous patterns of drug use, which are clearly highlighted in our study.

Our results show that the large majority of patients under methadone-maintenance treatment present cognitive abnormalities that are apt to interfere with their daily activities.

Independent of certain behavior explained in light of neuropsychological models, to understand the importance of a specific treatment and benefit from a psychotherapeutic intervention (e.g., during a detoxification procedure), it is necessary to encode new data, compare them with events stored in memory and, if necessary, carry out adjustments. Compared to those without deficits, the patients with cognitive deficits could have more difficulty in achieving successful treatment. The early identification of cognitive deficits, therefore, can give crucial information to the clinical team that takes into account these deficits in the daily management of patients, which in turn increases the effectiveness of treatment by limiting the dropout rate and preventing risk of relapse during follow-up.

Consequently, it appears highly necessary to systematically evaluate the cognitive functions of patients admitted to detoxification at the beginning of their treatment to adjust the therapeutic strategy accordingly. Particular attention must be paid to a patient's history of alcohol and/or medical problems to help the clinicians identify the patients most likely to suffer from cognitive disorders. Nevertheless, even if several studies suggest that drugs induce specific cognitive impairment,[13,15,17,19,21] it is not clear whether drug use is more of an aggravating factor than an initial cause of cognitive deficit. Consequently, assessing the cognitive function and identifying a history of associated alcohol and somatic problems seems much more important than solely focusing on patterns of drug use.

In the practical evaluation of cognitive functions in methadone-maintained patients admitted to a detoxification program, a focus on history of alcohol abuse/dependence and medical problems (e.g., overdoses, head trauma) combined with a test like the GDS seem to adequately identify cognitive problems. Results obtained by such a procedure could help to identify patients presenting profiles "at risk" for cognitive problems, lead to further neuropsychological investigation, and/or bring about a more efficient therapeutic strategy. Indeed, the cognitive problems could interfere with a patient's capacity to take part in a therapeutic program. Therefore, efforts should be made to gradually integrate a pragmatic cognitive evaluation in setting up a therapeutic strategy. This approach would help the patient in his/her efforts as much as possible and lead to a successful treatment. Even if using cognitive tests in a noncompliant psychiatric population raises an additional problem, the use of GDS in conjunction with careful attention paid to certain aspects of a patient's history could lead to pertinent clinical information. This information could be communicated to the clinical team, which could adapt the therapeutic strategy accordingly—for example, by involving a member of the family in the supervision of treatment for a patient with memory problems.

CONCLUSION

In conclusion, our study indicates that a majority of the patients present cognitive abnormalities to varying degrees of severity. These abnormalities exist mainly among patients presenting the antecedents of alcoholism and various associated somatic deficits but are also correlated with the gravity of drug abuse and psychiatric condition. The testing procedure makes it possible to rapidly identify patients presenting cognitive impairments and to communicate this information to the clinical team, which in turn can decide on the best course of action to take (e.g., complementary examinations, etc.). Complementary studies are necessary to confirm our results, to specify which cognitive investigation would be most useful, and to learn how to communicate the results to the clinical team to improve the management of patients.

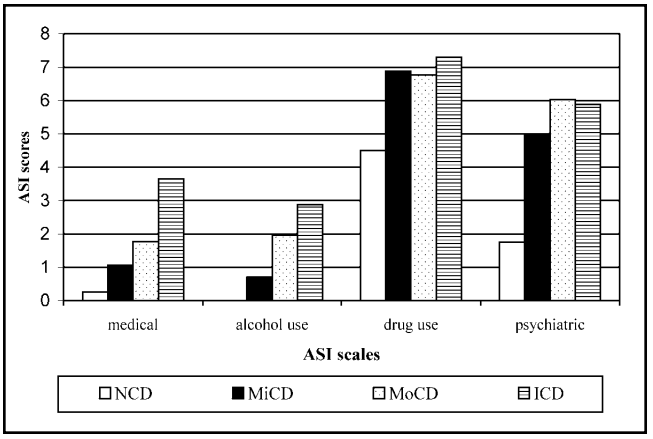

Figure 2. ASI scores in groups with different levels of cognitive deficit. Shows the four groups of patients (NCD, MiCD, MoCD, ICD) with their respective score on significant ASI scales.

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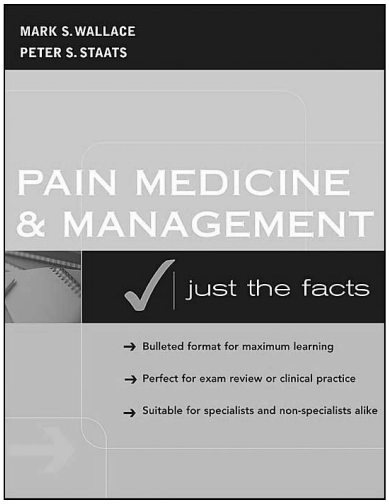

***Pain Medicine and Management: Just the Facts*, edited by Mark S. Wallace and Peter S. Staats. New York: McGraw-Hill, 2005; 379 pages.**

In the preface, the editors describe the purpose of this book as "a study guide for the pain physician who is studying for the board certification or recertification exam." Drs. Wallace and Staats are both respected and accomplished educators, researchers, and clinicians who are well-qualified to organize such a text. They have assembled a group of distinguished authors to contribute content. At least five of the chapter authors have been directly involved with the examination committee responsible for creating and administering the American Board of Anesthesiology (ABA) exam; an equivalent number of authors have been involved with the American Academy of Pain Medicine (AAPM) exam; and most of the authors are leaders in the field of pain medicine.

Certification in pain medicine requires knowledge from diverse areas. Candidates for the examination administered by the ABA include trainees from anesthesiology, neurology, physical medicine and rehabilitation, and psychiatry. Certification by the AAPM permits certification for any physician. Many pain specialists are certified by one or both equally discerning accrediting organizations.

The 70 chapters are written in outline form with useful figures and tables that cover the vast bulk of material likely to be tested on the certification exam. Pain medicine is a multidisciplinary specialty, which is addressed skillfully by the editors. The chapters are written by pain specialists from a variety of disciplines, all of whom are leaders in their fields, and they approach their topics from the perspective of their primary specialty background. For example, Dr. Kenneth Follett, a neurosurgeon pain specialist, wrote the chapter "Neurosurgical techniques"; Dr. Rollin Gallagher, psychiatrist pain specialist, wrote the chapter "Biopsychological Factors"; and Misha-Miroslav Backonja, MD, neurologist pain specialist, wrote the chapter "Anticonvulsant Drugs."

Examination question writing is a difficult process because good questions rely more on science than art. The authors, with few exceptions, are proponents of evidence-based medicine, and that bias is reflected in most of this book. The book is well-organized into nine sections, and the chapter numbers as well as titles are included in the headers on each page. The first section is "Test Preparation and Planning." Stephen Abram, MD, does a superb job describing the examination process and includes the examination content outline, useful web sites, and study techniques and preparation.

There is room for improvement in any first edition, and reviewers should identify weak or inadequate areas. Six and a half pages addressing prolotherapy is excessive, especially in a board review book based on evidence-based medicine. Elementary concepts, such as central and peripheral sensitization, need better definition, and the "Basic Physiology" section needs to be enhanced. Examinees will need to supplement their knowledge of basic physiology from another source.

I was disenchanted by the crucial chapter on "Low Back Pain" (LBP). This chapter stands out as being less well-organized, biased, and, in many places, unclear and misleading. A table describing "red flags" for back pain left out the factors of age greater than 50 and elevated ESR, even though they were included in the text and are extremely important. The authors state, "Although LBP may be severe, it is rarely described as excruciating." In using the McGill Pain Questionnaire as a tool to distinguish between various types of pain, investigators have found that 50 percent of cancer patients describe their pain as unbearable, compared with 40 percent of patients with back pain. Other inaccurate statements in this chapter include the authors' assertions that implanted drug infusion devices are a relative contraindication to MRI, acetaminophen should be used before NSAIDs in the treatment of acute LBP, and stocking-glove sensory loss during walking is suggestive of neurogenic claudication. I would suggest candidates skip this chapter altogether and obtain LBP material from a separate source.

I will not focus on a few chapters that can be improved because, far and away, this text is excellent and filled with easily acquired, evidence-based, testable information. In six pages, Michael Loes, MD, writes the best succinct summary of NSAIDs I have seen anywhere. His description contains tables providing starting doses for 24 drugs, elimination half-lives, structural classification, and comparative toxicity scores. I could single out many stellar and valuable chapters in an array of really good material and do not want to leave out the excellent work of the vast majority of the authors, but I found particular value in the "Tramadol" chapter, the "Topical Agents"

chapter, the "Substance Abuse" chapter, and the "Neurosurgical Techniques" chapter. There is ample material in the "Special Techniques" section to qualify nonproceduralist pain specialists to complete the interventional parts of the exam and to allow more procedurally oriented practitioners to acquire knowledge about rehabilitation, behavioral medicine, complementary and alternative approaches, and acupuncture.

Charles Argoff, MD, handled the controversial topic, "Botulinum Toxin Injections," deftly and fairly. "Intradiscal Electrothermal Annuloplasty," an equally controversial topic, also was described equitably by Drs. Derby, Lee, and Kim. The review of "Headaches" by Dr. Sapers contains all the important testable material, is clear and easy to read, and is an ideal, succinct board review summary.

Overall, this is a unique, well-edited and written, valuable asset for board candidates and anyone looking to review the core knowledge base of pain medicine. Fellows have been asking me for years to suggest a good review book for the boards, and I have been telling them there isn't one. Now, I can recommend this book. Drs. Wallace and Staats have probably been asked the same question and should be commended for solving the dilemma. *Pain Medicine and Management: Just the Facts* is the answer. It is an excellent board review source. I would recommend it highly to anyone preparing to take either the AAPM or the ABA board examination, either for initial certification or for recertification.

Reviewed by Gilbert J. Fanciullo, MD, MS, Associate Professor, Dartmouth Medical School; Director, Section of Pain Medicine, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire.

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Books—

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