Journal of Opioid Management™

A medical journal for proper and adequate use

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

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

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

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

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

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

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EDITORIAL

Cotton candy

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

> Cotton candy (n.): 1. A candy made of spun sugar. 2. Something attractive but insubstantial.
>
> —*Merriam Webster's Collegiate Dictionary (Tenth Edition)*

On July 27, 2004, a federal grand jury charged Dr. William Eliot Hurwitz with a 62-count indictment alleging drug trafficking conspiracy to distribute oxycodone and other pain medications, drug trafficking resulting in death and serious bodily injury, and various substantive counts in drug trafficking in pain medications and other criminal activities. He was arrested in the fall of 2004, and on December 15, was convicted on 49 counts of drug trafficking in 39 states. He was also linked to the deaths of three patients. On April 14, 2005, he received a 25-year sentence and a $1 million fine.[1,2]

Dr. Hurwitz was snared as part of an organized crime and Drug Enforcement Agency (DEA) task force investigation called "Operation Cotton Candy," which focused on the widely abused oxycodone (also known as OxyContin).

The high-profile nature of the Hurwitz case, punctuated by the trial's defense testimony of well-known pain experts, seems to only heighten the paranoia among the 10,000 physicians who specialize in treating pain. Physicians fear law enforcement action over perceived overprescribing and are concerned that underprescribing could result in malpractice complaints.[3] Not only are physicians in a no-win situation, but so are Americans with chronic pain.

So, before a solution is offered, let us return to the Hurwitz case. Personally, it is hard to believe that a physician who allegedly prescribed 1,600 pills a day to some patients was doing this as part of the Hippocratic Oath. In Bucks County, PA, where I live, there was a similar case of a physician who was writing prescriptions for enormous amounts of oxycodone in a "pill mill." He rarely examined his patients, kept no records, and lines to his office often were blocks long. He is now in jail. In the Philadelphia area, the street value of Oxycontin is $1 per milligram. Maybe the code name "Cotton Candy" was indeed appropriate. When you eat it at the local fair it tastes so sweet, but when you are done, your hands are sticky; in these cases the money (cotton candy) was alluring, but the resulting sticky hands led to handcuffs.

No matter how you feel about the Hurwitz case, there are several ways we physicians can protect ourselves:

- Do not write prescriptions for opioids as a favor to friends, other physicians, or nurses without an established physician-patient relationship.
- Protect your prescription pad and guard your DEA number at all times.
- When you write a prescription, document the physician-patient encounter with a history and physical, and also document the dose. I make a copy of each prescription for my records.

If you think these suggestions are too austere, simply ask one of my junior faculty how she felt when the DEA called. She wrote a prescription for an opioid for one of our temporary nurses as a "favor" because her back pain had flared up one day, and the nurse did not want to bother calling her primary physician. Unbeknownst to the doctor, the nurse then stole her prescription pad from our clinic. With the DEA number from the prior prescription, the nurse wrote numerous opioid prescriptions and forged the doctor's name. This clearly was a tough lesson, and one that she certainly will never forget.

Pain education of physicians, regulators, and law enforcement remains the answer. Part of this involves understanding what each of our roles is while never losing sight of the 75 million Americans needing relief of their chronic pain.

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

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3. Amednews.com: Prescriptions for pain care: More physicians, more treatment. Available online at *http://www.ama-assn.org/amednews/2004/12/13/prsa1213.htm.*

OXYCONTIN PATENT DEEMED INVALID IN FEDERAL COURT

A federal appeals court found that Purdue Pharma had deliberately misled the government to win patent protection for the painkiller OxyContin and ruled patents on the drug as unenforceable. The unanimous ruling by a three-judge panel of the US Court of Appeals opens the door for increased generic competition and potentially huge legal awards against Purdue. This is also a victory for Endo Pharmaceuticals (based in Chadds Ford, PA), which is seeking to market a generic form of OxyContin.

OxyContin is a timed-release formulation of oxycodone. Over the last five years, its annual sales have averaged approximately $1.5 billion. The drug has also gained notoriety because of widespread abuse.

Purdue Pharma, based in Stamford, CT, stated that it believed that it had properly obtained patent protection for OxyContin and that it planned to seek to have the court's full panel of 12 judges hear an appeal.

"Purdue believes that the court's decision is contrary to principles of patent law," the company said.

The appellate decision surprised some analysts and lawyers because it upheld the most critical and damaging portion of a trial court ruling against Purdue Pharma last year. In that ruling, Judge Sidney H. Stein of the US District Court in Manhattan found that Purdue Pharma had intentionally deceived patent officials by implying that the company had clinical evidence showing that OxyContin was easier for doctors to use to control pain, when in fact such data did not exist. That finding of "inequitable conduct" invalidated Purdue's patent. The three-judge Court of Appeals panel also found, in reviewing the facts of the case, that Purdue had "failed to disclose material information that was inconsistent with its arguments for patentability."

The financial consequence of the decision could be significant for Purdue. To date, 65 lawsuits have been filed by insurers and others seeking to force the drug maker to disgorge "monopoly," or excessive profits as a result of the improper patent and the higher prices of OxyContin. Any damages awarded against Purdue in those cases could be substantial because OxyContin is an expensive drug and because the law allows for a potential tripling of any awards in such cases as a way of penalizing a manufacturer. (Source: *New York Times*, June 8, 2005.)

GENERIC OXYCONTIN TO BE DISTRIBUTED BY MIAMI-BASED COMPANY

The Ivax Corporation, based in Miami, FL, has begun to distribute four strengths (10, 20, 40, and 80 mg) of a generic version of OxyContin. Ivax's subsidiary, Ivax Pharmaceuticals Inc., will sell an "authorized generic" for OxyContin's manufacturer, Purdue Pharma, LP. The move is intended to counter a generic version manufactured by Endo Pharmaceuticals Inc. Purdue Pharma will make the product for Ivax and receive a share of the profits.

The sudden entry of two generic versions of the controversial painkiller, which has been linked to drug abuse in many parts of the country, comes after a three-judge panel on a federal appeals court in Washington ruled that Purdue Pharma's patents for OxyContin were unenforceable.

Under federal law, Endo gets six months of exclusivity to sell its generic version. But the US Food and Drug Administration also allows the so-called "authorized generics," such as the one to be sold by Ivax, to compete for consumer acceptance. Authorized generics are identical to the brand-name drug and manufactured by the brand-name company, but marketed by another firm. Ivax spokesman David Malina said his company has previously marketed authorized generics for GlaxoSmith-Kline and Johnson & Johnson. (Source: Press release, *http://www.ivax.com*, June 8, 2005; and Ft. Lauderdale Sun-Sentinel, June 9, 2005.)

PHASE III STUDY OF REMOXY FOR OSTEOARTHRITIS

Pain Therapeutics, Inc., a biopharmaceutical company, has completed the enrollment and initiation of dosing in its Phase III study with Remoxy, an abuse-resistant form of long-acting oxycodone.

This double-blind, randomized, multicenter Phase III clinical study will evaluate the safety and efficacy of twice-a-day Remoxy against placebo over a one-month treatment period. More than 200 US patients with moderate to severe pain due to advanced osteoarthritis were enrolled. Pain Therapeutics expects to announce study results in the third quarter of 2005, and also expects to initiate a second Phase III study with Remoxy in the fourth quarter of 2005.

"Pain is a complex and chronic condition in these patients," said Remi Barbier, Pain Therapeutics' President and Chief Executive Officer. "Oxycodone can help, but its potential for abuse and illicit diversion remains of great concern to health officials and law enforcement groups. Remoxy's unique formulation makes it exceedingly difficult and frustrating for drug abusers to extract the oxycodone in Remoxy for purposes of getting high. We believe this feature strongly differentiates Remoxy

from currently marketed forms of long-acting oxycodone."

Remoxy is a novel, abuse-resistant form of long-acting oxycodone. Oxycodone is the active ingredient in Oxycontin, a brand-name drug with sales of nearly $2 billion. Remoxy's unique formulation incorporates several abuse-deterrent properties. (Source: PRNewswire, June 8, 2005.)

OPIATE COCKTAIL MAY REDUCE MORPHINE TOLERANCE

Although morphine is well known as a highly effective analgesic, its clinical use is limited by the development of tolerance and physical dependence, and the requirement for increasing doses to maintain analgesic effect. In the June 7, 2005, issue of *Current Biology*, Li He and Jennifer Whistler of the Ernest Gallo Clinic and Research Center and the University of California, San Francisco (UCSF) report a new study showing that the administration of a drug cocktail containing morphine along with small doses of two versions of methadone, a related opioid, significantly reduced tolerance and dependence in test animals.

The analgesic effects of morphine arise through the interaction of the drug with a specialized protein on the surface of cells, the μ opioid peptide receptor, or MOP receptor. MOP receptors are also activated by other opioid drugs and by endogenous opioids, such as endorphins. Morphine is unique, however, in that unlike other opioids, it does not cause the MOP receptor to be internalized into the cell's interior after activation. It is thought that the activated receptor's persistence at the cell surface leads to a compensatory overactivation of a particular signaling pathway in the cell, a signaling imbalance that is a hallmark of opiate tolerance and dependence. This suggests that the promotion of MOP receptor internalization might prevent such signaling imbalances, and indeed past work from author Whistler indicates that mutant versions of the receptor that are more readily internalized were associated with reduced levels of morphine tolerance in mice.

In the new work, He and Whistler sought a more clinically practical approach to facilitating MOP-receptor internalization in the presence of morphine. Reasoning that because other opioid drugs promote internalization of MOP receptors, and that their presence in combination with morphine may prevent the persistence of activated MOP receptors at the cell surface, the authors developed their drug cocktail containing morphine and two chemical versions of methadone.

He and Whistler found that the combination of morphine with the methadone mixture prevented the activation of cellular signaling pathways associated with morphine tolerance and dependence. They also showed, perhaps most importantly, that whereas rats receiving only morphine develop tolerance to the drug, those rats receiving the morphine/methadone cocktail did not show tolerance. Moreover, past work has not indicated whether the promotion of MOP-receptor internalization could altogether prevent the development of morphine dependence; however, in the new study, the authors discovered that rats receiving the morphine/methadone cocktail experienced reduced morphine dependence.

In light of their findings, the authors propose that an opiate cocktail that combines morphine with small doses of methadone would increase the effectiveness of morphine for the treatment of chronic pain.

This work was supported by a National Institute on Drug Abuse (NIDA) grant and funds provided by the state of California for medical research on alcohol and substance abuse through UCSF to Jennifer L. Whistler. The article is available online at *http://www.current-biology.com*. (Source: Cell Press news release, June 6, 2005.)

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GUEST EDITORIAL

In pain or drug-seeking? Resident continuity clinic, chronic nonmalignant pain, and addiction

Michael Weaver, MD

THE PROBLEM

Pain is the most common complaint with which patients present to physicians' offices. Ten to 16 percent of outpatients seen in a general practice have problems related to drug or alcohol addiction.[1] The distinct problems of pain and addiction are relatively common in medical practice, and are likely to be seen together in some patients. Patients who are addicted to drugs are subject to pain in the same manner as any other patient, so they can also benefit from appropriate treatment for relief of pain.[2] Successful treatment of pain may include prescription of medications with potential for abuse, such as opioid analgesics. Rates of drug abuse, dependence, and addiction among pain patients range from 3.2 to 18.9 percent,[3] which corresponds to prevalence estimates of alcohol and drug addiction among the general population.[4] Rates of abuse of opioid analgesics among patients with pain seen in primary care resident teaching practices are unknown.

Several professional societies have developed consensus statements for acute and chronic pain management in disease populations; however, there is no current standard for assessing, treating, and monitoring patients with chronic nonmalignant pain. This likely owes to the diversity of nonmalignant diagnoses for which chronic pain medications are used and the number of therapeutic options available, including nonpharmacologic therapy, nonopioid pain medications, and opioid analgesics. The result is inconsistency in training physicians to manage chronic nonmalignant pain and, thus, physician practice in assessing, treating, and monitoring these patients. Lack of consistency in evaluation, monitoring, and documentation for prescribing opioids for chronic pain results in higher rates of aberrant medication-taking behaviors among patients of residents in a primary care clinic.

As opioid analgesics have significant potential for harm due to side effects, medication interactions, misuse or abuse, and unlawful practice, there is a lack of comfort and confidence among physicians who have not been adequately trained in the use of these medications. This phenomenon has been labeled "opiophobia."[5] There is no consistent healthcare system approach to the outpatient management of chronic pain. Lack of consistency in the physician and healthcare system approaches to treating chronic pain using opioid analgesics may result in harm to patients from inappropriate prescribing practices. This includes overtreatment, medication interactions, side effects and medication abuse. Additionally, patients may be undertreated and experience severe pain that results in aberrant medication-taking behavior (i.e., pseudoaddiction).[6] Identifying training deficiencies as well as healthcare system variables that lead to inconsistency in opioid prescribing practices is the first step toward developing solutions that can reduce potential harm to patients and improve patient outcomes.

Referral sources for patients with chronic nonmalignant pain are inadequate, especially for those with limited financial resources. Increasingly, primary care resident continuity clinics are the default care centers for these complex patients. Most resident academic practices lack policies that ensure consistent prescribing practices, faculty and residents who are trained in assessing and managing patients with chronic nonmalignant pain, and the infrastructure that supports a multimodal treatment approach. Although the Accreditation Council for Graduate Medical Education (ACGME) guidelines require resident training in pain management, there is no current training standard for continuity clinics. Barriers in this particular setting include time limitations, infrequent patient visits, frequent physician turnover, and patient resistance.

THE CLINIC

With the goal of creating order out of chaos and thereby improving patient outcomes, our institution has attempted to address some of these issues regarding resident education in pain management within the context of a primary care continuity clinic. An initial step was creating a specialty pain clinic within the existing resident continuity clinic. The primary care pain clinic is staffed by an internist who specializes in pain management and addiction medicine, as well as two other internal medicine primary care attending physicians who have special interest in developing expertise in these areas. This allows physicians with experience in pain

management to teach by example, because residents rotate through this primary care pain clinic as part of their ambulatory care educational block. Residents not rotating through the pain clinic still have easy access to a pain expert for advice while in their own continuity clinic for issues that arise in the course of usual patient care, because the pain clinic is physically located within the continuity clinic setting. A second step is having the resident continuity clinic teach attending physicians as they rotate through the specialty pain clinic. This helps them to improve their practice with this common issue and learn clinical pearls to pass along to residents.

THE CURRICULUM

The team that implemented the primary care pain clinic is now in the process of developing a pain curriculum for residents. This is designed as interactive learning in modules for "multiple small feedings of the mind" that can be delivered between patient visits to highlight a few specific clinical points. An example of a module is a simple overview of interpreting urine drug screen results in the context of patients using multiple opioids.

Another key to providing consistent care for patients with complaints of chronic pain while educating residents in proper pain management is putting specific policies into place in the resident continuity clinic. Basic tenets of good pain management practice have been codified in a policy that also provides a set of guidelines for addressing commonly encountered issues. The policy includes monthly visits specifically for evaluating pain in patients on long-term opioids for chronic pain, consistency in obtaining information (including gathering corroborating information in the form of records from previous physicians), standardized forms, use of medication agreements, communication with other treatment providers, and urine drug screening guidelines. In our continuity clinic, the policies have provided guidance where there had been very little previously. Several of the residents have commented that they no longer have the same anxiety regarding visits with their chronic pain patients, and they are actually beginning to look forward to those visits because they have a therapeutic plan in place.

THE RESEARCH

The medical literature reveals very few studies of education of medical residents with regard to management of chronic pain and addiction. Guidelines established by the ACGME require residents to have education about treatment of pain. There has been at least one study on the effect of resident prescribing practices on the inpatient service after the intervention of a palliative care curriculum.[7] Little data are available, however, on prescribing practices of medical residents for chronic pain management in the outpatient setting. A study of opioids and the treatment of chronic pain in a primary care sample did involve medical residents but was not an exclusive description of the population and prescribing habits of a resident teaching clinic.[8] Prescribing practices among residents in a primary care clinic for outpatient management of chronic pain have not been studied previously.

Several clinical research projects have been integrated into the primary care pain clinic at our institution. An initial study underway is a simple chart review of patients with chronic pain on opioids for at least 12 consecutive months. This study will evaluate resident documentation with prescription of controlled substances for pain, and can also be used as feedback for residents and teaching attendings on proper procedures. Another planned study is an outcomes evaluation of the pain management curriculum. Having a research component to the primary care pain clinic provides additional learning opportunities for residents at an academic institution. We hope to report on these research findings in the future in publications such as the *Journal of Opioid Management*.

Our institution has developed an innovative approach to address some of the issues regarding education of medical residents in pain management, appropriate prescribing of controlled substances, and awareness of the impact of addiction on primary care practice. Having a pain clinic within the resident continuity clinic allows for a collaborative educational process and rapid dissemination of teaching points. The residents have responded very positively from the start. We plan to continue to evaluate our progress toward addressing these issues in resident education. If other academic institutions develop similar educational models, the next generation of physicians will be better equipped to deal with chronic pain and their patients will benefit.

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

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Taking back your turf: Understanding the role of law in medical decision making in opioid management (Part I—Overview)

Jennifer Bolen, JD

No clinician should ever feel like they have lost control of their medical decision making, especially when it comes to prescribing opioids and other controlled substances for the management of pain. Unfortunately, in today's healthcare system, clinicians engage in daily battles for control over their pain management practices, often wrestling with 1) healthcare benefit plans that do not provide benefits or cover services adequate or consistent with current, accepted clinical care standards and applicable legal/regulatory materials; 2) inadequate reimbursement for covered benefits and services; 3) lack of education by and information from state licensing board authorities; and 4) a legal/regulatory environment, including bullying and threats by patients, that often leaves the clinician afraid to prescribe opioids. This paper is the first in a series designed to help you understand legal/regulatory underpinnings for opioid management. I discuss only basic concepts due to space limitations and the sometimes complex nature of legal issues. My overall goal for the series is to enable you to make basic adjustments to office policies and medical record documentation so that you can "take back your turf" and prescribe opioids without fear of legal/regulatory sanction.[1]

THREE GENERAL RULES

To take back your turf, you must follow three basic rules—all designed to help you base your medical decision making on current, accepted clinical care standards and accurate and complete documentation, all within the existing legal/regulatory framework for controlled substance prescribing:

- Rule One: Read applicable federal and state guidelines, laws, and regulations related to the use of controlled substances in general and to the use of controlled substances for pain management. Keep these applicable materials in a notebook and update them quarterly.

- Rule Two: Stay current on accepted clinical care standards. Read appropriate journals and document your self-education. Attend continuing education events on the use of opioids for pain management.

- Rule Three: Develop and maintain a compliance program focused on assessing, selecting, and monitoring patients who take opioids for pain management. This compliance program should consider undertreatment of pain issues, your responsibility to minimize the potential for abuse and diversion of controlled substances, and patient accountability. Make sure your documentation incorporates and remains consistent with accepted clinical care standards and the current legal/regulatory framework identified through Rule One.

Obviously there is much more to taking back your turf, and these areas will be developed in future articles. The remainder of this article focuses on Rule One—Identifying Basic Legal/Regulatory Materials on Controlled Substance Prescribing.

IDENTIFYING BASIC LEGAL/REGULATORY MATERIALS ON CONTROLLED SUBSTANCE PRESCRIBING

Clinicians rarely receive formal training in legal/regulatory issues related to controlled substance prescribing, and many clinicians have never read their licensing state's guidelines, laws, and regulations pertaining to these matters. The purpose of Rule One is to help you become familiar with the applicable federal and state guidelines, laws, and regulations related to the use of controlled substances in general and to the use of controlled substances for pain management. After reading these materials, you will use the notebook you make to evaluate your current office policies and medical record documentation on controlled substance prescribing.

There are two basic levels of legal/regulatory authorities for controlled substance prescribing: federal and state

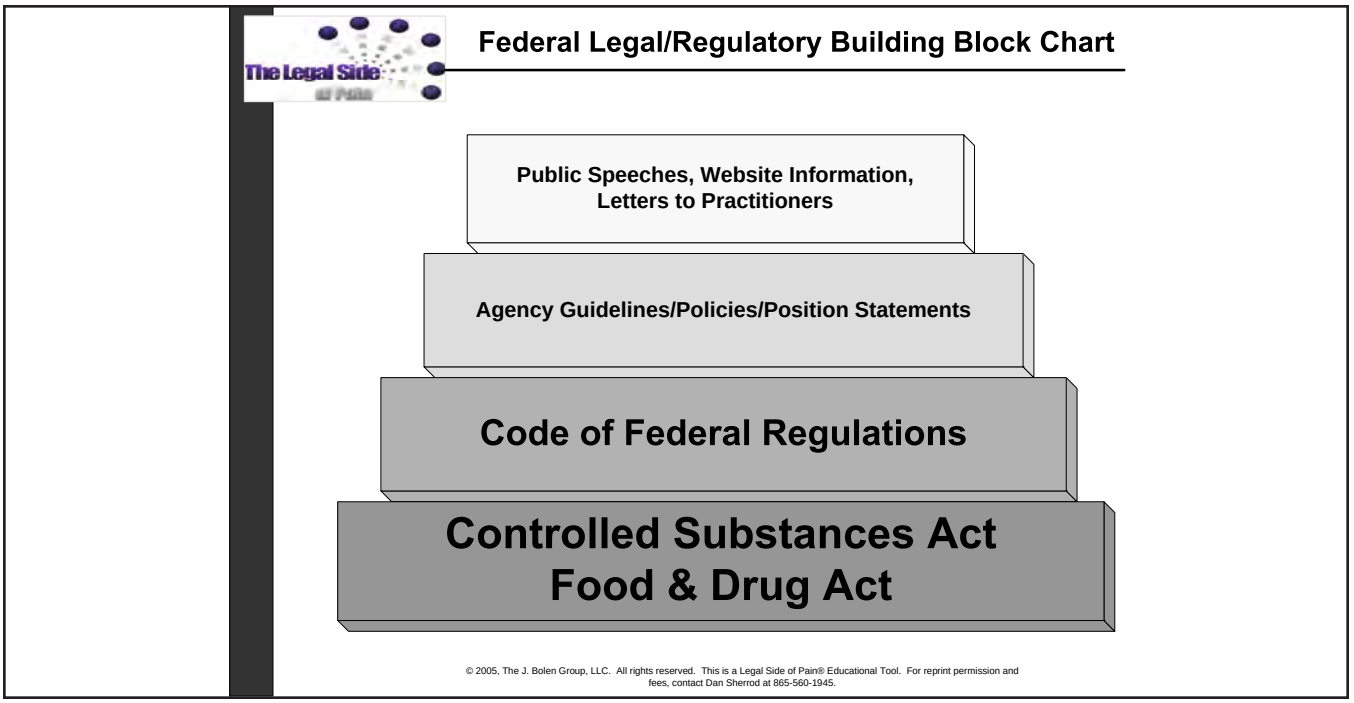

Figure 1. Federal Legal/Regulatory Building Block Chart.

governments and their agencies. Within the federal and state framework, there are three levels of legal/regulatory materials: laws, regulations, and guidelines/position statements [see Figure 1 (federal) and Figure 2 (state)]. I have given very basic definitions of laws, regulations, and guidelines here.

A law is usually embodied in a statute—federal or state. Examples include federal and state Controlled Substances Acts; state Medical, Nursing, and Pharmacy Practice Acts; state Intractable Pain Treatment Acts; and state Electronic Prescription Monitoring Acts. Laws like these form the base of the legal/regulatory pyramid for prescribing controlled substances in general and for pain management. Laws contain provisions that state the potential penalties, including civil and criminal sanctions, for failing to follow them. Laws give permission to federal and state agencies to regulate the flow of controlled substances and, with respect to state licensing boards, to protect the public by setting minimum expectations/standards for the practice of medicine and use of controlled substances for pain management.[2]

A regulation is usually embodied in a code or administrative rule. Regulations (sometimes called "rules") explain a corresponding law and set additional boundaries based specifically on the monitoring/sponsoring agency's interpretation of the law. Examples include the Code of Federal Regulations, which explains the Controlled Substances Act (CSA) of 1970, and gives the US Drug Enforcement Agency (DEA) oversight authority in this area. States have their own versions of regulatory codes explaining state controlled substances acts. Other examples include state administrative regulations governing the operation of licensing boards. Regulations give agencies additional permission to establish guidelines or other items further explaining the regulations. In some cases, state laws and regulations prohibit state licensing agencies from establishing guidelines or any materials. Regulations have the force of law, meaning that violating regulations normally results in sanctions, such as loss of licensing and civil fines and penalties. Some states have both regulations and rules.

A guideline contains an agency's position on a particular subject. Guidelines are not clinical care standards. Rather, agencies use guidelines to establish minimal expectations of licensees related to the specific subject matter. Guidelines are not laws and do not carry legal sanctions, such as civil or criminal penalties, but those who fail to follow guidelines may face administrative sanctions (e.g., licensing restrictions or educational orders) unless one can show good cause for the deviation from or failure to follow guidelines. Despite these basic distinctions between laws and guidelines, lawyers use guidelines to establish the framework of civil and criminal lawsuits, including medical malpractice and wrongful death cases. Guidelines sometimes contain directives and language that are outdated and inconsistent with current clinical care standards. It is important that you determine whether this is the case in your state. If so, I will provide a few ideas on how to handle out-of-date guidelines later in this series. Finally, some states use position statements instead of guidelines, but their meaning and application is essentially the same.

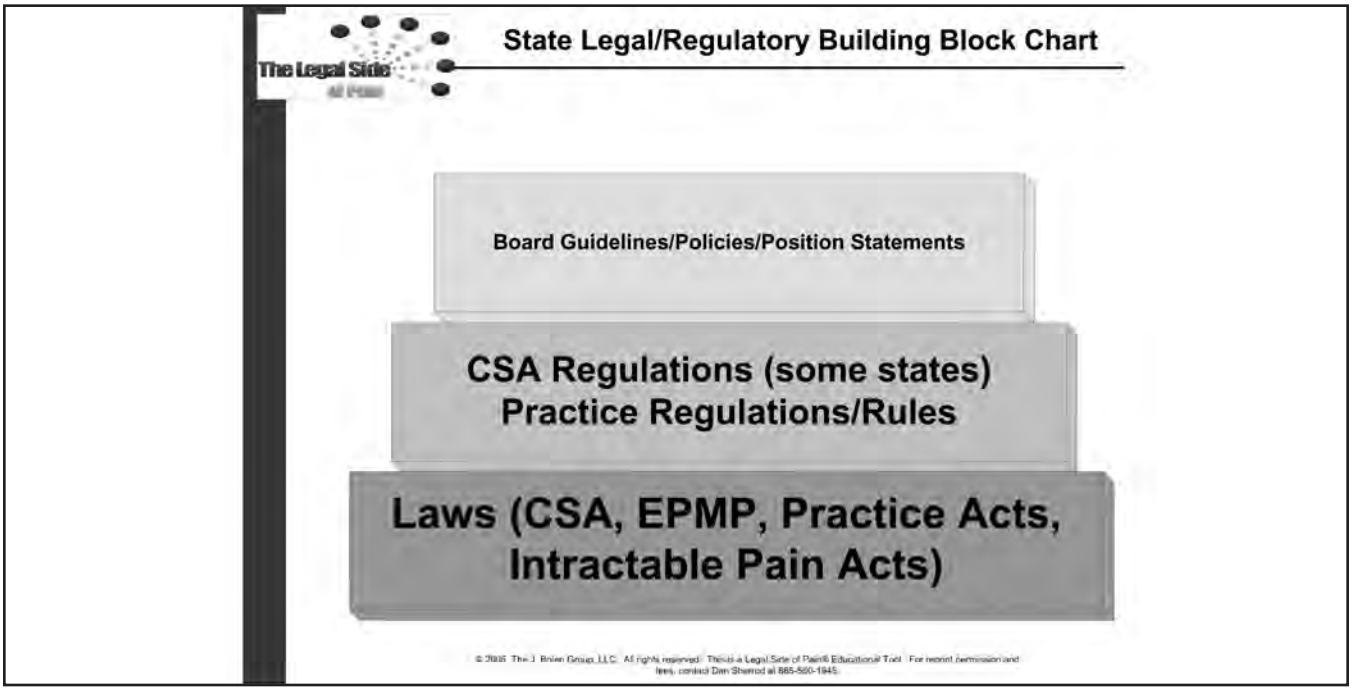

Figure 2.

Basic federal Controlled Substances Act materials and principles

The CSA[3] is the primary body of federal law concerning several actions: administration, dispensing, manufacturing, and prescribing of controlled substances. Congress gave the DEA, a division of the US Department of Justice, the authority to administer the CSA[4] and monitor the flow of controlled substances in this country.

The CSA lists drugs and chemicals subject to DEA control using five different schedules and miscellaneous provisions. The CSA contains the rationale for the classification and establishes different controls relating to the drugs listed in each schedule,[5] and the rationale relates to potential for abuse and psychological and physical dependence.[6] Controlled substances in Schedules II through V have an accepted medical use in the United States, and those in Schedule I do not. You can read more about these issues in the DEA's Pharmacist Manual.[7]

The CSA and supporting federal regulations do not limit the amount of drug that a physician can prescribe at one time. Likewise, the CSA does not establish "maximum doses" for controlled substances, does not limit the "life" of a controlled substance prescription, and does not limit the number of refills for controlled substance prescriptions under Schedules III through V. Some states, however, do have laws and regulations establishing limits in these areas. The CSA prohibits the refill of Schedule II prescriptions, and state law cannot deviate from the federal position here. The DEA has recently stated that the use of multiple Schedule II prescriptions with different fill dates is tantamount to circumventing the federal law prohibiting refills of Schedule II prescriptions.[8]

When a clinician/entity obtains a federal drug registration number, the DEA expects the registrant to follow federal laws, regulations, and policies pertaining to controlled substances. More specifically, the DEA expects clinicians to administer, dispense, and prescribe controlled substances for a legitimate medical purpose, within the usual course of professional practice. The DEA also expects clinicians to minimize the potential for abuse and diversion of controlled substances by adhering to applicable legal/regulatory boundaries and following current, accepted clinical care standards.[9] When a registrant fails to meet these expectations, the DEA has two main avenues through which to pursue the noncompliant registrant: administratively, through the suspension or revocation of the registration; or criminally, through a federal indictment or information, depending on the facts and charges involved. The DEA acknowledges that state licensing authorities and the medical community as a whole define and maintain primary authority over medical decision-making principles. If the state system fails to enforce applicable laws, regulations, and guidelines, the DEA often ends up with these cases and takes action to protect the public from the illegal flow of controlled substances.

The DEA works through a network of Department of Justice attorneys and Assistant US Attorneys (collectively known as "federal prosecutors") when it pursues administrative action against or the criminal prosecution of a registrant.[10] Over the last three years, federal actions

against clinicians have included allegations of healthcare fraud and drug trafficking. These prosecutions have been very public and unfortunately served to divide the pain management community because of the positions taken by law enforcement entities and medical experts. All involved in pain management have a responsibility to minimize the potential for abuse and diversion of controlled substances while ensuring that pain does not go untreated. This balance is difficult for any clinician to achieve under our current healthcare system and legal/regulatory environment. Nonetheless, clinicians must take steps to understand the interplay here if they want things to change.

Basic state materials and principles

States have controlled substances laws (often called "Uniform Controlled Substances Acts" and found in state statutes), and most parallel the federal law. Most state controlled substances laws prohibit nonmedical use of controlled substances. Some states have additional schedules for drugs that present regional issues of abuse and diversion. Some states have electronic prescription monitoring programs (sometimes called "Electronic Prescription Accountability Acts"), and these laws are intended to allow clinicians to use a database to determine whether their patients receive controlled substances from other sources.[11] Some states have Intractable Pain Treatment Acts and Patient Bill of Rights Acts, making it legal for a patient to request opioids for pain management, legal for clinicians to treat intractable pain using high doses of opioids and/or unusual combinations of drugs (but only if the clinician follows the law making up these acts), and legal for a clinician to refuse to treat patients with high doses or unusual combinations, as long as the refusing clinician points the patient in the direction of someone who does.[12]

When state licensing authorities grant healthcare professionals the privilege to practice, these authorities expect them to know and follow a body of guidelines, laws, and regulations, including those related to controlled substances. Most state licensing authorities publish these materials on Web sites and in handbooks. Some state boards even use law examinations to encourage healthcare professionals to learn and follow legal/regulatory materials. The organization of and terminology used by state authorities to refer to these materials varies, and a detailed discussion of these matters is beyond the scope of this paper. Clinicians should take time to identify and read their state's legal/regulatory materials pertaining to the use of controlled substances to treat pain and medical record documentation requirements. It is important to note that the federal law sets the outer parameters for legal matters pertaining to controlled substances.

Your state licensing board expects you to "control the flow of drugs" within the framework outlined by the federal and state legal/regulatory framework and according to accepted clinical standards. In the context of using controlled substances, especially opioids, for pain management, state licensing boards expect clinicians to take and document 1) the patient's history and a physical evaluation, 2) an individualized treatment plan, 3) an informed consent and treatment agreement, 4) a periodic review or patient follow-up justifying the continued use of the controlled substances, and 5) any relevant consultations and referrals.[13] When a clinician loses control of his/her prescribing practices or fails to document the items listed here, he/she is inviting scrutiny from federal and state authorities.

THE LEGAL SIDE OF PAIN® PROVIDER TOOLKIT: LEGAL/REGULATORY NOTEBOOK

Use the checklist associated with this article (Appendix) to assemble a notebook containing basic legal/regulatory material on prescribing controlled substances and pain management. Read through these materials, and find a way to impart the basic principles to your medical staff. Keep a record of your efforts to educate yourself and your staff on these materials. If you have trouble finding some of these materials, use the Legal Side of Pain® Web site (*http://www.legalsideofpain.com*) or contact me for further assistance.

CONCLUSION

When you know where to find applicable legal/regulatory materials on controlled substance prescribing and pain management, it becomes easier to evaluate your current compliance position. Take time to assemble the materials described previously, as you will need them to work through Part II of this series. In all cases, remember to use controlled substances when there are clinical justifications for them, and document your clinical rationale according to the legal/regulatory framework previously discussed in general and more specifically set out by your state licensing authority. Do not fear law enforcement or licensing board intervention, and do not hesitate to ask questions when you do not understand what is required of you from a legal perspective. Remember that pain management is a process tied to the individual circumstances of each patient. Your medical decision making and documentation must reflect this individuality within the legal/regulatory framework of controlled substances and using them to manage pain.

Jennifer Bolen, JD, founder, The Legal Side of Pain®, Knoxville, Tennessee.

NOTES

1. I do not intend for this paper to serve as specific legal advice. Instead, this paper contains a general outline of legal/regulatory responsibilities and assumes that the clinician will only prescribe controlled substances for a legitimate medical purpose within the usual course of professional practice. If you have a specific legal question, make sure you get legal advice from an expert in this area.
2. State licensing board expectations/standards generally are not the same as accepted clinical care standards. However, these expectations/standards set minimal boundaries, and licensees should learn and follow these materials.
3. See Controlled Substances Act, Public Law 91—513, 84 Stat. 1242, codified as 21 USC 801, and sections following (1970).
4. See 21 CFR 1306.04(a) and 1306.07(c) (1996) (authorizing the DEA to monitor and regulate use of controlled substances for medical use).
5. See 21 USC 811-12, 823, and 829.
6. See 21 CFR 1306.
7. Available online at *http://www.deadiversion.usdoj.gov.*
8. The DEA made this comment in the Interim Policy Statement published in the Federal Register on November 16, 2004. The DEA is likely to issue a Final Policy Statement and may clarify its position on this matter.
9. The DEA most recently emphasized this responsibility in the Interim Policy Statement, November 16, 2004, as published in the Federal Register. The formal citation for this document is Federal Register: November 16, 2004, Vol. 69, No. 220, at Notices, Pages 67170-67172. You may find a copy of the Interim Policy Statement online via GPO Access (*http://wais.access.gpo.gov)* using DOCID:fr16no04-82, or at *http://www.legalsideofpain.com* under "DEA Focus."
10. 21 USC 841; Recent cases include United States v. Hurwitz (Eastern District of Virginia), United States v. Knox (Western District of Virginia), United States v. Castle (Eastern District of Tennessee), and United States v. Michael Woodward, et al. (District of South Carolina). Each of these cases involves allegations of illegal drug trafficking through the issuance of prescriptions "outside the usual course of professional practice" and without a "legitimate medical purpose."
11. Not all states use electronic databases, and not all states have these. The terms of use of an electronic prescription monitoring program are described in state law and vary significantly. The DEA has published papers on these monitoring programs, and clinicians can use these papers to compare and contrast the various state programs. See *http://www.deadiversion.usdoj.gov*, and search for "prescription monitoring programs."
12. There are more requirements here. My comments are basic, and clinicians should learn whether their state has an Intractable Pain Treatment Act and/or Patient Bill of Rights and strive to understand the individual requirements of these laws.
13. These requirements will be discussed in more detail later in the series.

APPENDIX. THE LEGAL SIDE OF PAIN® PROVIDER TOOLKIT: CHECKLIST OF BASIC[1] LEGAL/REGULATORY MATERIALS ON CONTROLLED SUBSTANCES AND PAIN MANAGEMENT

Federal materials:

- Front page of DEA Diversion's Web site, at *http://www.deadiversion.usdoj.gov*
- DEA's Interim Policy Statement
- Applicable sections of the Code of Federal Regulations (21 CFR 1306)
- Applicable sections of the US Code (21 USC 801 and following)
- DEA's Pharmacist Manual

State materials:

- Front page of your state licensing board's Web site
- Practice Act
- Controlled Substances Act, including criminal offenses relating to controlled substances
- Intractable Pain Treatment Act (if you have one)
- Patient Bill of Rights (if you have one)
- Electronic Prescription Accountability or Monitoring Act (if you have one)
- Practice Rules/Regulations
- Controlled Substances Rules/Regulations (if you have them)
- If you have them, Guidelines and/or Position Statements on the following:
  - Pain Management
  - Using Controlled Substances (or Opioids/other individual substances) to Treat Pain
  - Physician-Patient Relationship
  - Ending the Physician-Patient Relationship or Patient Abandonment
  - Medical Record Documentation
  - Newsletters containing information about any of the above topics (you may have to search back several years)

Miscellaneous materials:

- Federation of State Medical Boards' Model Policy for the Use of Controlled Substances for the Treatment of Pain
- Federation of State Medical Boards' Model Policy for the Office-Based Treatment of Opioid Addiction

NOTE

1. I have listed only the basic materials in this checklist. You should review your state licensing board's Web site carefully to determine whether other materials may apply to your individual practice situation.

Tramadol: Does it have a role in cancer pain management?

Eric E. Prommer, MD

ABSTRACT

Tramadol (Ultram, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ) is considered a Step 2 analgesic under the World Health Organization's guidelines for the treatment of patients with cancer pain. It is a centrally acting analgesic that has affinity for opioid receptors and influences the action of norepinephrine and serotonin at the synapse. This dual mechanism of analgesia makes it unique among Step 2 agents. It is metabolized by CYP2D6, which increases the potential for drug interactions. Unlike other opioids, it does not cause respiratory depression. Tramadol has been studied in cancer pain and neuropathic pain. It compares well with low-dose morphine as an analgesic. The purpose of this review is to critically examine the pharmacodynamics, pharmacology, drug interactions, and adverse effects of the drug, and, based on the data presented, discuss the drug's role in cancer care.

Key words: tramadol, cancer pain, neuropathic pain, analgesia, pharmacology

INTRODUCTION

Pain is one of the most common and incapacitating symptoms experienced by patients with advanced cancer. Current treatment is based on the World Health Organization (WHO)'s concept of an "analgesic ladder," which involves a stepwise approach to the use of analgesic drugs.[1] Medication potency increases at each step of the WHO ladder, from nonopioid (Step 1; e.g., aspirin and nonsteroidal anti-inflammatory drugs) through weak (Step 2) opioids (e.g., codeine) plus a nonopioid, to strong opioids (Step 3; e.g., morphine) plus a nonopioid analgesic.[2] Tramadol (Figure 1) is considered a Step 2 analgesic under the WHO guidelines for the treatment of patients with cancer pain.[3] Tramadol is a centrally acting analgesic that possesses a dual mechanism of analgesia.[1] It is a racemic compound that has affinity for opioid receptors and also affects the actions of norepinephrine and serotonin at the synapse.[4]

PHARMACODYNAMICS

Tramadol and its chief metabolite (M1) are racemic compounds.[5] The parent compound, the enantiomers of the parent compound, and the enantiomers of the chief metabolite all have different affinities for opioid receptors and have different effects on adrenergic and serotonergic metabolism at the synapse.[6]

Opioid receptor interaction

Tramadol has low affinity for opioid receptors. Comparatively speaking, its affinity for μ-opioid receptors is several thousand-fold less than that of morphine and 10-fold less than that for codeine.[6] The parent compound and its enantiomers have no interaction with the δ-opioid receptor and have an extremely weak interaction with the κ-opioid receptor.[5] Of the metabolites, the + enantiomer of the M1 metabolite has the highest affinity to μ-opioid receptors (Ki 153).[5] The preceding suggests that the relative contributions of tramadol and M1 to human analgesia depend on the plasma concentrations of each compound.

Interaction with the monoaminergic system

It is well known that analgesia can be achieved centrally and peripherally by interference with a variety of neurotransmitter systems (nonopioid mechanisms).[7] Pain control is subject to descending modulation by brainstem groups such as the locus coeruleus/subcoeruleus and the raphe complex, containing noradrenaline (NA) and serotonin (5-HT), respectively.[8] Tramadol has effects on the serotonin and noradrenergic systems.[9] The ability to interfere with the monoaminergic system occurs at concentrations at which it binds to μ-opioid receptors.[10] Interestingly, tramadol has strong structural similarities to the antidepressant venlafaxine, which has effects on NA and 5-HT at the synapse.[11]

Noradrenergic effects

Enantiomers of tramadol and its chief metabolite act differently on the noradrenergic system. In locus coeruleus brain slices, racemic tramadol and its (+)- and (-)-enantiomers significantly increased stimulated norepinephrine

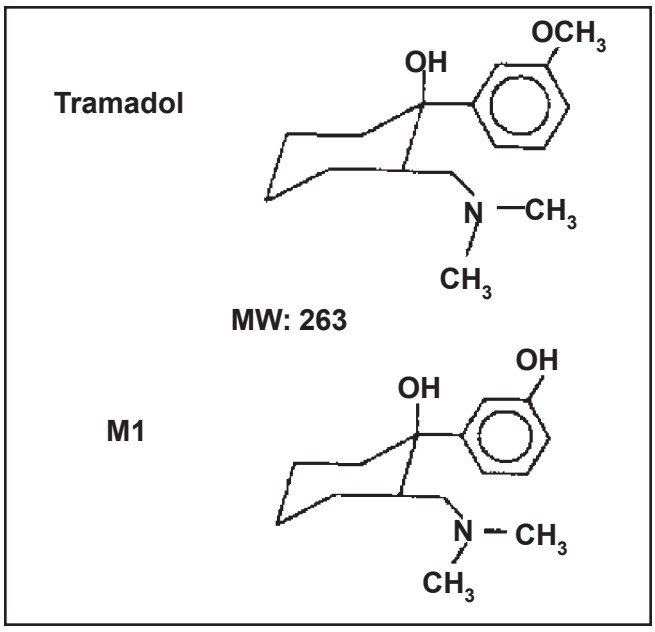

Figure 1. Structure of tramadol and M1 metabolite.

efflux.[12] However, only (-)-tramadol blocked norepinephrine reuptake. The chief metabolite M1 also affects the noradrenergic system. The (+)-M1 metabolite causes NA release, whereas the (-)-M1 metabolite blocks NA uptake.[13] Clinically, administration of α2-adrenoceptor antagonists such as yohimbine can affect the analgesia of tramadol.[14]

Effect on serotonergic pathway

The parent compound, its enantiomers, the chief metabolite, and its enantiomers have different effects on 5-HT at the synapse. Studies involving the actions of (+/-)-tramadol, (+)-tramadol, (-)-tramadol, and O-desmethyltramadol (M1 metabolite) in dorsal raphe nucleus brain slices have revealed that racemic tramadol and its (+)-enantiomer significantly block 5-HT uptake and increase stimulated 5-HT efflux.[7] The (-)-enantiomer of tramadol and its metabolite, M1, are inactive.[7]

Other receptor interactions

Tramadol inhibits muscarinic type-3 receptor function, which primarily mediates smooth muscle contraction and glandular secretion.[15] Tramadol has no effect on arachidonic acid metabolism and does not interact with nonsteroidal anti-inflammatory drugs.[16]

PHARMACOKINETICS/ROUTES OF ADMINISTRATION

Tramadol has been administered orally, rectally, intravenously, intramuscularly, subcutaneously, and via regional anesthesia.[17] The intravenous and rectal forms are unavailable in the United States. In the United States, the immediate-release form is available as tablets and is marketed as Ultracet (conjugated to acetaminophen, Ortho-McNeil Pharmaceutical, Inc.) and Ultram (tramadol immediate release, Ortho-McNeil Pharmaceutical, Inc.). In Europe, the immediate-release form is available in capsules and as an elixir.[18] A fast-release orodispersible tramadol tablet that can be taken without liquids has been developed.[19] A sustained-release form, in capsules, is available in Europe.[20] The sustained-release product available in the United States is in tablet form.

Tramadol is well absorbed orally, with an absolute bioavailability of 75 percent, and has a volume of distribution of approximately 2.7 L per kg.[21] It is only 20 percent bound to plasma proteins. Tramadol is characterized by extensive tissue distribution (apparent volume of distribution, approximately 3 L per kg). The observed plasma half-lives are 6.3 and 7.4 hours for tramadol and M1, respectively.[21] The clearance of tramadol is moderately high (600 mL per min).[22] The t_{max} value for both enantiomers of tramadol occurs two hours after administration, and that for the active (+)-M1 metabolite occurs after three hours.[14] Analgesia for racemic tramadol and the M1 metabolite in humans begins within approximately one hour after administration and reaches a peak in approximately two to three hours. Onset of analgesia for the long-acting form occurs at a median time of five hours.[23] In general, both enantiomers of tramadol and M1 follow a parallel time course in the body after single and multiple doses, although small differences (approximately 10 percent) exist in the absolute amount of each enantiomer present.[21] Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. Oral administration of tramadol hydrochloride tablets with food does not significantly affect its rate or extent of absorption. Tramadol is extensively metabolized after oral administration. Sixty percent of the drug is excreted as metabolites. Elimination is primarily by the hepatic route and partly by the renal route (up to 30 percent of the dose as unchanged drug).[22] After rectal administration of tramadol suppositories, the extent of absolute bioavailability is equal to that of an oral administration of tramadol.[24]

METABOLISM

While cytochromes CYP2D6, CYP3A4, and CYP2B6 are involved in the metabolism of tramadol, the chief cytochrome responsible for metabolism is CYP2D6. Other metabolic pathways involved in the metabolism of tramadol are O-demethylation, N-demethylation, cyclohexyl oxidation, oxidative N-dealkylation, dehydration, and conjugation.[25] These pathways lead to multiple metabolites, of which only one, M1, is of clinical significance. The formation of M1 that results from the

Table 1. Adverse effects of tramadol	
Adverse effect	**Frequency (percent)**
Dizziness/vertigo	26
Nausea	24
Constipation	24
Headache	18
Somnolence	16
Vomiting	9
Pruritus	8
Central nervous system stimulation	7
Sweating	6
Asthenia	6
Dyspepsia	5
Diarrhea	5
Dry mouth	5
Adapted from package insert.	

O-demethylation of tramadol is catalyzed by human hepatic CYP2D6.[26] Patients with dysfunctional CYP2D6 are unable to form M1 (5 to 10 percent white, 18 percent African American, 1 percent Asian).[27,28] The AUC for M1 is significantly decreased in these patients. There is a correlation between the number of functional alleles and the ratio of tramadol to M1.[28] Hui-Chen et al. found the values of C_{max} for the enantiomers of trans-T and M1, and AUC_{0-8} for (-)-trans T, (+)-M1, and (-)-M1 were higher in women than in men.[31]

DRUG INTERACTIONS

Dependence of the metabolism of tramadol on CYP2D6 (and to a lesser extent CYP3A4) for the formation of its chief metabolite leads to concerns that interactions with drugs that inhibit this cytochrome may lead to clinically significant toxicities or alterations in analgesic properties. Important drugs used in palliative care that are metabolized by CYP2D6 are codeine, oxycodone, hydrocodone, haloperidol, tricyclic antidepressants, risperidone, and phenothiazines.[29] Important inhibitors of CYP2D6 are quinidine, fluoxetine, and its metabolite norfluoxetine.[29] In vitro studies involving liver microsomes suggest that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine,[30] as well as amitriptyline and quinidine,[22] can inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1.[22] The actual pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Therefore, until further information is available, caution should be used when tramadol is administered with other drugs that inhibit CYP2D6.

A major interaction of clinical importance can occur when tramadol is given with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors. This can result in the serotonin syndrome. The serotonin syndrome is characterized by a symptom triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction; the absence of hyperthermia and rigidity as well as the presence of a normal creatine phosphokinase level distinguish it from the neuroleptic malignant syndrome.[32] The serotonin syndrome has been reported when tramadol has been administered concomitantly with venlafaxine,[33] citalopram,[34] sertraline,[35] fluoxetine,[36] paroxetine,[37] and monoamine oxidase inhibitors such as phenelzine and isoniazid.[38,39] Not surprisingly, it also has occurred with newer antidepressants such as mirtazapine.[40] The overall incidence of the serotonin syndrome is rare, but should be watched for when other serotonin-modifying drugs are given.

Administration of α-adrenergic blockers can decrease the duration of analgesia of tramadol.[14] Administration of serotonin inhibitors such as ondansetron has lead to increased tramadol requirements, probably by blocking spinal 5-HT (3) receptors.[41] Carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine, which is metabolized via CYP34A.[21] Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of tramadol.[21] Case reports of Coumadin potentiation by tramadol have not been substantiated.[42,43]

Table 2. Adverse effects of tramadol versus morphine (frequency)		
Adverse effect	**Morphine**	**Tramadol**
Nausea/vomiting	15 to 30 percent	24 percent
Constipation	40 to 70 percent	24 percent
Sedation	20 to 60 percent	16 percent
Cognitive failure	Mild common; severe unknown	Unknown
Myoclonus	With high doses	Not reported
Pruritus	2 to 10 percent	8 percent

Table 3. Tramadol and chronic malignant pain			
Author	**Number of patients**	**Intervention**	**Outcome**
Tawfik, 1990[66]	32	Patients treated with tramadol (mean dosage, 217 mg per day) or with sustained-release morphine (mean dosage, 50 mg per d) for up to eight weeks	Morphine produced better analgesia but was associated with more intensive adverse effects; crossover study of 20 patients suggests same analgesic efficacy as morphine but fewer adverse effects
Osipova, 1991[67]	124 (cancer patients)	98 patients receiving tramadol (mean dosage, 368 mg per day) and 26 patients receiving sustained-release morphine (mean dosage, 69 to 96 mg per day) for relief of severe cancer pain	Morphine produced better analgesia but was associated with more intensive adverse effects
Wilder-Smith, 1994[49]	20 (cancer patients)	Doses of oral solutions of tramadol or morphine were individually titrated in a double-blind, randomized, crossover study; crossover was after day four	Pain intensity was similar with morphine and with tramadol; relative potency of 4:1 with oral dosing; adverse effects per person were lower on the fourth day with tramadol with respect to nausea and constipation
Bono, 1997[68]	60 (44 men, 16 women; average age, 61.4 years; controlled crossover trial with randomized sequences; severity of pain measured before and during the four hours after taking study drugs)	Tramadol was prescribed at the daily dosage of 300 mg orally, and buprenorphine at 0.6 mg per day as a sublingual preparation	Buprenorphine and tramadol had a similar analgesic effect, although tramadol had a quicker onset of action
Brema, 1996[69]	131 (adults with neoplastic pain no longer responsive to nonsteroidal anti-inflammatory drugs)	Tramadol (one 100 mg slow-release tablet every eight to 12 hours), or buprenorphine (one sublingual 0.2 mg tablet every six to eight hours); mean treatment period was 58 days for tramadol and 51 for buprenorphine	Similar pain control acutely for both drugs; superior pain control for tramadol after one week
Grond, 1999[60]	1,658 (cancer pain, retrospective study)	810 patients received oral tramadol for a total of 23,497 days, and 848 patients received oral morphine for a total of 24,695 days	Constipation, neuropsychological symptoms, and pruritus were observed significantly more frequently with low-dose morphine; pain intensity did not differ between arms
Petzke, 2001[20]	146 (moderate-to-severe cancer pain and insufficient pain relief from nonopioid analgesics)	Treated with slow-release tramadol for initial dose finding and as long-term treatment; immediate-release tramadol and a standard nonopioid analgesic (1,000 mg naproxen daily) were provided for treatment of breakthrough pain	Number of patients with good/complete pain relief increased from 43 percent after week one to 71 percent after week six, with maximum daily dosages of tramadol up to 650 mg; most (70 percent) still needed less than 400 mg tramadol per day; common adverse effects such as fatigue, dizziness, and constipation decreased in frequency; other adverse events such as nausea, vomiting, and sweating did not change

Table 4. Tramadol and neuropathic pain				
Author	**Type of trial**	**Number of patients**	**Intervention**	**Outcome**
Harati, 1998[61]	Double-blind, randomized, controlled trial	131 with painful diabetic neuropathy	Treated with tramadol (n = 65) or placebo (n = 66), administered as identical capsules in divided doses four times daily	Tramadol, at an average dosage of 210 mg per day, was more effective than placebo for pain control
Boureau, 2003[62]	Multicenter, randomized, double-blind, parallel-group study	127 with post-therapeutic neuralgia	The dosage of tramadol could be increased from 100 mg per day to 400 mg per day compared with placebo	Better pain relief (via pain measurement over time) over six weeks; tramadol versus placebo
Sindrup, 1999[63]	Double-blind, placebo-controlled and crossover	45 with painful polyneuropathy and allodynia	Tramadol slow-release tablets, titrated to 200 to 400 mg per day, versus placebo	Pain, paraesthesia, and touch-evoked pain levels were lower with tramadol than with placebo, as were ratings of allodynia (0 vs. 4, p = 0.012)

ADVERSE EFFECTS

Common adverse effects with frequencies greater than 5 percent are listed in Table 1. The incidence of adverse effects is higher in the clinical trial data than in outpatient postmarketing surveillance.[44]

Central nervous system

Central nervous system (CNS) adverse effects are common and include drowsiness, dizziness, headache, and agitation.[21] Headache with tramadol differs from that of other opioids and may be related to serotonin blockade. Rare CNS adverse effects include mania[45] and musical hallucinations.[46] Seizures have occurred after the first therapeutic dose of tramadol. However, seizures have occurred when other factors predisposing to seizures are present, such as concomitant administration of other medications that lower the seizure threshold, patients with a history of epilepsy, and other patients at risk for seizures.[47] Tramadol may cause or exacerbate cognitive impairment in patients older than 75 years.[48]

Gastrointestinal

The most frequent adverse gastrointestinal effects in clinical trials of tramadol were nausea (24 percent), vomiting (9 percent), and constipation (24 percent); however, postmarketing surveillance suggests a lower incidence (4.2 percent and 0.5 percent, respectively) for nausea and vomiting.[21,44] Tramadol has less effect on colonic transit time than morphine.[49] There is no effect of intravenous tramadol on bile duct sphincter.[50]

Genitourinary

Urinary retention or urinary frequency has been reported in up to 5 percent of patients taking therapeutic doses of tramadol.[51]

Respiratory

Tramadol was not associated with respiratory depression and does not suppress the hypoxic ventilatory response.[52]

Other adverse effects

Diaphoresis has been reported in up to 20 percent of patients treated with oral or parenteral tramadol.[4] Fatigue as well as skin reactions have been reported with tramadol use.[20,53] Tramadol has been associated with exacerbation of attacks of acute porphyria.[54] A small percentage (0.1 percent) of the administered dose passes into breast milk.[55]

COMPARISON WITH MORPHINE

Table 2 compares the adverse effects of morphine with those of tramadol. In contrast with morphine, tramadol has not been shown to cause myoclonus or hyperalgesia. Although it reportedly causes less histamine release, pruritus can still occur (Table 1).[56] Tramadol is not associated with respiratory depression and does not suppress hypoxic ventilatory response.[52] Tramadol may be less immunosuppressive than morphine.[57] Tramadol has minimal cardiovascular adverse effects.[22]

Table 5. Cost comparison of Step 2 opioids		
Drug	**Average wholesale price (generic)**	**Average wholesale price (trade name)**
Ultram 50 mg	$0.84	$1.25
Ultracet	$1.07	$1.14
Codeine 30 mg	$0.35	–
Tylenol #3	$0.05	$0.36
Tylenol #4	$0.08	$0.80
Vicodin	$0.45	$0.84
Oxycodone 5 mg	$1.14	–

Withdrawal has been reported with chronic use of tramadol, but because of the drug's weak interaction with opioid receptors, it is considered a nonhabit- and nondependence-forming analgesic and is not classified as a controlled substance by the US Food and Drug Administration.[58,59] Surveillance studies and case reports suggest that abstinence symptoms can occur. In most cases, the withdrawal symptoms consisted of classic opioid withdrawal, but in some cases were accompanied by withdrawal symptoms not normally observed in opiate withdrawal, such as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and unusual sensory experiences such as numbness and tingling in one or more extremities. These cases were more likely to occur after abrupt cessation of intake, especially when the compound had been taken for more than one year. Therefore, patients should be advised of such an effect whenever they decide to stop intake or their physician is planning to switch them to another medication. To avoid abstinence symptoms, doses should be slowly tapered.[59]

TRAMADOL FOR CANCER PAIN

Table 3 reviews the studies involving tramadol and cancer pain. Grond and colleagues[60] compared the efficacy and safety of high dosages of oral tramadol (= 300 mg per day) with low dosages of oral morphine (= 60 mg per day). Patients were included in this nonblinded and nonrandomized study if the combination of a nonopioid analgesic and up to 250 mg per day of oral tramadol was inadequate. The average dosage of tramadol was 428 ± 101 mg per day (range, 300 to 600 mg per day); the average dosage of morphine was 42 ± 13 mg per day (range, 10 to 60 mg per day). The mean pain intensity was similar between the two study groups. Constipation, neuropsychological symptoms, and pruritus were observed significantly more frequently with low-dose morphine; other symptoms had similar frequencies in both groups.

In a study of patients with moderate to severe cancer pain and insufficient pain relief from nonopioid analgesics, Petzke and colleagues[20] examined slow-release tramadol for initial dose findings and as a long-term treatment. Immediate-release tramadol was provided for the treatment of breakthrough pain, in addition to oral Naprosyn 500 mg twice a day. Ninety of 146 patients (62 percent) completed the six-week trial. Average and maximal pain intensity decreased from day one to day four. The number of patients with good and complete pain relief increased from 43 percent after week one to 71 percent after week six. The maximum daily dosages of tramadol were up to 650 mg. However, 70 percent of the patients still needed less than 400 mg tramadol per day in week six. The frequency of some common adverse effects of opioids such as fatigue, dizziness, and constipation, decreased during the six weeks. The frequency of other adverse events such as nausea, vomiting, and sweating did not change. Slow-release tramadol provided fast and efficient pain relief in almost two-thirds of patients during initial dose finding and during long-term treatment.

TRAMADOL FOR NEUROPATHIC PAIN

Table 4 summarizes the studies involving tramadol and neuropathic pain. Tramadol was better than placebo for pain control in diabetic neuropathy and postherpetic neuralgia.[61,62] In patients with polyneuropathy, Sindrup found tramadol to be effective for allodynia.[63] Harati found that use of tramadol in diabetic neuropathy was associated with improved quality of life.[61] There are no data available for neuropathic pain in the cancer setting.

PHARMACOECONOMICS

The average wholesale price of Ultram (tramadol 50 mg) is $1.21 per tablet. The price of generic tramadol is $0.84. The cost of Ultracet is $1.07. Table 5 compares the cost of tramadol with other Step 2 agents.

SCHEDULE OF ADMINISTRATION

The oral dosage of tramadol is one or two 50-mg tablets up to four times daily; maximum dosage is eight tablets per day. The fixed combination of tramadol/acetaminophen is available as tablets containing 37.5/325 mg with a recommended dosage of two tablets every four to six hours. The extended-release formulation of tramadol hydrochloride (tramadol ER), given as 100 mg twice daily, is considered therapeutically equivalent to the immediate-release formulation of 50 mg administered four times daily. If kidney (creatinine clearance below 30 mL per min) or hepatic function is severely impaired, some dosage reduction (approximately by 50 percent) or extension of the dosage interval should be considered.[22]

The relative potency of tramadol to morphine is approximately 1:5 to 1:4 for the oral route and about 1:10 for the subcutaneous and intravenous routes.[64] The oral dose in pediatric patients is of 1 to 2 mg per kg every four to six hours.[65]

DISCUSSION

Tramadol is a centrally acting analgesic with a dual mechanism of action. As a Step 2 agent, it has affinity for opioid receptors and has a potent metabolite with strong affinity for the μ-opioid receptor. It is also unique in that part of its mechanism of action also involves effects on the uptake/release of serotonin/norepinephrine at the synapse. This makes it more versatile than the currently available Step 2 agents and potentially useful for neuropathic pain. Clinical trials suggest efficacy in neuropathic pain and equivalency with low-dose morphine in cancer pain. The study comparing tramadol with low doses of morphine was nonblinded and nonrandomized. Adverse effects were comparable or better than those of low-dose morphine. Offsetting the increased versatility of the drug is the potential for drug interactions because of its dependence on CYP2D6 for metabolism. The drug appears to have a ceiling effect, whereupon adverse effects occur at increased frequency. For now, it represents an option for patients with pain not responsive to nonopioid analgesics. Superiority over low-dose Step 3 agents requires further testing in randomized clinical trials.

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The metamorphosis of hydromorphone

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INTRODUCTION

Hydromorphone hydrochloride, one of the oldest of the extant opioid analgesics, has been in clinical use for more than 70 years. Its use by the oral route in chronic pain and hospice/palliative medicine settings has been limited, however, largely owing to its relatively short duration of action. With the recent US Food and Drug Administration (FDA) approval of a once-daily extended-release formulation of the drug (Palladone, Purdue Pharma LP, Stamford, CT), hydromorphone joins morphine, oxycodone, and fentanyl as the only extended-release opioids available on the United States market. Here, we review the history, pharmacokinetics, and other relevant issues concerning this invaluable opioid, and also discuss the role of the new formulation in the management of chronic pain.

HISTORY

Hydromorphone [also Dilaudid (Knoll Laboratories, Mount Olive, NJ), dihydromorphinone, dihydromorphenone, morphinone] was synthesized, patented, and clinically introduced in post–World War I Germany.[1] It was only the second semisynthetic derivative of morphine (Figure 1). The first, diacetylmorphine (heroin), introduced by Bayer Laboratories in 1898, was outlawed by Congress in 1924.[2,3] By the time hydromorphone was introduced in the United States in 1932, it had already been the subject of more than 200 scientific papers in Europe.[4] Championed by Alvarez of the Mayo Clinic, it was purported to be superior to morphine, the only other strong opioid at the time, in most essential respects: less nausea and vomiting, constipation, euphoria, tolerance, respiratory depression, sedation, and most importantly, addiction potential.[4-7] Indeed, it was even briefly lauded as a possible cure for morphine addiction. An early newspaper article[8] described the new drug as follows:

> "AN IMPORTANT NEW DRUG
>
> "Di-hydro-morphinone-hydrochloride. "That's it. The Mayo Clinic at Rochester developed it, the word and the drug, for it means a drug, a pain relieving drug, five times as potent as morphine, as harmless as water and with no habit forming qualities.
>
> "The medical journals say it is particularly useful in the operation of cases where other drugs seem to offer no relief from pain. Unlike morphine, there are no pleasurable sensations to its use, however, and if the doctors reckon correctly its use may go far toward curing addicts of the morphine habit."
>
> *Montgomery (AL) Advertiser*, Dec. 18, 1932

From 1929 to 1939, the National Research Council's Committee on Drug Addiction conducted exhaustive research on the morphine molecule and its analogs, producing more than 150 semisynthetic and more than 300 synthetic compounds, of which more than 30 were tested clinically.[9] None of these drugs—including hydromorphone—proved to be the "holy grail" of opioids: a morphinelike analgesic with few side effects and little or no potential for addiction. As the search for the perfect analgesic continued, hydromorphone research decreased dramatically, and it took its place among a growing number of opioid analgesics.[10]

The social upheaval that characterized the 1960s was accompanied by a surge in drug abuse that would reach ever-higher peaks in the 1980s.[2] In 1971, President Nixon named drug abuse "public enemy number one," and declared a war on drugs. As if rising to meet this challenge, hydromorphone would begin to chart a parallel history as an opioid of choice for illicit use. (Ironically, Elvis Presley, enlisted by Nixon in his drug war, and made a "Federal Agent-at-Large" in the Bureau of Narcotics and Dangerous Drugs, was probably addicted to hydromorphone at the time he served. When he died in 1977, the drug was among an assortment of pharmaceuticals found in his body.[11,12])

Hydromorphone tablets, known by abusers as dillies

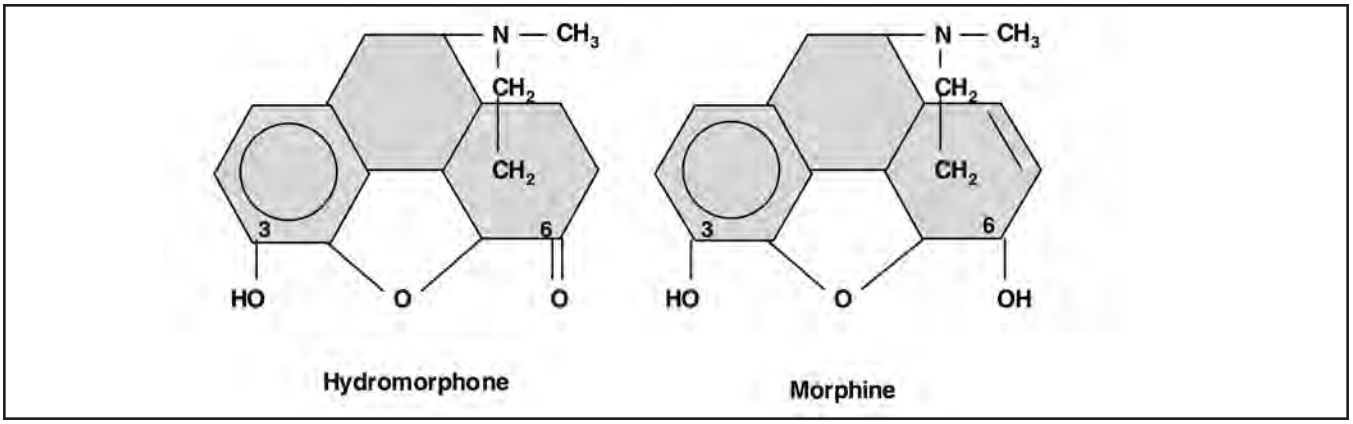

Figure 1. Molecular structures of hydromorphone and morphine.

(also dust, D, little D, juice, smack, footballs, and, tellingly, drugstore heroin), have acquired significant street value, in part because the rush of the injected drug is described as being akin to that of heroin.[13,14] In 1971, approximately 1 percent of patients admitted to drug treatment facilities in Miami-Dade (FL) were hydromorphone abusers. By 1974, the figure had risen to 10 percent. More than 90 percent of these hydromorphone abusers were injecting the oral formulation of the drug, and 83 percent were also abusing heroin.[15] In 1976, more than 50 percent of patients applying to another south Florida drug treatment program were addicted to hydromorphone.[16] Apparently, this changed little by 1984.[17] The drug became a feature of popular culture—the subject of television (Hill Street Blues 1983 episode, "Praise Dilaudid"), cinema (Gus Van Sant's 1989 "Drugstore Cowboy"), and popular music (Velvet Acid Christ's 1999 "Dilaudid (postponed)"). The problem continues to the present, with diversion of hydromorphone reported by Drug Enforcement Agency (DEA) field offices in many large US cities.[18]

The drug sells for a premium on the street, with current prices ranging from $5 to $100 per tablet (2, 4, 8 mg), depending on the geographic region.[18,19] In comparison, the street price for the more available OxyContin (Purdue Pharma LP) generally does not exceed $1 per milligram.[20] According to the DEA, the number of hydromorphone-related emergency room visits increased by approximately 300 percent from 1996 (937) to 2001 (2,667)[18]—about the same as oxycodone, but far fewer than fentanyl.[21] To put these numbers into context, the abuse of the Schedule III hydrocodone [e.g., Lortab (UCB Pharma Inc., Smyrna, GA), Vicodan (Knoll Laboratories)] exceeds that of hydromorphone and each of the other Schedule II opioids, and the abuse of illicit drugs greatly exceeds that of all prescription opioids.[21]

Of note, it has recently been reported that generic hydromorphone—as opposed to brand-name Dilaudid—has little street value.[22] The generic formulation is apparently more difficult to extract from its inert, bulk-adding filler (i.e., is poorly water soluble, even when heated to the boiling point), and therefore more likely to become blocked in the hypodermic needles of intravenous abusers.[13,22]

And yet, hydromorphone is an excellent opioid analgesic and an invaluable part of the pain pharmacopoeia. As a pure μ-receptor agonist, it has no analgesic ceiling. It is one of the most potent oral opioids—roughly five times as potent as morphine—a feature that compensates for a relatively low oral bioavailability. Its oral use is increasing: the number of hydromorphone prescriptions more than doubled from 1998 (470,000) to 2003 (970,000), owing in part to a parallel decline in OxyContin prescriptions.[18] Its intravenous use is increasing as well, as meperidine [Demerol (Sanofi Winthrop, Morrisville, PA)] begins its fade into obsolescence.[23] Successful use by a variety of other routes, including rectal, subcutaneous, intramuscular, epidural,[24] intrathecal,[25] and inhalational,[26] has also been reported. Phase I studies of its intranasal use are underway.[27]

PHARMACOKINETICS

Hydromorphone has relatively poor oral bioavailability due to high hepatic first-pass metabolism,[28] but this is offset by its relative potency (Table 1). Its short elimination half-life (i.v., 2.5 to 3.0 h; p.o., 2.5 to 4.0 h) necessitates frequent administration.[29] It is metabolized in the liver, primarily via glucuronidation, to hydromorphone-3-glucuronide (H3G) in a manner analogous to that of the metabolism of morphine to morphine-3-glucuronide (M3G), with traces of dihydromorphine and dihydroisomorphine.[28] None of the metabolites are believed to have significant analgesic action. H3G, however, is neuroexcitatory—10 times more so than its parent compound and 2.5 times that of M3G—although it has not yet been determined how readily this metabolite crosses the blood-brain barrier.[30,31] Steady-state concentrations of H3G may exceed that of the parent compound by 20- to 50-fold.[31] The metabolites, along with approximately 6 percent

Table 1. Common opioid equivalents		
	Intravenous (mg)	**Oral (mg)**
Hydromorphone	1.2	6
Morphine	10	30
Oxycodone	N/A	20
Methadone*	1 – 3	2 – 6
Meperidine	75	300

* Methadone conversion ratios remain to be further elucidated and conversions should be done with caution. See, for example, Lawlor PG, Turner KS, Hanson J, et al.: Dose ration between morphine and methadone in patients with cancer pain. *Cancer.* 1998; 82(6): 1167-1173.

unchanged hydromorphone, are excreted via the kidney and accumulate in renal insufficiency.[28,32]

CHOOSING HYDROMORPHONE

There are several reasons to consider the use of hydromorphone for the treatment of moderate to severe pain:

1. Converting patients from parenteral to oral opioids (and vice versa) is simplest when the opioid moiety remains the same. Thus, for example, for a patient who has done well on intravenous hydromorphone—with an acceptable balance between analgesia and side effects—and who requires continued therapy with a strong oral opioid, it is clinically simple and pharmacodynamically logical to continue with oral hydromorphone, using a 5:1 oral-to-parenteral conversion ratio.[33]

2. Similarly, in patients with moderate to severe pain requiring a strong opioid analgesic, and with a history of good response to hydromorphone, it is logical and appropriate to initiate therapy with this drug.

3. For patients who have responded well to hydrocodone (Vicodan, Lortab, and others) for moderate pain, they may do well with hydromorphone for severe pain. The hepatic metabolism (via the CYP2D6 enzyme system) of hydrocodone yields hydromorphone as an active, O-demethylated metabolite, with 30 times the μ-receptor binding affinity of the parent compound. It has been suggested that hydromorphone contributes to the analgesic effect of hydrocodone.[34-36]

4. Hydromorphone, thus far, appears to have no significant stigma among the general population and may be more acceptable to patients with a legitimate need for strong opioid therapy, but who balk at the mention of some of the Schedule II agents. This may seem a small matter, but opioids acquire baggage that may discourage their appropriate use by patients in pain. OxyContin is only the most recent and devastating example of this. Others, including methadone, and, indeed, even morphine have their own baggage. For this reason it is inconceivable that heroin, a fine opioid (and widely used in the treatment of cancer pain in the United Kingdom), could ever be accepted as a legitimate analgesic in the United States.

5. Individual variability in opioid response to satisfactory analgesia as well as intolerable side effects are commonly seen and likely owe to a number of factors including genetic polymorphism, differing pain mechanisms, and accumulation of opioids and/or their metabolites.[33,37] Hydromorphone can thus be a valuable option for patients who do poorly on other opioids. For example, a retrospective study of 55 palliative care patients who underwent opioid rotation because of intolerable side effects found that 80 percent of patients rotated from morphine to hydromorphone experienced statistically significant symptom improvement, as measured by visual analog scale (for pain, nausea, and drowsiness), Mini-Mental Status Examination (for cognitive dysfunction), and physician and nursing notes.[38] Another retrospective study of 80 cancer patients who underwent opioid rotation (most from morphine to hydromorphone)

Table 2. Approximate palladone conversion ratios				
Palladone (mg) Oral CR hydromorphone	12 q 24 h	16 q 24 h	24 q 24 h	32 q 24 h
MS Contin (mg) Oral CR morphine	30 q 12 h	45 q 12 h	60 q 12 h	90 q 12 h
Avinza, Kadian (mg) Oral CR morphine	60 q 24 h	90 q 24 h	120 q 24 h	180 q 24 h
OxyContin (mg) Oral CR oxycodone	20 q 12 h	30 q 12 h	40 q 12 h	60 q 12 h
Duragesic (mcg/hr) Transdermal CR fentanyl	25	25 – 50	50	75

because of side effects and/or lack of effective analgesia, found that 73 percent clinically improved, as measured solely by physician and nursing notes.[37]

6. In settings in which urine opioid screening is contemplated, hydromorphone—but not, for example, hydrocodone, oxycodone, or fentanyl—will reliably screen positive in available field test kits.[18]

Likewise, the following are relative contraindications to the use of hydromorphone:

1. Allergy (absolute contraindication) or intolerance to hydromorphone favors use of an alternate opioid analgesic.

2. Renal insufficiency reduces the clearance of the putative neuroexcitatory metabolites H3G and the 6-hydroxy epimers.[32] As noted previously, steady-state plasma levels of H3G may exceed that of the parent drug by 20- to 50-fold.[31] In patients with renal insufficiency this ratio may exceed 100.[31] Hydromorphone, however, has been used successfully in patients with renal insufficiency as well as those on dialysis.[38,39] In this population, caution should be used and patients should be closely monitored.[39]

3. Hepatic insufficiency may decrease metabolism and elimination of hydromorphone.[28] Caution should be exercised in this patient population.

4. Morphine-induced neuroexcitation is thought to owe to M3G accumulation. Because of the structural similarity between and M3G and H3G, strong consideration should be given to opioid rotation (i.e., substitution) to a structurally dissimilar opioid.[30]

5. A history of drug addiction is an important consideration. Hydromorphone has been shown to be more "likeable" than morphine (at equianalgesic doses) to addicts and normal volunteers.[40,41] This may be related to hydromorphone's greater lipid solubility, which leads to more rapid passage across the blood-brain barrier.[42]

STUDIES OF CONTROLLED–RELEASE HYDROMORPHONE

There are several reasons to consider using a controlled-release opioid formulation for stable, moderate to severe pain. The major drawback of hydromorphone has been its short elimination half-life, necessitating frequent administration. Minimizing the dosage frequency is more convenient for patients and facilitates uninterrupted sleep. It also increases treatment compliance, which in turn improves consistency of analgesia and quality of life.[43] For patients with a history of substance abuse, controlled-release products may decrease the positive reinforcement associated with the frequent, as-needed use of immediate-release opioids.[42]

Until this year, only three non-parenteral opioids were available in the United States in controlled-release forms: morphine [MS Contin (Purdue Pharma LP), Kadian (Astra Zeneca Pharmaceuticals LP, Wilmington, DE), Avinza (Ligand Pharmaceuticals, San Diego, CA), and generic], oxycodone (OxyContin and generic), and transdermal fentanyl (Duragesic, Janssen Pharmaceutical Products LP, Titusville, NJ). Hydromorphone is now the fourth. Controlled release hydromorphone formulations, however, are not new—they have been available as twice-daily formulations in Canada and Europe since the 1990s.

Table 3. Listing of retail prices for medications				
Palladone #30	12 q 24 h $237.29	16 q 24 h $278.09	24 q 24 h $385.59	32 q 24 h $487.49
MS Contin #60	30 q 12 h $130.79	45 q 12 h	60 q 12 h $248.69	100 q 12 h $368.899
Morphine (generic) #60	30 q 12 h $69.69	45 q 12 h	60 q 12 h $183.49	100 q 12 h $270.09
Avinza #30	60 q 24 h $207.59	90 q 24 h $312.69	120 q 24 h $343.59	180 q 24 h
Kadian #30	60 q 24 h $198.99	100 q 24 h $276.99	120 q 24 h	180 q 24 h
OxyContin #60	20 q 12 $192.29	30 q 12	40 q 12 $341.39	60 q 12
Duragesic #10	25 q 72 h $192.69	25 – 50 q 72 h	50 q 72 h $343.39	75 q 72 h $486.39
*Walgreens Pharmacies, Jacksonville, FL, 1/24/05.				

REPORTS OF IMMEDIATE- AND CONTROLLED-RELEASE HYDROMORPHONE

The first report on the Canadian product appeared in 1994. In this multicenter study, 48 patients with stable, severe cancer pain were enrolled in a randomized, double-blind, double-dummy crossover evaluation comparing controlled-release with immediate-release hydromorphone. The results showed no significant differences between the two formulations in daily opioid dose, rescue medication use, pain intensity, side effects, or patient drug preference.[46] Of note, three of the investigators on the study were employed by the drug manufacturer, Purdue Frederick.

A report of another Canadian controlled-release hydromorphone, this one a Knoll Pharmaceuticals product (Eduardo Bruera, MD, *personal communication*, 11/10/04), appeared in 1996. In this multicenter study, 95 adult patients with stable, severe cancer pain were enrolled in a randomized, double-blind, double-dummy crossover study of controlled-release and immediate-release hydromorphone. The controlled-release drug was found to be as safe and effective as the immediate-release drug, with no differences in total daily opioid dose, rescue medication use, pain scores, side effects, or patient drug preference. Patient acceptance was high, with 95 percent of patients choosing to continue the controlled-release drug in the open follow-up phase of the study.[47]

A Canadian product, Palladone XL (Purdue Pharma LP), which is reported to be identical to the American product (Sharon Weinstein, MD, *personal communication*, 10/27/04), was the subject of a recent abstract that reported the results of two well-controlled, multicenter clinical trials involving more than 300 (mostly cancer pain) patients. Both trials demonstrated stable and satisfactory analgesia over the entire 24-hour dosing period, as measured by numeric rating scale and number of rescue doses.[48]

COMPARISONS WITH OTHER CONTROLLED-RELEASE OPIOIDS

A 1997 Canadian study compared extended-release hydromorphone with extended-release oxycodone.[49] Forty-four patients with stable, chronic cancer pain were enrolled in this randomized, double-blind, double-dummy crossover evaluation. There were no significant differences in pain scores, as measured by visual analog and 5-point categorical scales (with mean daily doses of 124 ± 22 mg oxycodone, and 30 ± 6 mg per day hydromorphone); rescue medication use; or patient drug preference. Drowsiness, also measured by visual analog scale, was more common with oxycodone than with hydromorphone (28 vs. 19 patients), but the side effect profile was otherwise similar.

PALLADONE

Palladone (probably from the Latin, *pallium*, or "cloak") was approved by the FDA on September 24, 2004,[50] and started shipping to wholesale drug distributors on January 6, 2005.[51] A Schedule II opioid, it is available in four strengths: 12-, 16-, 24-, and 32-mg, once-daily, controlled-release capsules. The capsules contain hydromorphone in an ammonio methacrylate copolymer core.[29] The nominal 12-mg dosage is approximately equal to 60 mg of oral morphine (e.g., MS Contin, 30 mg p.o. q 12 h) and, as such, is appropriate for use only in

opioid-tolerant individuals with constant, moderate to severe pain, and with an anticipated extended period of use (Table 2).

Palladone is not intended for use in opioid-naïve individuals or those in whom planned duration of strong opioid therapy is less than weeks. Neither the capsules nor the contained hydromorphone pellets should be chewed or crushed, but in patients who cannot swallow the capsule, the opioid pellets contained therein can be sprinkled on soft foods such as applesauce or pudding. The pellets can also be mixed with water and administered via gastrostomy tube with no change in the absorption profile. Food has a negligible effect on absorption,[29] but alcohol can compromise the integrity of the controlled-release mechanism and should therefore be avoided during use.[52] Thus, in patients with alcohol use disorders, Palladone should probably be avoided.

The drug displays a biphasic absorption profile, with an initial early peak and a later, more sustained peak, with C_{max} occurring at a mean of 8.4 hours, and therapeutic plasma levels maintained over 24 hours. Compared to immediate-release hydromorphone, Palladone displayed nearly 40 percent less fluctuation in plasma levels (Purdue Pharma LP, 6/99).

Palladone is the most expensive of the extended-release opioids, although not dramatically more costly than the once-daily morphine formulations. The cost differential also tends to diminish at higher dosages (Table 3).

Palladone is subject to the same restrictions as all Schedule II opioids. In addition, in an effort to avoid a repeat of the OxyContin debacle, the manufacturer, in conjunction with the FDA, has instituted further safeguards in an effort to minimize inappropriate prescribing, diversion, and illicit use, without limiting access to patients with legitimate need for this opioid. These safeguards include the following:

- a carefully phased rollout of the drug over the initial 18 months;
- educational efforts directed toward physicians, patients, and caregivers;
- clear and appropriate drug labeling, including a "black box" safety alert warning of the dangers of abuse, addiction, and respiratory depression;
- an FDA-approved patient medication guide, to be distributed with each prescription;
- appropriate training for sales agents; and
- a multifaceted program for monitoring and surveillance of the drug.[50]

Although these measures may serve to minimize nonmedical use of this drug, some misuse of Palladone is inevitable due to the inherent abuse liability of opioids, their widespread availability for legitimate medical purposes, the criminal demand for such substances, and the imperfect nature of control systems.[21]

SUMMARY

Hydromorphone, one of the oldest and most potent of opioids, is an effective alternative to morphine. With a variety of routes of administration, it has an efficacy similar to that of morphine. The FDA has recently approved the first commercially available extended-release formulation, a once-daily hydromorphone for the management of moderate to severe pain in opioid tolerant individuals with an anticipated extended period of use. The formulation exhibits less peak-to-trough fluctuation in plasma concentration, while providing analgesia statistically indistinguishable from its immediate-release counterpart. The manufacturer and the FDA have articulated a plan to minimize unskillful prescribing and abuse/diversion through education, supply-chain integrity, and surveillance. It is anticipated that Palladone will be a valuable addition to the limited armamentarium of extended-release opioids.

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ORIGINAL ARTICLE

Opiate replacement therapy at time of release from incarceration: Project MOD, a pilot program

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ABSTRACT

Approximately 7 million people in the United States are in jail, in prison, or on probation or parole, many as a result of drug-related offenses. Individuals who use opiates account for a significant minority of this population. Methadone maintenance treatment (MMT) of opiate addiction is highly effective in reducing drug use, drug-related criminal activity, and risk of human immunodeficiency virus transmission. Recently released inmates are at particularly high risk for overdose and disease transmission. Project MOD (Managing Opioid Dependency) provides services to eliminate logistical and financial barriers to MMT entry immediately on release from incarceration. Such programs provide a promising opportunity to facilitate reentry into the community, combat disease transmission, and reduce recidivism.

Key words: methadone maintenance treatment, opiate addiction, incarceration, rehabilitation

INTRODUCTION

The United States incarcerates more people per capita than anywhere else in the world. The US Department of Justice Bureau of Justice Statistics reports that in 2003, 6.9 million people, or one in 32 adults in the United States, were on probation, in jail, in prison, or on parole.[1] In the 1990s, the United States experienced a 239 percent increase in the number of people in jails and prisons, resulting primarily from the so-called "war on drugs," and a threefold increase in drug-related arrests.[2,3] As a result, an estimated 80 percent of incarcerated individuals have substance abuse problems.[3,4] More specifically, up to 25 percent of inmates report a history of heroin use, and as many as 20 percent report a history of injection drug use (IDU).[5,6]

Given the high prevalence of individuals grappling with addiction in the corrections system, relapse into illicit drug use after incarceration is a substantial problem.[7] The consequences of relapse include increased criminal activity,[7-9] additional risk of human immunodeficiency virus (HIV) infection,[10] overdose death,[11-13] and reincarceration.[14] Fifty-five percent of former prisoners relapse into substance abuse within one month of release from incarceration.[7] This high rate of relapse suggests that although physical dependence on drugs may wane during the relative sobriety associated with incarceration, the behavioral manifestations of addiction and life stressors related to drug use are still present and require treatment. Many incarcerated drug users are addicted to heroin. One study found that a minimum of five years of heroin abstinence considerably reduced the rate of relapse, but 25 percent of participants still relapsed even after 15 years of abstinence.[15] This suggests that even long periods of incarceration and sobriety cannot be considered sufficient for recovery from addiction. Indeed, because heroin can cause physiological changes in the brain, addiction may be a lifelong problem.[16-18]

The goal of opiate replacement therapy (ORT) is to provide long-term stability and medical support for addiction through pharmaceutical replacement. The most common treatment is methadone. Long-term methadone maintenance treatment (MMT) programs have been shown to reduce risks of relapse, criminality, HIV transmission, mortality, and recidivism.[18-22] MMT has also been shown to be more effective at achieving these goals than ORT detoxification programs alone.[23] Although only a few MMT programs exist in prisons and jails around the world, the potential benefits of implementing such programs have been well documented.[24-27] One such effort, Project KEEP, on Rikers Island, New York, has successfully initiated MMT for prisoners, but linkage to aftercare post-release remains a challenge, and many participants report difficulty negotiating community placement in treatment after release.[28,29]

Newly released prisoners are especially vulnerable to the heightened risks associated with relapse into illicit drug use. Satisfying basic survival needs including housing, income, and food, often supercedes their ability to focus on less immediate concerns, such as drug treatment and disease prevention.[30] To alleviate these problems, the Centers for Disease Control and Prevention and the World Health Organization recommend that individuals be provided with prevention programs that would seamlessly transition prisoners to the community.[27,31,32] Relapse into illicit drug use and the accompanying heightened risk of disease merit attention as a target for prevention efforts.

We describe here an ongoing service program designed to provide increased linkage to MMT at time of release from incarceration, and offer our practical experience for others in the opiate treatment community in hopes of encouraging creation of similar programs.

PROGRAM DESCRIPTION

Our program, Project MOD (Managing Opioid Dependency), is a five-year, federally funded service initiative that aims to reduce recidivism, improve health, and increase personal stability among opiate-addicted exoffenders through linkage to MMT. Project MOD is housed in the Miriam Hospital, a well-established, nonprofit hospital in Providence, Rhode Island. The project is funded by the Center for Substance Abuse Treatment (CSAT), an agency of the Substance Abuse and Mental Health Services Administration (SAMHSA).

Members of the RI Department of Corrections staff provide referrals for interested inmates with a history of opiate addiction. Recruitment is now almost entirely from jail or prison, but during the startup stage of the project individuals were also enrolled who had been recently released from incarceration. Project MOD staff screen inmates to establish addiction and treatment history and whether MMT is practical (i.e., can the inmate afford it; is there a geographically convenient clinic; is there an existing debt with the clinic; is s/he committed to the rigors of clinic—daily attendance, regular meetings, regular toxicology screens; does s/he have daily transportation, etc.). While clients are still incarcerated, we work with them to facilitate and ensure entry into MMT within 24 to 48 hours of release. These efforts include arranging an appointment with an MMT program, acquiring documentation necessary for clinic entry (i.e., legal identification and social security card), and arranging transportation to the first clinic appointment.

After clients are released and enter a community treatment program, we provide temporary financial assistance for treatment costs (100 percent coverage for 12 weeks and 50 percent for the next 12 weeks). During screening, each client creates an individualized work plan that delineates the steps needed to help ensure payment for treatment costs when program financial assistance ends. Project MOD staff meet with the client several times in the first six months to reassess the plan and provide assistance with job referrals and training, applications for Medicaid or other insurance, and state-subsidized treatment slots. Additionally, throughout program participation, staff provide referrals for healthcare, housing, and other social services. Clinical care is entirely managed by the MMT program staff.

Project MOD has an annual budget of $450,000 in direct costs; the average cost per Project MOD client is $2,665, of which approximately $1,500 amounts to fees paid to the methadone clinics. The remaining costs include personnel, local travel for staff (e.g., to the Department of Corrections, area methadone clinics, the Social Security Administration, the Department of Motor Vehicles, Vital Records in the Department of Health, etc., all of which is service oriented and does not pertain to the evaluation aspects of the project), staff training, transportation assistance for clients (i.e., bus tickets and cab rides for the first clinic visit, when necessary), and assistance with paying for identification cards and birth certificates.

The RI Department of Corrections and all of the state's MMT facilities have been partners in the effort to develop and implement this program. We rely on RI Department of Corrections staff, including discharge planners, medical personnel, and counselors, for referrals. The RI Department of Corrections permits MOD staff to be present during inmate informational sessions, facilitating outreach to potential clients. Collaboration with MMT facilities includes special billing arrangements; providing space for MOD staff to meet with clients; and communicating discharge status, length and dates of treatment, and results of urine toxicology screens (all information is shared only with client's consent). Additionally, methadone clinics have been flexible with appointments, understanding that release dates may change unexpectedly.

Project MOD follows clients for one full year with assessments at baseline, six months, and 12 months. Data are gathered through client self-report, methadone clinic chart review, and RI Department of Corrections records. An interview combining the Addiction Severity Index (ASI) and CSAT-mandated Government Performance and Results Act (GPRA) measures seven general areas: 1) medical status, 2) psychiatric status, 3) substance use, 4) employment/support status, 5) legal status, 6) family history, and 7) family/social relations. Methadone clinic chart review is used to measure clinic attendance, methadone dosing, and urine toxicology results. Review of public corrections records is used to measure reincarceration.

PRELIMINARY RESULTS AND PRACTICAL EXPERIENCE

Between May 2003 and September 2004, we enrolled

217 clients. At baseline, clients were 64 percent male, 70 percent Caucasian, 13 percent Latino, and 11 percent African American. In the 30 days before assessment, many reported being unstably housed: 13 percent were homeless, 14 percent were institutionalized (prison or jail), and 53 percent stayed with friends or family. Many struggled with mental health issues that persisted for at least two weeks in the 30 days before assessment—30 percent had serious depression; 38 percent had anxiety; and 33 percent had difficulty understanding, concentrating, or remembering. Only 11 percent had received inpatient, outpatient, or emergency mental health treatment. Illicit and polydrug use was substantial: 90 percent of clients reported illegal drug use in the last 30 days. The most common drug was heroin (81 percent), followed by cocaine (43 percent). Notably, 73 percent also reported recent illicit drug injection, and 38 percent reported sharing syringes and other paraphernalia.

Of the 217 enrolled clients, 175 had completed six months in the project by September 2004. Approximately one-half (46 percent, n = 81) were still in treatment at six months. Of the 54 percent (n = 94) who left MMT, we have completed six-month interviews for 79. Of those, 38 percent were discharged owing to their inability to pay for treatment costs, 34 percent were discharged owing to reincarceration, and 25 percent left on their own against staff advice. Overwhelmingly, project participants reported that they would have been unable to enter MMT without the assistance provided by the project.

The quantifiable results to date are promising, and our subjective experiences reflect that as well. For instance, attitudes at the RI Department of Corrections initially fell in line with many other correctional and substance abuse treatment settings that stigmatized MMT as "just another drug," and total abstinence the only worthwhile goal. Attitudes toward methadone as a viable treatment option have gained considerable ground in the last two years, however, and the RI Department of Corrections has been a true partner in developing and implementing Project MOD. This is evidenced in part by the array of staff in all of the security facilities from whom we receive referrals, by our invitations to speak before the parole board, and by our regular involvement in discharge planning meetings and training.

Tight-knit collaboration with the methadone treatment facilities has likewise been crucial and productive. Special billing arrangements, transferring between clinics, and clinic discharge and re-entry have all gone smoothly. Each of the clinics has been welcoming of project staff and helped to facilitate our meeting with clients. Although not all clinics were accustomed to working with recently released inmates, they have trained staff regarding the federal regulations that specify slightly different entry criteria for those individuals. Likewise, clinics accommodated last-minute rescheduling of appointments that occurred as a result of sudden changes in prison release dates. In short, the clinical and correctional staffs' investment in providing services for this population has been crucial to ensure prompt treatment entry.

Our results are preliminary. We plan to examine many outcomes, including risk behaviors (self-reported drug use and injection behaviors, urinalysis results from chart review), reincarceration (incarcerated for old offense) versus recidivism (incarceration for new offense), length of stay in treatment, and length of time between prison release and clinic initiation.

DISCUSSION

Project MOD is one of few projects to provide linkage to MMT and funding support for individuals recently released from incarceration. The vision behind Project MOD is that linking individuals to treatment, covering treatment costs, and assisting with referrals for other needs contributes to the stability clients need to sustain long-term treatment. Preliminary evidence supports this vision. We have reached this underserved population and provided support for entering and continuing treatment. We have formed strong partnerships with the RI Department of Corrections and community methadone programs that lay the groundwork for further development of this program.

Financial assistance

Although considerable effort goes into arranging all the logistical details for treatment initiation and providing medical and social service referrals, it is clear that the project's most desired service is temporary financial assistance. This is not surprising, because a significant barrier to methadone treatment is the cost. For example, in Rhode Island, the cost of MMT programs averages more than $80 per week. As a result, MMT is not feasible without stable employment or assistance through a third-party payer.

Financial discharge

Although approximately one-half of Project MOD clients remained in treatment at six months, treatment was interrupted for one in five clients owing to their inability to pay at the end of MOD financial assistance. In general, this is a suboptimal outcome, because heroin-addicted patients who undergo short-term MMT frequently relapse. Since the project's inception, we have been aware of the possibility of financial discharge and have addressed this problem in the following ways:

- pre-enrollment emphasis on the possibility of

financial discharge to clients thinking about entering treatment and completing a work plan with each client to develop concrete steps toward paying for treatment when the project no longer does so; and

- working with clients to pursue third-party payers (e.g., Medicaid, state-subsidized treatment slots) and referrals for job training and placement (although these resources are scarce).

In response to the fact that one-fifth of MOD clients have undergone financial discharge, despite these continued efforts, we have recently adopted the strategy of offering the choice of a four-month treatment episode—eight weeks ramping up and maintaining a therapeutic dose, and an approximately eight-week taper—the cost of which is fully covered by Project MOD. Although far from optimal, this option may provide protection and stability during the initial transition back into the community. Additionally, a completed short-term treatment episode may be a steppingstone to longer-term treatment in the future.

Comparison of public costs

Although MMT costs are a barrier for many individuals, it may be cost effective at the policy level in comparison to the costs of incarceration. The average annual cost of incarceration is at least $22,630 per inmate in state or federal prison.[33] Conversely, the annual cost of MMT (based on average costs at Rhode Island clinics of $75 to $90 per week) is approximately $4,420. There may be additional costs in supporting individuals recently released from incarceration, such as social services and governmental support (e.g., welfare, food stamps, etc.). As individuals stabilize in MMT, however, many are able to secure employment, obviating the need for some social services. Therefore, an emphasis on substance abuse treatment could mean governmental savings over the costs of incarceration and offsetting of social service costs.

Limitations

The results we present here are primarily from practical operational experience, meant to inform other agencies interested in providing similar services. Because this is a service initiative, the outcomes that we report may not be generalizable to all incarcerated opiate-addicted individuals. For instance, there was a selection bias because all our clients sought out MMT services. We had contact only with those who were specifically interested in MMT and needed assistance in accessing that treatment. Also, MMT is not appropriate for all people who use heroin.

Currently, minorities are under-represented in our client population. Although whites account for 70 percent of our clients, they make up only 50 percent of the incarcerated population.[34] Although there are not accurate numbers regarding race of heroin users in Rhode Island, a reasonable indicator would be new HIV infection rates and IDU-related HIV infection rates, both of which indicate a higher percentage of minority IDUs than are represented in the Project MOD sample.[35] This discrepancy, in part, reflects under-representation of minorities in Rhode Island methadone clinics, where whites comprised 80 percent of patients treated for heroin addiction in 2003.[36] We are attempting to address this problem by collaborating with local minority service organizations to increase the diversity of our outreach.

Our efforts for recruiting women have been more successful, owing in large part to our collaboration with the Women's Division at the RI Department of Corrections. We seek to recruit women to represent at least one-third of our clients. This is the ratio consistently reported in the literature for heroin users in the community. This is also the ratio of men to women being treated in Rhode Island for heroin addiction, although it is a considerable over-representation of women as compared to their numbers in the prison population (6 percent).[34,36]

CONCLUSION

The demand for linkage and funding support through Project MOD underscores the public health importance of facilitating continuous and sustained care during the transition from prison to the community. The intense cooperation with the RI Department of Corrections and MMT programs facilitated by Project MOD has produced promising results. Nearly one-half of our baseline clients remained in treatment at six months, and even those who were discharged received important protection from relapse during the high-risk period immediately after incarceration. Overwhelmingly, our clients reported that they could not have entered MMT without assistance from Project MOD. Through analysis of our six- and 12-month assessments, we hope to demonstrate that immediate MMT linkage and funding at time of release from prison decreases recidivism and improves health and personal stability, thereby improving the community's health. Data from small demonstration projects such as Project MOD may be helpful in convincing policymakers, correctional administrators, and the general public of the merits of this approach.

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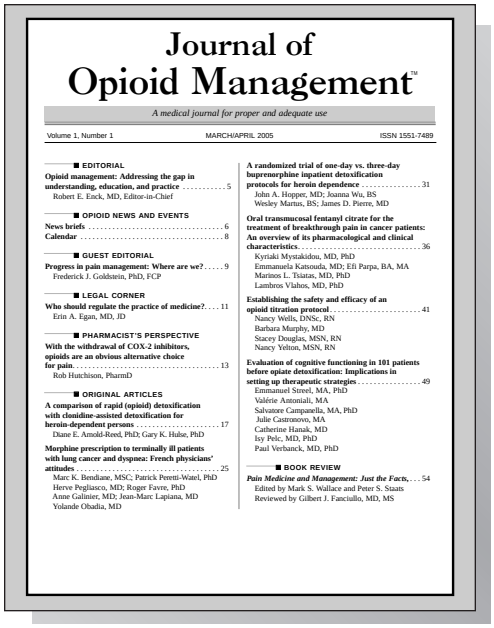
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ORIGINAL ARTICLE

The opioid bowel syndrome: A review of pathophysiology and treatment

Mellar P. Davis, MD, FCCP

ABSTRACT

Opioids are responsible for 25 percent of constipation in terminally ill patients. Patients in pain require prophylaxis to prevent opioid bowel syndrome (OBS). Laxatives are the treatment of choice, but are marginally effective. The development of quaternary opioid receptor antagonists is a step toward target-specific therapy for opioid-induced bowel dysfunction. This review will discuss the pathophysiology and management of OBS.

Key words: opioid bowel syndrome, pathophysiology, prophylaxis, bowel dysfunction

INTRODUCTION

Opioids have been used as antidiarrheals for centuries. The reasons for benefit are reduced intestinal propulsion, reduced transit, improved fluid absorption, reduced intestinal secretions, and prolonged mucosal contact time secondarily allowing absorption of bowel fluids.[1,2] On the other hand, opioids may cause opioid bowel syndrome (OBS) in individuals without diarrhea. OBS is associated with upper and lower abdominal symptoms—abdominal pain, bloating, colic, constipation, early satiety, nausea, and vomiting—and can mimic bowel obstruction.[1,2] Although OBS is frequently equated with constipation, and constipation remains the hallmark symptom, upper abdominal symptoms may be just as distressing to patients. If OBS remains untreated, anorexia, fecal impaction, inadequate absorption of medications, malabsorption of food, pseudo–bowel obstruction, and urinary incontinence will supervene.[1] Opioids will worsen and prolong postoperative ileus, which is also a type of OBS, because exogenous and endogenous opioids are one of the major factors contributing to prolonged hospitalizations and delayed recovery of bowel function postoperatively. Patients may limit opioids and forego pain relief to avoid constipation for fear of OBS. Many patients may, in fact, prefer poorly controlled pain and normal bowel habits to well-controlled pain and opioid-related gastrointestinal symptoms. Like other opioid-related side effects, OBS corresponds poorly to the opioid dose and there is no tolerance with time.[1,3]

Constipation occurs in more than 50 percent of patients on opioids and is five times greater in frequency than in the normal population.[3] Constipation is frequently underdiagnosed, and most physicians do not provide bowel prophylaxis for constipation when starting opioids.[3] Comedications such as anticholinergics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and calcium-channel blockers add to the risk of constipation with opioids. Patients on opioids are frequently immobile and dehydrated, which further increases the risk for OBS. Recent surgery and gastrointestinal metastases also compound the risk.[3]

ASSESSMENT

The initial step to evaluating OBS is a history of associated symptoms followed by plain radiographs of the abdomen. An upright radiograph of the abdomen will detect air fluid levels consistent with a bowel obstruction and crucial to the differential diagnosis. Also, plain abdominal radiographs provide a means of scoring the severity of constipation (Table 1).[3]

PHYSIOLOGY AND PHARMACOLOGY OF THE GASTROINTESTINAL TRACT

Intestinal motility is dependent on the electrophysiological activity of smooth muscle, neural input from the central nervous system (CNS), and coordinated activity from the "gut" brain located within the myenteric plexus (between the outer longitudinal smooth muscle and the inner circular muscle). The submucosal neural plexus lies between the mucosa and circular muscle and coordinates motility absorption and secretion in conjunction with the myenteric plexus. Enteric neurohormones such as vasoactive intestinal peptide (VIP), secretin, neuropeptide Y, peptide YY, serotonin (5HT), acetylcholine, noradrenaline (NA), and endogenous opioids govern motility, secretion, and absorption. The extrinsic autonomic nervous

Table 1. Radiographic constipation score	
1 point	< 50 percent of stool in an abdominal quadrant
2 points	> 50 percent of bowel in a quadrant has stool
3 points	100 percent of the bowel within a quadrant has stool
Add the score for the four quadrants of the abdominal radiograph. If the score is ≥ 7 out of a possible 12 (4 × 3 points), then severe constipation is present.[3]	

system includes sympathetic and parasympathetic fibers that coordinate peristalsis, reflex motor activity, and secretory activity between the enteric nervous system (ENS) and the CNS.[1,2]

Smooth muscle normally has a continuous undulating electrical membrane depolarizing pattern.[4] Opioids have no effect on this undulating or rhythmic resting potential or slow-wave activity. Pacemaker cells called interstitial cells of Cajal govern the rate of undulating depolarization.[4] Electrical spikes from the ENS lead to smooth muscle contraction. Depolarization is initiated with luminal distension, which stretches the muscular wall, releases acetylcholine, and initiates longitudinal smooth muscle contraction. Smooth muscle is hyperpolarized by NA, which prevents smooth muscle contraction.[5,6] Myocytes of the stomach and small bowel contain gap junctions that pass electrical current from one cell to another, thus allowing a coordinated smooth muscle contraction.[5,6] A syncytial electrical oscillating contraction is due to these interconnections between long sheets of myocytes.[1] In counterdistinction, colonic myocytes lack gap junctions and fail to function as an intrinsic unit. Colonic contractions and motility are therefore more dependent on extrinsic neural input.[1]

The alimentary tract has three functional motor responses: long segment propulsion, short segment propulsion or segmentation, and nonpropulsion.[5-8] Propulsive movements require a coordinated contraction/relaxation response between longitudinal and circular muscle.[5-10] This coordinated movement is initiated with a bolus of food, which stretches the gut wall. The ENS then initiates a coordinated propulsive movement by contracting the proximal longitudinal muscle and relaxing the distal circular muscle. This is accomplished through activation of ascending excitatory cholinergic motor neurons, which innervate longitudinal smooth muscle, and simultaneous activation of inhibitory nitric oxide- and VIP-containing descending motor neurons, which innervate distal circular smooth muscle.[4,11,12]

The small bowel and the colon also produce regular segmenting contractions that are nonpropulsive and that mix food and digestive secretions.[1] In the colon, segmentation results in prolonged mucosal exposure and facilitates fluid absorption. During fasting and after feeding the stomach, the small bowel and colon have coordinated migrating motor complexes that sweep bowel contents distally, usually at 90-minute intervals.[1]

Enteric nervous system

The gut has as many neurons as the spinal cord. Between the two plexuses there are a complex array of neurons that are as complex in interaction and function as the neuronal structure of the spinal cord. There are submucosal intrinsic primary afferents, submucosal secretomotor neurons, myenteric intrinsic primary afferents, noncholinergic secretory and vasodilator neurons, excitatory circular muscle motor neurons, inhibitory circular muscle motor neurons, cholinergic secretomotor and vasodilator neurons, descending interneurons for secretomotor reflexes, descending interneurons for muscle motor reflexes, and migrating motor complexes.[1-3,5,6] A network of pacemaker cells, the interstitial cells of Cajal, along the myenteric and submucosal borders generates the rhythm of intestinal contraction, the loss of which causes idiopathic constipation and paraneoplastic pseudo-obstruction.[10] The ENS governs overall motility, secretion, blood flow, and gut-related immune function.

The brain-gut axis consists of cholinergic fibers derived from vagus and pelvic parasympathetics and NA-containing sympathetics from splanchnics derived from T5-L2 sympathetic paraspinal ganglion. Motor and secretory function is modulated centrally through the brainstem nucleus tractus solitarius and dorsal motor nucleus of the vagus. Sensory A delta and C sensory fibers travel, mostly with sympathetics, to govern visceral pain responses, and contain predominately κ opioid receptors.[10] Parasympathetics stimulate motility and secretion, whereas sympathetics do the opposite.

Neurohumeral mediators

Local and circulating neurohumeral factors govern motility and alter myoelectrical smooth muscle activity, muscle tone, bowel wall compliance, and intestinal transit (Table 2).[5] Hormones from the gut influence the ENS before and after meals. Plasma ghrelin released from the stomach increases gastric motility before meals and stimulates

Table 2. Influence of neurohumeral mediators on intestinal circular smooth muscle contraction[8]	
Stimulators	**Inhibitors**
Acetylcholine	GLP-1 glucagon-like peptide
Grehlin	Nitric oxide
Motilin	Noradrenaline
Opioids	Somatostatin
Prostaglandin E_2	Vasoactive intestinal peptide
Substance P	

neuropeptide Y release for appetite.[5-7] Postprandial endocrine responses include release of insulin, neurotensin, gastrin, glucagonlike peptides (GLP-1), and glucose-dependent insulinotropic polypeptides, which reduce motility and interrupt migratory motor complex frequency (Table 2).[5-7] VIP and nitric oxide are released from descending inhibitor motor neurons to inhibit circular muscle contraction, increase bowel compliance, and stimulate digestive secretions. Hormones regionally released by enterochromaffin cells—principally 5HT—reduce motility by activating enteric sensory neurons and vagal and intrinsic primary afferents, which in turn feed back on endocrine cells in an autoregulatory fashion.[5-7] Motor neuron excitation and contraction are stimulated by tachykinins and substance P, as well as acetylcholine, and in part by 5HT, which induces different responses depending on the receptors that are activated.[5-7] Peristalsis is governed by coordinating ascending cholinergic excitatory motorneurons, which stimulate longitudinal muscle to contract, and simultaneous activation of inhibitory noncholinergic nitric oxide—containing motor neurons, which prevents circular smooth muscle contraction (and increases bowel wall compliance). Ascending and descending motor neurons both contain opioid receptors.[6,9,10,12-14]

A neuroreflex occurs between primary intrinsic neurons of the submucosal plexus and mucosa, with integrating circuits within the myenteric and submucosal plexus, which control secretory responses. Noncholinergic neurons use substance P and VIP to stimulate secretions. Serotonin and NA released from enterochromaffin cells within the mucosa prevent primary intrinsic neurons from depolarizing cholinergic and VIP-containing neurons within the submucosal plexus and block fluid and chloride secretion.[5-7]

Serotonin plays a major role in initiating a diverse number of gastrointestinal responses, including nausea, vomiting, secretion, and peristalsis. In general, serotonin is prokinetic and prosecretory. There are 14 different 5HT receptors in the gut, however, three of which are known to be excitatory (5H2b, 5HT3, and 5HT4), and at least one of which is inhibitory (5HT1a). Serotonin responses may therefore be regionally different depending on the receptor subtype.[5,6]

OPIOID AGONISTS AND RECEPTORS

Opioid agonists and their receptors have a major influence on gut motility, visceral sensation, secretion, and absorption.[14-16] Enkephalins, β-endorphins, and dynorphin are found in enteric neurons in the myenteric and submucosal plexus and innervate smooth and circular and mucosal endocrine cells and immunocytes.[17] Opioid receptors μ, κ, and δ are found in high density in both plexuses, particularly in the gastric and upper small intestines. κ receptors are found predominately in the myenteric plexus, and μ receptors are abundant in the myenteric plexus and dominate the submucosal plexus.[17,18] There are species-specific differences in opioid receptor distribution, however.[9,12-14] For example, κ and μ receptors are found in neurons within the circular muscle, but κ receptors are selectively absent in longitudinal muscle.[13,18,19] The stomach and proximal colon have the greatest density of κ and μ receptors. The functional role of δ opioid receptors is relatively unknown.[20] Opioid receptors are not found on smooth muscle, but are located prejunctionally on various ENS neurons that innervate smooth muscle.[17,20] Within the gastric wall, μ and κ opioids cause circular smooth muscle contraction by blocking inhibitory ascending motor neurons, and μ receptors prevent longitudinal muscle contraction through preventing the release of acetylcholine from activating ascending motorneurons.[21-23] Opioids also block vagal firing in the brainstem through the nucleus tractis solatarius, leading to decreased autonomic output, which impairs gastric emptying.[24] Morphine increases gastric smooth muscle amplitude, but reduces the frequency of contraction and also peristalsis, leading to antral spasm and early satiety.[6,25,26] Opioids do not influence esophageal motility, but prevent relaxation of the lower esophageal sphincter, pylorus, ileocecal value, and rectal sphincter.[20] μ Agonists reduce gastric secretion by peripheral and central mechanisms.[27] Morphine increases serotonin release from submucosal neurons and serotonin binds to 5HT2 receptors, which in turn causes NA release. NA binds to α2 adrenoceptors on enterocytes and prevents secretion.[9,14,20,21,26,28-31]

The endogenous opioid system is a defense mechanism that modulates motility in the face of pathologic intestinal distention and inflammation. Exogenously administered opioids impair transit that is already slow, however, whether postoperatively or through medications, inflammation, sedentary existence, or dehydration. OBS is a combination of increased release of endogenous

opioids from enteric neurons, increased expression of enteric opioid receptors due to inflammation, and administration of exogenous opioids.[17,20]

Morphine prevents secretions stimulated by prostaglandin E2 and VIP2. This owes to morphine-induced release of serotonin from the submucosal and myenteric plexus. This is, again, a regional effect through 5HT1 or 5HT2 receptors, because systemic serotonin actually increases secretions. Chemical or mechanical sympathectomy abolishes the antisecretory effects of morphine.[2] Methylsergide blocks serotonin receptors, reverses the antisecretory effects of morphine, and impairs the increased absorption response caused by μ agonists.

OBS correlates best with opioid concentrations within the ENS, rather than plasma or CNS levels.[4] It was initially thought that increased fluid absorption from opioids was caused predominately by delayed intestinal transit, but it is now known that opioids directly suppress secretomotor neurons in the submucosal plexus and reduce secretion, as well as stimulate absorption independent of motility.[6]

POSTOPERATIVE ILEUS AND OPIOIDS

Postoperative ileus basically is a loss of coordinated motility and predominantly arises from colon dysmotility. Recovery of the small bowel occurs quickly, usually within 24 hours, and the stomach recovers between 24 to 48 hours, but the colon will not recover for 48 to 72 hours.[32] Postoperative paralytic ileus, therefore, by definition, is when ileus lasts more than three days.[32] Postoperative ileus is caused by increased sympathetic output from stress, by release of endogenous opioids as a result of intestinal manipulation during the operation, and by exogenous opioids. The duration of postoperative ileus is related to the degree of surgical trauma and is greatest after colonic surgery.[32]

Gut paralysis postoperatively is biphasic. The initial phase owes to release of enteric nitric oxide. Mucosal trauma then leads to infiltration of leukocytes and activation of endogenous macrophages. VIP, substance P, and calcitonin gene-related product are released locally due to trauma and inflammation. Cyclo-oxygenase 2 is upregulated in motor neurons, opioid receptors are expressed, and endogenous opioid peptides are released.[32] The result is smooth muscle paralysis and increased sensitivity to exogenous opioids.[11] Physical findings and the passing of gas or stool correlate poorly with the course of ileus, the normalization of intraluminal pressures, intestinal migration measured by radio-opaque markers, and normalization of ENS electrical activity.[1] Trials of postoperative nasogastric suctioning have not demonstrated benefits in accelerating the resolution of ileus because it does not treat the primary cause and may predispose individuals to atelectasis and pneumonia.[1] There are no data to substantiate the use of prokinetics in the management of postoperative ileus.[11,31,32] Early feeding leads to resolution of the ileus.[11,32] Epidural local anesthetics and opioid-sparing strategies using ketorolac for analgesia will reduce pain and postoperative ileus. The other option is the use of less-constipating opioids, such as tramadol, fentanyl, and buprenorphine, in substitution for morphine.[1] Recently, the use of peripheral-acting opioid-receptor blockers has significantly shortened the time to recovery and hospitalization.[18,20,33,34]

OPIOID BOWEL SYNDROME IN A NONSURGICAL PATIENT: NONPHARMACOLOGICAL MEASURES

At least three nonpharmacological approaches can be pursued to prevent or minimize OBS: 1) increased fluid intake, 2) exercise with frequent ambulation, and 3) promotion of a regular bowel habit.[1,3] Privacy is frequently neglected within the hospital, as rounds or radiographic studies occur at inopportune times. A respect for privacy may go a long way in promoting good bowel habits as well as dignity.[3]

LAXATIVES

Laxatives are bulk-forming agents, osmotics, surfactants, or stimulants. Laxatives increase fluid in the gut lumen, decrease fluid and electrolyte absorption, and increase motility of the upper gastrointestinal tract. Laxatives do not reverse opioid dismotility. The drawbacks to laxatives are that they increase the medication burden in those prone to nausea and are not "target specific" for opioid receptor-mediated side effects.[1]

In a series of 413 patients referred to palliative specialists and or daycare, 54 percent had constipation, 15 percent severely so.[35] One hundred sixty-five patients were using opioids at the time of referral, and 80 percent of these complained of constipation. Despite the use of stimulating laxatives and osmotic laxatives, 75 percent did not improve despite the fact that most were satisfied with the management of their constipation. There were no changes in constipation between users and nonusers of laxatives. Paradoxically, patients on strong opioids plus laxatives were more likely to be constipated than those on strong opioids alone, although this may be a selective bias. Nursing assessment poorly corresponded to patient grading of constipation severity. Only one out of five identified that a healthcare professional explained the rationale for laxatives.

In a prospective trial, laxatives were required in 87 percent of patients on potent opioids, but 64 percent of patients not on opioids also required laxatives.[36] Interestingly, opioids accounted for only 25 percent of constipation in terminally ill patients. Individuals varied widely in their sensitivity to laxatives. There did not

appear to be a fixed-dose relationship between laxatives and opioids. Stool frequency did not differ between patients on opioids and those not on opioids.[36] In summary, these two survey studies suggest that laxatives appear to be suboptimal in the management of OBS.

In randomized controlled trials of laxatives in the elderly, there is a nonsignificant trend in the number of stools per week and laxative use. Most trials were small, however, and lacked statistical power. There is no evidence that one laxative is better than another.[37-41]

Bulk laxatives

Bulk laxatives/softeners are nondigestible substances that increase fecal volume and (hopefully) stimulate a stretch reflex, thus initiating peristalsis. They are fermented in the colon, generating substances that stimulate colonic motility. Bulk agents work poorly in OBS, however, owing to the facts that peristalsis is already impaired and the distension reflex inhibited, bulk agents do not inhibit opioid-induced absorption. Intestinal secretions are inhibited by opioids such that bulk agents are desiccated within the bowel lumen. An additional 200 to 300 mL of water is necessary over and above the usual daily intake. Early satiety limits the tolerability of bulk agents. Bulk agents will not reverse severe opioid-induced constipation, but will promote constipation in dehydrated patients, and do not relieve opioid-induced upper gastrointestinal symptoms.[3]

Osmotic laxatives

Osmotic laxatives consist of magnesium salts or poorly digested carbohydrates. Magnesium salts work in the small and large bowel to promote peristalsis, whereas carbohydrates stimulate laxation through bacteria digestion in the colon. Fluid is drawn into the bowel by osmotic laxatives, which can be problematic in dehydrated patients. Magnesium salts interfere with absorption of medications, and should be avoided in renal failure.[3] In one study in terminally ill patients, 20 to 30 mL of lactulose was required twice daily to relieve constipation associated with opioids. Relief took three to four days, and less than one-half of the days were associated with a bowel movement while on lactulose. Twenty-one percent continued to have hard stools despite aggressive lactulose dosing.[42] To obtain a bowel movement, 60 mL or more of a carbohydrate laxative may be necessary. Sorbitol and lactulose produce the same laxation; however, sorbitol is less expensive and less nauseating.[37] Polyethylene glycol, compared to lactulose, produces less flatus and more stools in the short term. Twenty grams of polyethylene glycol is equivalent to 20 g of lactulose.[40,43,44]

Stimulating laxatives

Stimulating laxatives are anthraquinones (dantron, senna, or cascara) or diphenyl-methanes (bisacodyl, phenolphthalein). Stimulants encourage peristalsis in part through longitudinal muscle contraction and secondarily through inhibiting ATPase K^+ NA^+ activity (absorption). The bioavailability of most stimulating laxatives is 15 percent. Laxatives do not coordinate peristalsis, but stimulate muscle contraction and are not "target specific" for OBS. Colonic bacteria transform senna to an aglycone that gives senna its laxative properties. Long-term use of anthraquinones is known to damage neurons within the myenteric plexus, however. Colonic melanosis caused by anthraquinones is a result of apoptotic epithelial cells that are phagocytized by macrophages and remain within the mucosa.[3] There is not an advantage of one stimulating laxative over another or between stimulating laxatives or osmotic laxatives, although one early study suggested that osmotic laxatives worked better than stimulating laxatives. There are few randomized trials to guide choices or doses. Almost all recommendations are by expert opinion, however, because there are few randomized trials.[38]

Rectal measures in laxation

One-third of patients require rectal measures for laxation. Suppositories, enemas, and manual disempaction are required in those with dysphagia, those who are nauseated, or those who have a bowel obstruction. Suppositories work by causing reflex emptying through rectal distension.[3] Glycerol suppositories also act as a lubricant. Bisacodyl suppositories have a dual action of mechanical and chemical colonic stimulation. Enemas are used only as rescue measures. A "mini enema" (60 cc) and larger-volume phosphate enema of 130 mL have similar benefits. Mini enemas should be used only when soft stool is present in the rectum.[3] High-volume enemas and manual disempaction are needed for fecal impaction. Enemas using cottonseed oil, paraffin, or mineral oil soften hard stool and will help relieve a hard impaction. Saline or oil enemas should be delivered at the highest descending point in the rectum above the impaction, to wash the impaction downstream, and not in the rectum or anus, below the impaction. Failure to disempact is as much a technical failure as a failure of the enema, per se.[3]

MISCELLANEOUS NONSPECIFIC THERAPY

Colchicine, used for acute gout, causes diarrhea as a side effect that can be beneficially used to relieve chronic constipation. There are no trials of colchicine in OBS. Prokinetics such as erythromycin, domperidone, cisapride, and metoclopramide have been used for OBS.[31] Erythromycin stimulates upper gastrointestinal motilin

Table 3. Less-constipating opioids
Tramadol
Buprenorphine
Fentanyl
Methadone

receptors, but is unlikely to produce a colonic action. Metoclopramide has been successfully used as a continuous infusion but can cause extrapyramidal side effects.[3] Cisapride (not commercially available) and erythromycin can both cause ventricular arrhythmias, particularly when combined with medications that inhibit CYP3A4. Misoprostol, a synthetic prostaglandin used to reduce the risk of gastric ulcers associated with nonsteroidal anti-inflammatory medications, causes diarrhea. Misoprostal is expensive, however, and untried in OBS. Finally, clonidine has been successfully used to treat OBS in a case report.[45]

OPIOID ROTATION AND OPIOID SPARING

Intractable OBS while on morphine may be an indication for opioid rotation. Morphine concentrates within the intestinal lumen and intestinal smooth muscle. Other opioids, such as methadone and fentanyl, are less constipating.[46] Buprenorphine is the least-constipating opioid, with it occurring in only 5 percent of treated patients (Table 3).[47] Adding ketorolac to morphine may reduce opioid doses and facilitate laxation.[48-51]

OPIOID RECEPTOR ANTAGONISTS

Opioid receptor antagonists are target-specific therapy for OBS. There are two types of antagonists: poorly absorbed oral opioid antagonists, and peripherally restricted μ opioid antagonists.[1,3]

Poorly absorbed opioid antagonists

Naloxone, a lipid-soluble tertiary multiple-receptor opioid antagonist, has an oral bioavailability of 2 to 3 percent owing to extensive hepatic first-pass clearance.[1,8,9] Absorption is increased with dose, however, and so naloxone has a narrow therapeutic index.[1,8,9] Doses of 0.4 to 4.0 mg daily by mouth are ineffective; doses of 8 to 12 mg reverse OBS, but can precipitate systemic withdrawal.[8] Initial doses should be 5 mg daily to avoid precipitating opioid withdrawal. The usual doses are 8 to 10 mg daily, up to 10 to 20 percent of the total daily morphine dose, or a dose equivalent to the four-hour dose.[3,8] In randomized controlled trials 10 percent of the morphine dose was used, but in open trials doses up to 20 percent of the total oral morphine equivalent were used. Some patients developed withdrawal symptoms and resurgence of pain with oral naloxone titration.[52] More than one-half of patients will have laxation with oral naloxone. Dosing based on the opioid dose may not be correct. Constipation from opioids is poorly related to opioid dose. Patients who have been on long-term opioids are more sensitive to opioid withdrawal when treated with oral naloxone than those on short-term opioids.[8] The risk of withdrawal will be greater on higher doses of opioids if naloxone dosing is based on a percentage of the daily opioid dose. Gastrointestinal opioid receptors may be completely bound before adequate analgesia (and CNS levels), and a "ceiling effect" on dose-constipation effects thus may occur. Approximately 10 to 15 percent of opioid analgesia is lost with the use of oral naloxone.[8,53,54]

Nalmephene is an active, long-acting antagonist derived from naltrexone. Glucuronide derivatives of nalmephene have been developed to reduce OBS in those on methadone maintenance therapy.[55] It is thought that glucuronide metabolites are poorly absorbed and, thus, will not reduce analgesia or precipitate withdrawal. Colonic bacteria contain β-glucuronidase, which liberates nalmephene from its glucuronide side chains and allows nalmephrene to interact with opioid receptors in the colon and antagonize opioid-induced constipation. Nalmephene is also absorbed systemically through the colonic wall, and precipitates an abstinence syndrome in opioid maintenance therapy.[55]

Peripherally restricted opioid antagonists

Peripherally restricted opioid receptor antagonists are polar, less lipid soluble, and quaternary in structure, which restricts them from crossing the blood-brain barrier.[8] Both quaternary opioid antagonists in development, methylnaltrexone and alvimopan, may be given orally or parenterally without reversing analgesia. Both have the potential of producing laxation within hours, and both may relieve upper and lower gastrointestinal symptoms related to OBS.

Methylnaltrexone. Methylnaltrexone improves orocecal transit time in a dose-dependent manner in normal volunteers given parenteral morphine. Transit time decreased from 155 ± 27.9 minutes to 110 ± 41.0 minutes with 0.1 mg per kg of parenteral methylnaltrexone and from 140 ± 88 minutes to 108 ± 60 minutes with 0.3 mg per kg of parenteral methylnaltrexone.[56] Methylnaltrexone may also reverse opioid-induced nausea, pruritus, and flushing.[57] A methylnaltrexone dose of 0.45 mg per kg will prevent 97 percent of morphine-induced orocecal transit time; 0.3 and 0.1 mg per kg subcutaneous prevented 77 percent and 64 percent of morphine-induced transit time, respectively.[58]

Patients on methadone maintenance therapy and with

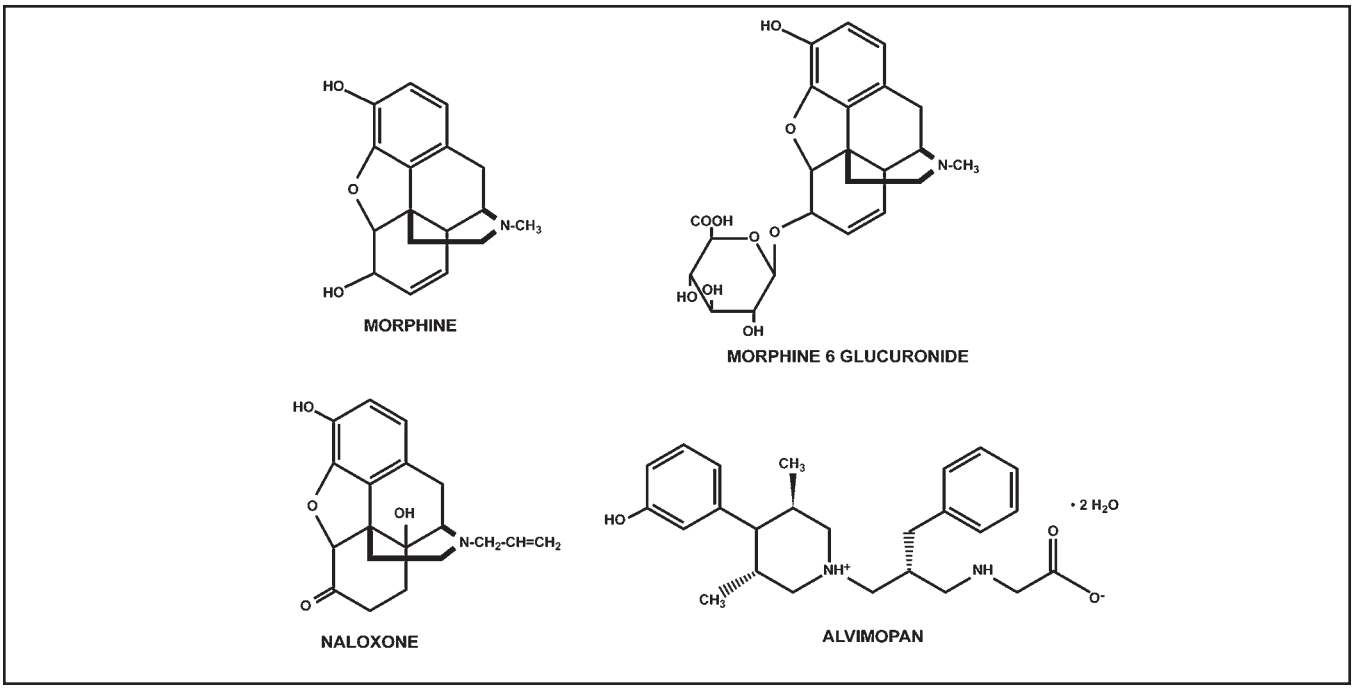

Figure 1. Molecular structures of morphine, morphine-6 glucuronide, naloxone, and alvimopan.

constipation (defined as one to two stools per week) respond with immediate laxation to methylnaltrexone doses of 0.35 to 0.45 mg per kg given intravenously twice daily. Orocecal transit time was reduced from 150 minutes to 60 to 90 minutes by the methylnaltrexone. Abdominal cramps were experienced particularly at the higher doses, but withdrawal did not occur. Both methadone maintenance therapy and chronic opioids for cancer pain increase sensitivity to methylnaltrexone, and lower doses (i.e., 0.1 mg per kg) should be used.[55,59]

In a randomized blinded trial, oral methylnaltrexone in doses of 1 and 3 mg per kg produced immediate laxation in individuals on oral methadone maintenance therapy who had significant constipation. Mild abdominal cramps were experienced by most, but systemic withdrawal symptoms did not occur.[60]

Oral bioavailability of methylnaltrexone is less than 1 percent; however, absorption is individually variable.[7,61,62] Laxation is not related to plasma level. The dose equivalents when converting from oral to subcutaneous are by a factor of 100.[56] Peak free methylnaltrexone is significantly less when given subcutaneously as compared to intravenously. An intravenous dose of 0.08 mg per kg is equivalent to a subcutaneous dose of 0.1 mg per kg. The time to maximum levels is 16 to 20 minutes for subcutaneous injection and is shorter for intravenous administration. The half-life is two hours. Clearance of methylnaltrexone is independent of route of administration.[56]

Alvimopan. Alvimopan is a potent μ opioid receptor antagonist (Figure 1). The inhibitor constant (Ki) is fourfold lower than naloxone demonstrating a greater affinity (and inhibition) to the μ receptor. Alvimopan also binds with a lesser affinity (inhibition) to κ and δ opioid receptors.[34]

Alvimopan, in a phase I study, completely prevented loperamide-induced changes in gastrointestinal transit in normal volunteers. Doses ranged from 2.4 to 24.0 mg by mouth.[34] Additional studies in normal volunteers found that 4 mg of alvimopan normalized orocecal transit when given with morphine 0.05 mg per kg. Oral alvimopan 3 mg three times daily reversed the delayed lower gastrointestinal transit caused by oral morphine 30 mg twice daily.[34,63-65] In phase II trials there is a dose-dependent increase in the number of bowel movements, stool weight, reduced hard stools, and need to strain.[34]

In a randomized controlled trial of alvimopan 0.5 mg and 1.0 mg compared to placebo, alvimopan increased the number of stools, reduced the time to first bowel movement, and improved patient satisfaction compared to placebo in patients on chronic opioids. Eleven percent discontinued alvimopan due to cramps, nausea, vomiting, diarrhea, and flatulence. Two of 105 had worsening pain on alvimopan.[66] Alvimopan has also been tested in the management of postoperative ileus. Two randomized trials have demonstrated that 6 and 12 mg of oral alvimopan improve time to gastrointestinal recovery and decrease the time in hospital compared to placebo.[33,67]

Oral bioavailability of alvimopan is 6 percent.[18] Metabolites of alvimopan are derived from gut flora rather than hepatic metabolism. There is no evidence that alvimopan is metabolized by cytochrome P450 metabolism

or by glucuronidation. The time to maximum plasma concentrations for oral dosing is 1.5 to 3.0 hours, and the half-life is 1.3 hours for a 12-mg dose. The half-life of intravenous alvimopan is 10 minutes. Alvimopan does not accumulate with repeat dosing.[18]

SUMMARY

OBS is almost inevitable for patients on potent opioids who do not receive prophylactic laxatives. There is no one right laxative program, and most guidelines are by expert opinion. All laxatives have drawbacks regarding efficacy and toxicity. Target-specific opioid receptor antagonists are either opioid antagonists with high first-pass hepatic clearance or quaternary opioid antagonists that do not cross the blood-brain barrier. Both classes of opioid antagonists have clinical use, although naloxone has a narrower therapeutic index. Both classes of peripherally limited opioid receptor anatagonists have advantages over laxatives in specificity and onset to laxation and may relieve upper abdominal symptoms. Both quaternary opioid antagonists are ideal for prophylaxis. Further research is necessary to clarify clinical use. Cost and versatility will also be a major factor for routine use.

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ORIGINAL ARTICLE

No potentiation of fentanyl by use of transdermal buprenorphine in patients undergoing fast-track anesthesia for open-heart surgery

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ABSTRACT

Simultaneous use of opioids with a different pharmacological profile during anesthesia may lead to unexpected prolongation of effects. In addition, long-term use of transdermal buprenorphine may result in a reduced sensitivity to opioid anesthesia.

In a prospective study, possible overlap of opioid effects and vigilance was determined in a group of patients (n = 22) using a buprenorphine patch for at least two months for treatment of chronic pain, and undergoing fentanyl-based fast-track enflurane anesthesia for open-heart surgery. The patients using buprenorphine were compared with a control group (n = 21) undergoing similar open-heart procedures with no opioid other than fentanyl on board. Aside from time to extubation, total dose of fentanyl, postoperative blood gases, and vigilance assessment score were used to determine possible overlap of opioid effects and/or development of opioid tolerance in the buprenorphine group compared to the control group. Both groups had similar operation and anesthesia times and comparable doses of fentanyl (0.69 mg ± 0.23 vs. 0.67 mg ± 0.16 SD). There was no significant difference in postoperative arterial blood gases (PaO_2 136 ± 48 torr vs. 128 ± 35 torr SD; PCO_2 43.3 ± 3.3 torr vs. 41.9 ± 1.2 torr SD), time until extubation (27 ± 22 min vs. 33 ± 24 min), and postanesthetic vigilance and recovery score (6.8 ± 1.0 vs. 7.5 ± 0.8, arbitrary units) between the two groups.

Because of adaptive mechanisms and the development of tolerance in patients using buprenorphine, respiratory depression or sedation does not project into the postoperative period. The significant ($p < 0.05$) lower incidence of nausea and emesis in patients with transdermal buprenorphine owes to the development of tolerance to these opioid-related side effects.

Key words: transdermal buprenorphine, fentanyl, opioid anesthesia, prolongation, potentiation, side effects, open-heart surgery

INTRODUCTION

An increasing number of patients receive an opioid for the relief of chronic benign pain.[1,2] Little is known regarding patients who have used opioids over a long period of time because of chronic pain who subsequently undergo an operation using an opioid-based technique. It is the general belief that a mixture of opioids with different modes of action results in an unpredictable interaction, causing additive, or even synergistic, effects[3] with potential cardiovascular depression, prolonged awakening, and longer intubation times.

Also, in such patients, the rational choice of the anesthetic agent is crucial because tolerance may have developed,[4] and an opioid-based anesthesia technique may require higher than normal doses to achieve sufficient antinociceptive effect.[5,6]

With the recent introduction of transdermal buprenorphine (Transtec, Napp Pharmaceuticals, Cambridge, UK; Grünenthal, Aachen, Germany) for the treatment of chronic pain, an increasing number of patients scheduled for operation are receiving this potent opioid.[7-9] Our prospective open-label study was therefore undertaken to assess the response of these patients when they received an additional opioid for anesthesia.

Patients undergoing open-heart surgery were selected because in these cases anesthesia is rarely administered without the addition of an opioid. In such cases, it is important to establish whether patients receiving buprenorphine are resistant to the antinociceptive action of fentanyl, as demonstrated by patients receiving morphine.[10] Also, because fentanyl is a necessary adjunct to the anesthetic regimen, evaluation of potential interaction is of particular interest, especially because buprenorphine has been shown to act as a partial agonist at the μ-opioid receptor, capable of reversing the action of a pure μ-ligand such as fentanyl.[11] On the other hand, it has also been demonstrated in pain therapy with buprenorphine that higher than normal doses of the pure agonist morphine

Table 1. Demographic data of two groups of patients undergoing open-heart surgery with and without transdermal buprenorphine medication

Group	Gender (M/F)	Age (years)	Height (cm)	Weight (kg)	Operation time (min)	Anesthesia time (min)	Total fentanyl (mg)
Buprenorphine plus fentanyl (n = 22)	17/5	62 ± 13	175 ± 8.9	80 ± 18	224 ± 46	285 ± 44	0.69 ± 0.23
Fentanyl alone (n = 21)	17/4	65 ± 12	172 ± 8.0	79 ± 11	225 ± 58	309 ± 71	0.67 ± 0.16

are not required when it is administered concurrently.[12] Therefore, the following questions remain: Is there an increased need for fentanyl during an opioid-based anesthetic technique in patients using buprenorphine? Does the anesthesiologist have to anticipate a possible prolonged respiratory depression after a fentanyl-based enflurane anesthetic technique when patients have been using buprenorphine chronically? And, lastly, do patients with two opioids on board demonstrate a prolongation of awakening that results in the need for a longer intubation time, conflicting with the contemporary, fast-track motif?

METHODS

After Institutional Review Board approval, 22 patients scheduled to undergo coronary artery bypass grafting (CABG, n = 17), mitral valve replacement (n = 3), or closure of an atrial septal defect (n = 2), and who had been using transdermal buprenorphine for at least two months for chronic back pain [35 µg per h (n = 19) or 70 µg per h (n = 3); Table 1] were incorporated in a prospective and open-label study. Patients received the following premedication: 0.15 mg per kg diazepam plus 2.8 mg per kg phenobarbital given orally the night before operation. On the morning of operation, a further oral dose of 0.15 mg per kg diazepam was followed by a combination of 0.7 mg per kg pethidine and 0.35 mg per kg promethazine given subcutaneously 60 minutes before surgery.

In the induction area, in addition to electrocardiogram pregelled electrodes (lead II), a frontotemporal three-lead Bispectral Index (BIS) electrode was attached to measure the depth of anesthesia. The left radial artery was cannulated to measure blood pressure, and a catheter introduced via the jugular vein to measure the central venous pressure. Also, a rectal temperature probe was placed for continuous temperature monitoring during controlled hypothermia. Once instrumentation was complete, control values for blood pressure, heart rate, and arterial blood gases were recorded, and anesthesia induced with a loading dose (4.5 µg per kg, i.v.) of fentanyl. This was followed by the neuromuscular-blocking agent pancuronium bromide (0.12 mg per kg, i.v.). If the hypnotic effect was insufficient (BIS > 40) and the patient still responded to verbal commands, an additional dose of thiopental was given (1.5 mg per kg, i.v.). After laryngoscopy and intubation, anesthesia was maintained with enflurane (1.0 to 2.5 vol percent in oxygen) to obtain steady hypnotic effects using a BIS value between 30 and 40. An additional dose of fentanyl (1.5 µg per kg) was administered to guarantee stress-free anesthesia before sternal split, when the BIS value rose above 50 and/or the cardiovascular response increased by 20 percent above preinduction levels. During cardiac bypass, anesthesia was maintained by direct administration of the volatile agent (1 vol percent) into the oxygenator. Whenever possible, no opioid was administered after bypass. Fast-track anesthesia was achieved by tapering down the volatile agent toward the end of surgery. Patients with stable cardiovascular parameters were extubated within 60 minutes of the end of operation. Exclusion criteria for patients not undergoing fast-track anesthesia were as follows: an unstable cardiovascular system with need for catecholamines and/or arrhythmia, pathologic preoperative pulmonary function test with high $PaCO_2$ and/or low PaO_2 values, and postoperative bleeding through chest tubing.

For comparison purposes, a similar group of patients (n = 21) undergoing elective open-heart surgery (CABG, n = 13; tricuspid valve replacement, n = 1; closure of an atrioseptal defect, n = 2, atrioventricular defect, n = 5), underwent the same anesthetic procedure, with no opioid other than fentanyl on board.

In addition to intraoperative antibiotics, all patients received the nonsteroidal anti-inflammatory drug metamizol (2 g i.v.) plus acetaminophen (1 g i.v.) before extubation for postoperative pain relief.

Before anesthesia and 60 minutes after extubation, the following variables were measured:

- Heart rate and blood pressure via an indwelling arterial catheter.
- BIS value from an Aspect (Newton, MA) electroencephalogram monitor using a frontotemporal electrode montage.

- Arterial blood gases (PaO_2, $PaCO_2$) from repetitively drawn arterial blood samples.

Postoperatively, the state of the patient was assessed using a modified postanesthetic vigilance and recovery score, as originally devised by Aldrete and Kroulik[13] (Table 2). An independent observer unaware of the anesthetic regimen evaluated parameters such as muscle activity, respiration, circulation, state of consciousness, and temperature 60 minutes after extubation. The time at which patients required a postoperative analgesic was also recorded, using the visual analog scale (VAS; from 0 to 10). When a score above 5 was noted for the last three assessments, piritramide (3 mg i.v.) was administered until the VAS score dropped below 3. Last, but not least, the incidence of nausea and/or emesis was recorded in all patients by the independent observer who, while taking pain scores, also questioned patients on these side effects. If any patient complained of nausea, the HT3-antagonist granisetron (2 mg) was administered intravenously.

STATISTICAL ANALYSIS

Before starting the prospective open-label study, a priori power analysis was performed. This was necessary to calculate the number of patients needed to demonstrate a possible statistical significance between the buprenorphine and a control group. Based on a previous study of patients after open-heart surgery, it was necessary to detect a difference of maximal power values by 50 percent, an effect level of 1.0, with an error of 5 percent. To demonstrate significance with a power of 80 percent, at least 20 patients were necessary.

The multiple analysis of variance (ANOVA) nonparametric test was used to calculate statistically significant differences within one group at different time points. Because patients did not fulfill Gaussian distribution, the Mann-Whitney two-tailed test was used when computing a significant difference between groups. Statistical significance was defined as a p-value of < 0.05.

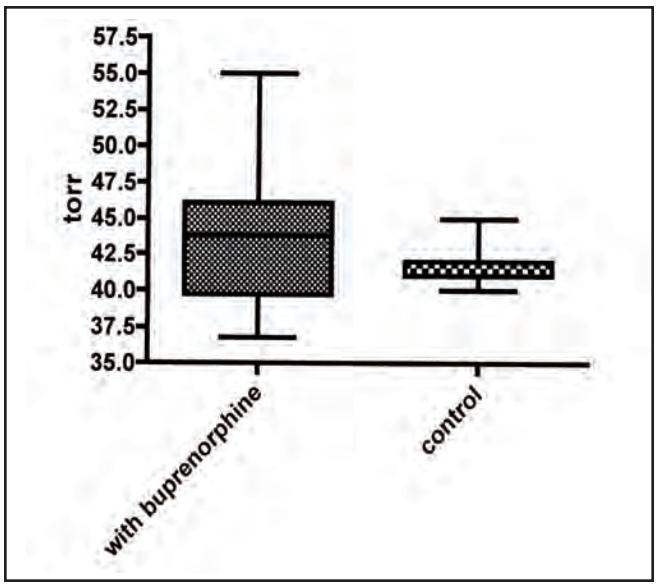

Figure 1. Box plots of arterial $PaCO_2$ values in two groups of patients after open-heart surgery with and without a buprenorphine patch (mean ± SD).

RESULTS

There was no significant difference in demographic data of patients using a buprenorphine patch for at least two months for chronic back pain and those patients without transdermal buprenorphine undergoing open-heart surgery (Table 1). In addition, there was no significant

Table 2. Modified Aldrete score

	0	1	2
Conscious state	Nonresponsive	Responds to stimuli	Fully awake
Activity	No movement of extremities	Moves two extremities voluntarily or on command	Moves four extremities voluntarily or on command
Respiration	Apneic	Dyspnea, shallow or limited breathing	Able to breathe deeply and cough freely
Circulation	Systolic BP > 20 percent of preanesthetic level	Systolic BP ± 11 to 20 percent of preanesthetic level	Systolic BP within 10 percent of preanesthetic level
Temperature	< 35.0°C or > 37.5°C	35.0°C to 36.5°C	36.5°C to 37.5°C

BP, blood pressure.

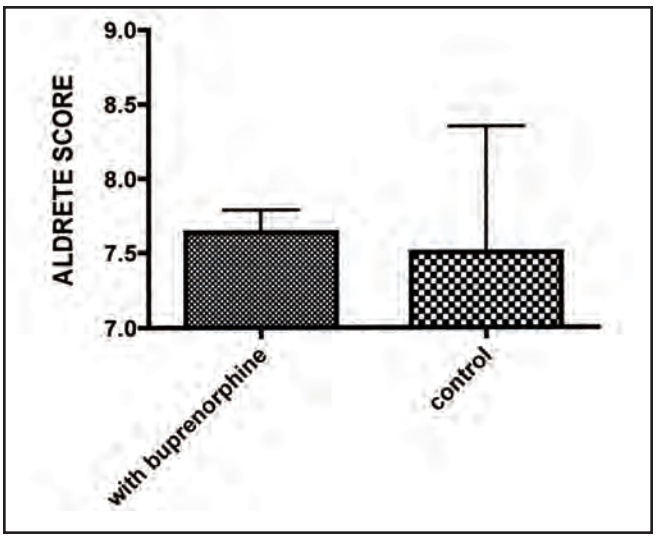

Figure 2. Postoperative vigilance assessment score in two groups of patients with and without buprenorphine after open-heart surgery in fentanyl-based enflurane anesthesia (mean ± SD).

difference between the two groups in regard to total time of operation, total time of anesthesia, and the total dose of fentanyl being administered for anesthesia (Table 1).

In the postoperative period there was no difference in arterial blood gases 60 minutes post extubation. With pure oxygen inhalation, arterial PaO_2 was characterized by a mean of 136 torr (± 48 SD) in the group with and by a mean of 124 torr (± 16 SD) without buprenorphine. With regard to arterial $PaCO_2$, there was a mean of 43.3 torr (± 3.3 SD) in patients with buprenorphine and a mean of 41.9 torr (± 1.2 SD) in the group without, reflecting no significant difference between the two sets of patients (Figure 1). Also, none of the patients in both groups had to be reintubated because of a late respiratory depressive effect.

Such lack in prolongation of opioid effects with an overlap into the postoperative period is also reflected in the postoperative vigilance assessment score. Data were taken 60 minutes after extubation when patients were supervised in the intermediate-care unit with no arousal stimuli around them, which may have accounted for any change in the state of vigilance. Aldrete score was 7.6 (arbitrary units) in the group with buprenorphine, compared to a mean of 7.5 (arbitrary units) in patients having received only fentanyl (Figure 2). These data demonstrate no significant difference between the two groups of patients.

Similar to the state of vigilance, postoperative cardiovascular parameters were similar in both groups, 60 minutes after extubation. Mean systolic blood pressure was 133 mmHg (± 11 SD) in patients receiving buprenorphine, and 124 mmHg (± 11 SD) in patients that were not. Such lack in difference was also mirrored in the diastolic pressure, which was 69 mmHg (± 9 SD) in patients with and 68 mmHg (± 8 SD) in patients without buprenorphine.

Statistical analysis of heart rate changes in the postoperative period had to be omitted because nine patients in the group with and 13 patients in the group without buprenorphine were paced with an external pacemaker using a fixed frequency of 90 beats per minute.

The majority of patients (85 percent) required additional analgesia for postoperative pain relief as early as 20 to 30 minutes after extubation. Although there was no significant difference between the two groups in regard to the time of first demand, there was a tendency of patients with buprenorphine for a later demand (22.5 ± 10 minutes SD vs. 15.8 ± 12.7 minutes SD).

Even though total intraoperative requirement for fentanyl was not appreciably higher in patients not receiving transdermal buprenorphine, none of the 22 patients receiving the buprenorphine complained of nausea or experienced bouts of emesis postoperatively. This is significant ($p < 0.05$), because 24 percent of all patients not receiving buprenorphine demonstrated nausea, emesis, or both.

DISCUSSION

These are, to our knowledge, the first results obtained in patients receiving transdermal buprenorphine for chronic pain who underwent open-heart surgery while using fentanyl during anesthesia. Such data are important, as they reflect a possible interaction of two opioid analgesics with different characteristics. One is the potent opioid fentanyl, 200 to 300 times more potent than morphine, and a pure μ-agonist.[14] The other opioid, buprenorphine, is a partial μ-agonist with a potency 40 times that of morphine, which unlike fentanyl is an antagonist at the opioid κ-receptor,[15] characterized by a long duration of action.[16] More importantly, we addressed the question of whether the coadministration of fentanyl on buprenorphine results in an additive effect, with sequelae that involve the cardiovascular, respiratory, and central nervous systems, as reported by others.[17]

Few researchers have used buprenorphine during CABG surgery.[18-20] Contrary to these studies, however, buprenorphine was administered by the transdermal route in our patients. Although a decline in the plasma level of buprenorphine can be anticipated with the start of cardiopulmonary bypass, resulting in an increase in the elimination half-life ($t_{1/2}\beta$), there was no prolongation of respiratory depressive and sedative effects. Such increase in $t_{1/2}\beta$, although not measured, can be derived from data seen with other opioids (fentanyl, alfentanil, and sufentanil),[21,22] an effect owing to hemodilution and hypothermia, and which should have resulted in a prolongation of $t_{1/2}\beta$ of buprenorphine. However, because receptor occupation and not plasma level is the relevant

factor in mediating an opioid effect, any possible increase in $t_{1/2}\beta$ is irrelevant. This assumption is underlined by receptor binding and displacement studies,[23,24] in which buprenorphine has an eight- to 11-fold higher affinity than the short-acting fentanyl.[25,26] Furthermore, buprenorphine demonstrates a much slower dissociation rate from the receptor site than fentanyl,[15] so it may be concluded that, despite any probable decline in plasma levels, receptor occupation remained high in the group of patients receiving buprenorphine. Thus, receptor occupancy in the present patient population can be assumed to be similar during pre- and intraoperative periods, especially because buprenorphine patches had been used previously over a long term. With a steady binding of buprenorphine at receptor sites, any additional injection of fentanyl would be likely to interact with the pre-existing opioid. Contrary to widely held belief, however, the injection of fentanyl did not result in an additive effect followed by a prolongation and possible potentiation of opioid action. This is demonstrated in postoperative arterial blood gases and vigilance assessment scores, which reflect a possible prolongation of opioid action after patients have been extubated. Because all patients inhaled pure oxygen via a facemask at a flow rate of 3 to 6 L per min, high values are typical. Therefore, arterial $PaCO_2$ can be considered a more sensitive marker for prolonged opioid action on respiration. Because arterial $PaCO_2$ and the Aldrete score were not different among the two groups, one may presume that receptor occupation by buprenorphine was not high enough to enhance the opioid effects of fentanyl. This presumption can be excluded because patients' transdermal patches were not removed and they induced sufficient analgesia in chronic pain patients, lasting for at least three days preoperatively.

Such lack of additive effects, when compared to a control group without buprenorphine, may be explained by the following reasons. First, fentanyl is metabolized in large amounts during the course of anesthesia, and hemodilution takes place during cardiopulmonary bypass; consequently, clinically relevant plasma concentrations may no longer exist postoperatively, so no effects of the opioid combination can be detected. Although fentanyl plasma concentrations may have declined with the start of cardiopulmonary bypass, it is receptor occupation and not plasma level that is the relevant predictor in mediating an opioid effect.[27] Most importantly, however, long-term prior use of buprenorphine (minimum period, two months) means that these patients cannot be regarded as opioid naïve. Adaptive mechanisms, especially those regarding respiration and sedation, have led to a compensatory mechanism and the development of adaptation such that a lower level of respiratory depression, a lower incidence of nausea and emesis, and, similar to patients without buprenorphine, no increase in the sedative effect and depression in vigilance score can be expected. This adaptation process is a typical trait in chronic pain patients taking opioids for a protracted period, resulting in the respiratory center being less sensitive to opioids and having a tolerance to their sedative and emetogenic effects.[1,28] This is in line with our results, in which the presence of buprenorphine before the administration of fentanyl did not prolong respiratory depression or time until extubation when compared to a control group. On the contrary, development of selective adaptation led to an observable reduction in nausea and emesis.

The previous use of buprenorphine did not induce an antagonistic effect[11,29] in the present patient population, because both groups needed similar amounts of fentanyl during surgery. One reason for this lack of antagonism is the receptor reserve, a characteristic feature of buprenorphine,[16] which allows an additional opioid to interact with so-called free, unoccupied receptors and initiate an analgesic effect. Such receptor reserve owes to the high affinity of buprenorphine to the receptor site, resulting in a smaller fractional occupancy than fentanyl, with lesser dosages and lesser receptor binding to elicit an analgesic effect.[30,31] Moreover, the antagonistic effect of buprenorphine only becomes apparent when the partial agonist is administered after a pure opioid ligand such as fentanyl, thus reversing the depressed respiratory drive and increased vigilance.[11,29] Because of the high affinity for the opioid μ-receptor,[32] buprenorphine is able to reverse the respiratory depressant effect of fentanyl. As buprenorphine was not given after fentanyl in these open-heart surgery patients, no antagonistic effect could be observed in the present patient population. In addition, there was no evidence of tolerance to the antinociceptive effect of fentanyl, which would have been indicated by a need for higher doses than the group not being on buprenorphine. Contrary to the present patient population, Leon-Casaola and coworkers observed dosages three times higher of an opioid for postoperative analgesia in opioid-dependent patients.[33] This difference very likely owes to the diverse antinociceptive mode of action of buprenorphine, which contrary to fentanyl is mediated via μ-opioid receptor subtypes[26,34,35] and the interaction with a different subset of intracellular G-proteins,[36] resulting in less development of tolerance to the analgesic effect.

In summary, this prospective study clearly demonstrates that patients who use transdermal buprenorphine over a long period, and who require opioid-based anesthesia, experience neither an additive nor an antagonistic effect. The reason is that such patients cannot be regarded as opioid naïve and they have already adapted to an opioid agent. When a pure μ-receptor ligand such as fentanyl is subsequently given as a bolus, because of partial tolerance and higher levels for respiratory and cardiovascular depression and sedation, there is no consequential overlap of effects into the postoperative period.

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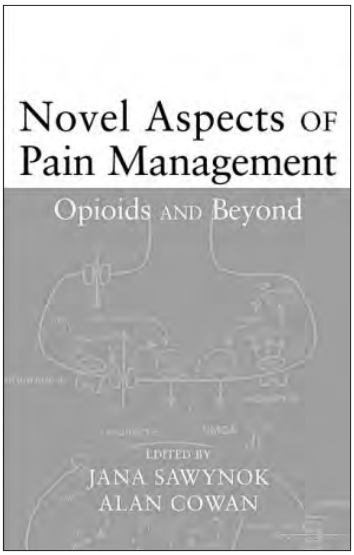

***Novel Aspects of Pain Management: Opioids and Beyond*. Edited by Jana Sawynok and Alan Cowan. Published by Wiley-Liss Inc., New York, 1999; 373 pp.**

Over the past four decades, significant changes have occurred in our understanding of pain signaling and pain suppression. After the development of endogenous opioid peptide discoveries, receptor-binding technologies, and the role of central sensitization in inflammatory and neuropathic pain states, additional awareness now surfaces with the multimodal multiplicity of neurochemical mediators that mediate pain signaling. This phenomenon occurs at peripheral sites and at the dorsal spinal cord sites where pain information initially enters the central nervous system and initiates supraspinal site activity where pain is processed.

This unique text develops the properties of many new and novel chemicals that mediate pain processing and reviews in a comprehensive scientific and systematic manner the involved technology, which helps us negotiate pain in a more effective and efficient manner. The recognized authors of this text are international scientists and clinicians who are experienced in pain research and educational and clinical endeavors. Each author provides a historical perspective for a class of agents and assesses their potential for therapeutic development. Professionals that may benefit from this text include academicians, scholars, pain fellows, clinicians that negotiate pain management/medicine, educators, and neuropsychopharmacologists that are involved in developing new technologies to mediate pain. A clinician whose goal is to increase functionality and activities of daily living for their patients who are victimized by pain will also find this text very valuable.

This text is organized into 17 chapters, as follows: neurophysiology of acute and chronic pain, animal models of pain, advances in pharmacology of opioids, new insights into the pharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs), peripherally acting analgesics, vanilloids as analgesics (i.e., capsaicin), neurokinin antagonists, excitatory amino acid antagonists and their potential analgesics for persistent pain, α-2 adrenergic agonists that are used as analgesics, serotonin and its receptors in pain control, the value of purines as potential for development as analgesic agents, gamma amino butyric acid and pain, cholinergic agonists as analgesics, dopaminergic drugs as analgesics, tricyclics and other antidepressants as analgesics, voltage-gated ion channel modulators and superb channel, and spinal drug interactions.

Each chapter culminates in a very extensive bibliography, and each page is footnoted precisely within the article. Each chapter may stand independently as a peer-reviewed article. All tables and figures are easy to read and excellently referenced, with good legends under each. Many of the subjects are presented in different chapters, projecting a different point of view. A list of these include the following: acute pain, adenosine, analgesics, antidepressants, antinociception, calcitonin gene-related peptide, dorsal root ganglion, excitatory amino acid antagonist, glutamate, 5-hydroxy tryptamine, morphine, neuropathic pain, N-methyl-D-aspartate, NSAIDs, opioids, spinal cord, substance P, and voltage-gated ion channels.

This text is extremely well written. It is a must for any clinician who wishes to examine the past and project themselves into the future of pain medicine. The size of the print is very appropriate and provides us all with a glimpse into the future based on significant scientific principles.

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