Journal of Opioid Management™

A medical journal for proper and adequate use

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Official Journal of Opioid Management Society

CONTENTS

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Call for manuscripts

Editorial Policy

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

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

Manuscript Format

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

Figures & Tables

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

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

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

References

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

Journal articles—

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

Books—

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

Book chapters—

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

Web sites—

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

Ethics

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

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

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

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Journal of Opioid Management™

A medical journal for proper and adequate use

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

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

Editorial Review Board

OPIOID MANAGEMENT SOCIETY
470 Boston Post Road
Weston, MA 02493

Dear Colleagues,

On April 22-23, the inaugural Opioid Certification Program was held in Boston, Massachusetts. This truly was a "happening" with more than a hundred attendees and a world class roster of speakers all focusing on the clinical use of opioids in pain management practice. The excitement throughout the weekend was contagious since a conference like this had never been done before and so much information was disseminated that the organizers ran out of pens to take notes! One unique aspect of the conference was the give and take between the attendees and the speakers extending well beyond their alloted presentation times.

Personally, I felt that my knowledge base concerning the use of opioids was more than adequate, since I prescribe these drugs as part of my academic medical oncology practice. However, I learned much more about them, which questions the validity of the axiom about teaching an old dog new tricks! Here are a few new tricks I learned:

- The DEA's mission is broader than merely looking over the shoulders of each practicing physician. Drug diversion including Internet acquisition of opioids is now the main area on their radar screen. We can protect ourselves by appropriate prescribing and documentation in the medical record. Above all, we must protect access to our DEA numbers.
- There is wide variation among states in regulations and statutes concerning opioids.
- Evidence-based medicine continues to support the use of these drugs for chronic nonmalignant pain.
- A broad array of adjuvant analgesics exist, some of which are underutilized.
- Opioid rotation is a useful tool when the arbitrary upper limit of an opioid is reached and the patient is tolerant and in pain. I think I am starting to become a believer in this concept.
- Interventional pain management, especially with the newer technology, is reaching broader use in practice.
- Lidocaine patches may be effective for neuropathic pain.
- Research into up and down regulating opioid receptors is becoming more translational into clinical practice.

My personal thanks to all the speakers and conference attendees for a great educational weekend. We were all there for one simple reason: to give our patients with pain the best care available.

If you missed the Boston conference, there are planned similar conferences around the country in the upcoming months, and we hope to see you there.

Robert E. Enck, MD

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

Inaugural Opioid Certification Program

Christopher V. Rowland, Jr., MD, Editor

As many of you know, the Opioid Management Society, in association with the *Journal of Opioid Management*, staged their inaugural Opioid Certification Program on April 22-23, 2006, at the Conference Center at Harvard Medical in Boston, Massachusetts. And this two-day intensive conference was, I can say without hesitation, a great success! Over 90 percent of the attendees rated the conference as "excellent" or "very good."

Here then is a quick review of the weekend's program, led by a renowned group of pain specialists, academicians, and legal experts.

SATURDAY, APRIL 22

Robert Enck, our Editor-in-Chief, opened the conference by reminding us that pain is part of our human lot and a worldwide problem causing needless suffering and economic burden. Opioids are the cornerstone of pain management but are often underused and poorly understood.

A group supervisor from the office of diversion control, New England field division, Drug Enforcement Administration, made a brilliant and frightening presentation of today's condition of the controlled substance wars. The DEA is clearly educated, sophisticated, and working hard to control illegal use and abuse of prescription drugs by physicians, pharmacists, and particularly Internet scams. Our intention is certainly to help our patients with these powerful medications, but the road to hell is still paved with good intentions, and this presentation is a very strong dose of education.

Attorney Jennifer Bolen came to the aid of the defense with a nicely balanced discussion of what documentation is needed, the importance of a detailed history and physical, the careful follow-up, and monitoring of patients for whom opioids are prescribed. All this done in good faith and with care, make it possible to use these powerful medications with safety to both patient and physician.

Professor of Law, Marshall Kapp, took up the challenge of legal and ethical issues for opioids in palliative care. Ethical and legal duties sometimes conflict, and the physician may be on his own to sort through them to do what is best for the patient. Again, there is the need for careful documentation and consultation. He points out the need for changes in the law, particularly as it is interpreted and enforced.

Tomasz Stefaniak, from the Medical University of Gdansk, Poland, considered the matter of legal aspects of opioids in everyday practice. We are damned if we underprescribe and damned if we overprescribe, and where lies the happy balance? There is acute pain, chronic pain, and intractable pain, and each requires its own approach. He helps us through this thorny thicket, with a detailed and thoughtful presentation.

Paul Sloan, professor of anesthesia, oncology, and palliative medicine, presented a most interesting discussion on the use of opioids for chronic pain. Again the legal issues were there, and he led us through his own highly informed way of looking at them and treating the patient properly.

Robert Barkin, from the Rush University Medical Center, gave us an overview of pain management from the pharmacologist's viewpoint, differentiating acute from chronic pain and somatization. Appropriate medications and how to use them were part of the discussion.

Professor Enck reminded us that pain is a complex condition, filtered through each person's age group, culture, personal experience, and neurophysiology. Physicians tend to underestimate pain by a third, by failing to take into account confounding external and internal factors. One size does not fit all.

Gilbert Fanciullo, professor of anesthesiology, related that, while acute pain from cancer and other noncurable illnesses required opioids, there were other options for pain control in chronic conditions or when addiction is an issue. There are behavioral interventions, pharmaceutical measures that are nonaddicive, and a number of other modalities that may be safe and effective.

SUNDAY, APRIL 23

Ricardo Vallejo, of the Millennium Pain Center, started day two of the conference with a history of opioids and how this history of their use and abuse impacts present-day conflict among law enforcement, lay people, and physicians. This results in their under utilization in general, and for chronic conditions in particular.

Mellar Davis, from the Cleveland Clinic, took on the formidable task of the science of opioids. Opioids function under opponent process theory that centrally reduces effect, which is the same as building tolerance. He discussed opioid withdrawal syndrome, opioid facilitated pain, and some basic science issues and facts.

For a second presentation, Professor Fanciullo chose the rotation of opioids. Escalating requirement may be the result of worsening disease or tolerance, until a ceiling is reached. Rotation may result in a 40 percent dose reduction and the same or better control.

Gary Reisfield, from the University of Florida, contributed a clear and useful talk on the types of opioids. Natural vs. synthetic, strong vs. weak, various durations of action, analgesic vs. nonanalgesic, legal vs. illegal, etc.

George Wilson, the second member of the tag team and also from the University of Florida, took up the uses of opioids. These include analgesia, anesthesia, antitussive, antidiarrheal, antispasmodic, drug abuse, opioid maintenance and detoxification, vasodilatation, and antiterrorism. That this good and useful medication is so much at controversy is surely a reflection of the good and evil in our nature, and not in opioids.

Ramsin Benyamin, a staff anesthesiologist, presented interventional techniques in pain management. Back, neck, and head pain have common causes, and interventions include sacroiliac injection, facet/medial branch injection, and a host of others.

Robert Kulich, a psychologist, rounded off the conference with a contribution on nonopioid strategies in managing pain. Psychosocial issues and careful screening were discussed in relation to treatment of chronic pain with opioids. Behavioral strategies were presented to achieve better adherence to medical treatment regimens.

FUTURE CONFERENCES PLANNED

Because everyone agrees, from the registrants to the presenters to the sponsors, that this conference was an unmitigated success, the Opioid Management Society is planning a series of similar conferences in major US cities across the country scheduled for the fall of 2006 and spring of 2007. For more information about upcoming conferences, including the 2006 schedule, go to *www.opioid managementsociety.org*.

Make your thoughts known!

Write *Journal of Opioid Management*!

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

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

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CALENDAR

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

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American Society of Pain Educators
Pain Educators Forum 2006
July 20-23, 2006
Sheraton Philadelphia City Center
Philadelphia, Pennsylvania

For registration information, contact:
American Society of Pain Educators
7 Oak Place, Suite 7
Montclair, NJ 07042
Tel.: 888-277-3734
Fax: 973-453-8246
Web site: *http://www.paineducators.org*

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

For registration information, contact:
American Academy of Pain Management
Tel.: 209-533-9744
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Web site: *http://www.aapainmanage.org/conference/Conference.php*

International Association for the Study of Pain (IASP)
Pain in Europe V
5th Congress of the European Federation of IASP Chapters (EFIC)
September 13-16, 2006
Istanbul Convention & Exhibition Centre (ICEC)
"Lufti Kirdar"
Istanbul, Turkey

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16th International Congress on Care of the Terminally Ill
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Montreal, Canada

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The Fairmont South Hampton, Bermuda

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COMMENTARY

Reality and responsibility: A commentary on the treatment of pain and suffering in a drug-using society

Steven D. Passik, PhD
Howard Heit, MD, FACP, FASAM
Kenneth L. Kirsh, PhD

ABSTRACT

While opioids are a necessary part of the armamentarium of pain management, there has been a growing trend toward prescription drug abuse and diversion in our society. Meeting the goal of treating pain while not contributing to drug abuse and diversion requires vigilance and education. Physicians and patients have been singled out as the main players in the societal problem of diversion of prescription drugs. In fact, the problem can only be overcome when not only physicians and patients but also healthcare practitioners, third-party payers, law enforcement agencies and regulators, the pharmaceutical industry, and the media finally work together to prevent it, instead of fingering any one party for the blame.

Key words: opioids, pain management, prescription drug abuse, prescription drug diversion

OVERVIEW

That 50 million Americans suffer with chronic pain is not news,[1-3] and as our population continues to age, this number is likely to grow. Unfortunately, pain continues to be undertreated, and sometimes poorly treated. Between 40 and 60 percent of people with severe pain associated with life-limiting illnesses are not receiving adequate treatment for their pain.[4-6] Millions of others with pain from chronic diseases such as arthritis, diabetes, and low back problems have difficulty finding and paying for qualified professionals willing to help them gain access to the medicines, physical and psychological therapies, and surgical/anesthetic interventions that can help improve the quality of their lives.

In the twenty-first century, and in a society with one of the most advanced healthcare systems in the world, patients should not have to bear relievable pain. Undertreatment of pain is due in part to another fact of life in our society: addiction. Nearly 10 percent of Americans are addicted to illicit drugs; 15 percent are addicted to alcohol, 25 percent are addicted to nicotine; and 33 percent have sampled illicit drugs at least once.[7-9] Four million Americans used prescription drugs for nonmedical purposes last year. Healthcare professionals, patients, regulatory agencies, law enforcement, media, and payer stakeholders have failed to address relief of suffering in the face of addiction. The pendulum has swung relentlessly from providing adequate treatment of pain to preventing addiction, without solving one or the other problem sufficiently.

In 1946, the head of the American Medical Association wrote that physicians should "spare their terminally ill cancer patients the indignity of morphine addiction." More recently, pain specialists have downplayed the assessment required to quantify the risk of addiction in patients, while regulators and law enforcers crack down on prescribers for the amount of morphine they provide or the dosages they prescribe. Payers also play a role in the problem, forcing poorly monitored, drug-only therapy on patients who require more monitoring or more resources. Refusing reimbursement and seeking the least expensive and most politically expedient approaches to the problem of chronic pain lead only to personal tragedy, suffering, loss, and ruined lives. We were moved to write this commentary because we believe these issues have been oversimplified, fostering misunderstanding and failing to reconcile issues of responsibility.

Addiction, identified as a unique combination of neurochemical, genetic, and socioenvironmental factors (e.g., economics, stress, boredom, loneliness, and despair), is alive and well.[10] Thus, markets for high-quality legal and illegal controlled substances thrive. Where there is pain, there will be people seeking access to these drugs. This problem cannot be eliminated by having members of the pain community issue platitudes about how pain medicines are unlikely to be abused by "our patients." Such arguments foster further polarization. Prescription drug abuse is real; the growth curve of misuse of these medicines is steeper than that seen with

crack cocaine, and the rate at which new and young users are getting into serious trouble and requiring admission to treatment programs is unprecedented.[11-13] All pain management in our society is conducted against a backdrop of addiction, diversion, and misuse.

Addiction thrives in a world where many suffer chronic pain. Concerns about the prevention of addiction must be addressed first by acknowledging the problem of untreated pain and suffering, even before legislative or other actions are taken to combat misuse or diversion. Unintended negative effects on those who legitimately require pain relief must take precedence. Stakeholders must jointly develop realistic strategies for using pain medicines and other treatments in the real world.

The ever-shortening American attention span and the hunger for anecdotal evidence of the misuse of prescription drugs by high-profile celebrities has unfortunately reduced a highly complex social, medical, and political problem to discussion over whether pain medicines are "good" or "bad" and whether or not they should be available. Of course, there is no question that these drugs should be available, and there should also be no debate over whether all pain patients should be treated in the same way. In fact, the chronic pain population is incredibly heterogeneous and varies tremendously with regard to vulnerability to addiction and abuse. The only way to make pain treatment available to all is to tailor it in such a way as to reduce pain and suffering. An individualized regimen for each patient would be required.

The increased use of opioids in the past 10 to 15 years has been a key element in expanding the accessibility of pain treatment. As a safe and affordable mode of pain treatment, opioids will remain an important part of the pain armamentarium. The only way to keep opioids available to those who need them is to have all of the stakeholders examine their pieces of the puzzle collaboratively.

ADDICTION AND DEPENDENCE

Healthcare professionals are often poorly trained with regard to pain and addiction and the interface between them.[14] This lack of training promotes the perpetuation of myths and confusion. There is little understanding about what distinguishes addiction from physical dependence. It is not universally understood that the presence of withdrawal symptoms is not necessarily an indication of addiction. Nor is it understood that periodic upward titration, sometimes required to maintain analgesic effects, is a matter of drug tolerance, not necessarily addiction. Heroin abusers are generally physically dependent, tolerant, *and* addicted. Pain patients usually are physically dependent and tolerant, but *not* addicted.

How do we make this distinction? Addiction is a chronic brain disease that is marked by the "four Cs": **C**ontinued use of drug despite harm, loss of **C**ontrol over the drug, **C**ompulsive use of the drug, and **C**ravings for the drug. Pain patients generally enjoy stabilization or improvement in functioning when opioid therapy is appropriately prescribed, whereas addicts almost always suffer a downward decline in function and quality of life when using drugs. Aberrant behaviors in pain patients might be totally unrelated to addiction. Patients might appear to exhibit addictive behaviors that actually stem from serious pain or emotional distress. This problem is called pseudoaddiction and should be distinguished from addiction.[15]

Some chronic pain patients suffer a decline in function on opioids. Their drug use might not be "out of control" or compulsive, but they are unable to truly abide by the parameters of treatment. Although these patients are not addicted in the same sense of the term as are illicit drug users, many of them should be considered for discontinuation of opioid treatment and provided other interventions for pain.

Opioid therapy is not without risk and is not for everyone. Pain therapy and opioid therapy are not synonymous (e.g., pain therapy may involve the use of opioids, but it also might consist of adjuvant medications, physical therapy, coping and relaxation training, interventional techniques, etc., alone and in combination), and not all symptoms of pain need to be, or necessarily should be, treated with opioids. Clinical judgment is always needed in evaluating and prescribing for a pain patient. Psychological, rehabilitative, and interventional techniques might be options for patients who do poorly on opioid drugs, or in some cases might be utilized prior to opioids for patients who are seen as being at an exceedingly high risk for addiction. As addiction is treatable, so is pain. Pain in the context of addiction is also treatable, provided the time and care are taken to individualize treatments.

The major stakeholders in achieving the appropriate balance in the treatment of pain and the prevention of drug abuse and diversion are healthcare practitioners, patients, third-party payers, regulatory bodies, law enforcement, the pharmaceutical industry, and the media. These groups should attempt a thoughtful and unemotional dialogue on this issue, so that opioid treatment can remain available while efforts are made to stem the tide of prescription drug misuse and addiction.

RESPONSIBILITY OF THE HEALTHCARE PRACTITIONER

The problem of prescription drug misuse is not media hype, and it is not confined to remote areas.[12] It requires a tactical and humane approach. The healthcare practitioner should perform an appropriate evaluation of the patient before writing a prescription for a controlled substance. A medical evaluation of the pain complaint

should include a vulnerability assessment for misuse or aberrant drug-related behavior. Thus, an understanding should be reached of the patient's risk factors with regard to a history of chemical dependency, psychiatric comorbidities, social and familial situation, genetic propensity, and spirituality. The results of this assessment should be used not to exclude patients from opioid therapy but to determine the necessary level of agreed-upon boundaries or the help that might be required to manage a patient effectively. A sober assessment should be made to determine whom a particular practitioner can treat given the practitioner's time, expertise in complex psychiatric issues, and resources. Determining whom a practitioner can treat alone or who should be referred is crucial for safe pain management practices. Therefore, healthcare practitioners should arrange consultations as needed. Drug therapy should be determined within the context of a rational treatment plan, based on informed consent of the risks and benefits of all medicines prescribed. Healthcare practitioners should discuss realistic expectations about pain reduction with their patients and help them formulate achievable goals. Helping the patient understand how success or failure should be measured in terms of pain control, function (stabilized or improved), toxicities (manageable or none), and aberrant behaviors (few or none) is crucial for gaining compliance. The healthcare practitioner must, of course, prescribe all medications consistent with state and federal regulations.

RESPONSIBILITY OF THE PATIENT

The patient must follow the agreed-upon treatment plan, which should be based on mutual trust and honesty, especially if opioids are indicated. The patient must also be realistic about what can be achieved by proper pain management. Pain reduction is possible in most cases; however, being pain free is often an unrealistic goal. The patient should discuss his or her expectations with regard to functional activity with the healthcare practitioner. The patient must be responsible enough to take medications as prescribed. The medication delivery system, especially in the case of controlled-release opioids, should not be altered. For example, with a pain medication such as an 80-mg OxyContin tablet, the oxycodone is delivered over a 12-hour period. If the controlled-release system is destroyed, 80 mg of medication would be immediately released within minutes, resulting in serious harm or possibly death, especially in an opioid-naïve patient. Genetically susceptible individuals might experience euphoria by breaking the OxyContin tablet[16]; this constitutes opioid misuse.

Patients should never share their medications and should be responsible for the safekeeping of their medications, since profiting from the "street value" might be a temptation. It is never acceptable for a patient to say his or her medication was lost. At the initial evaluation and follow-up visits, the patient and the healthcare practitioner should honestly report and evaluate the "four As": **A**nalgesia, increased or decreased **A**ctivities of daily living, **A**dverse reactions or side effects, and **A**berrant drug-related behavior.[17] By adhering to a well-thought-out treatment plan, patients can decrease their pain and increase their functioning and thus improve their quality of life.

RESPONSIBILITY OF THIRD–PARTY PAYERS

Third-party payers must recognize that pain treatments vary tremendously across the heterogeneous population of people with chronic pain. Uncomplicated patients (no major psychiatric comorbidity, no history of drug abuse, no contact with a substance-abusing subculture) will require little more than routine medical management. These patients are at low risk for abuse or diversion and can be well managed through optimization of an opioid dose and minimization of side effects. Brief monthly visits should suffice when a patient is stabilized. It is likely that more than half of the chronic pain population will respond to minimal monitoring; however, other pain patients will require having third-party payers ready to support their needs for specialist care, higher levels of monitoring, and psychological and rehabilitative therapies. Others will need concurrent addiction treatment during pain management. Although pain management can be initially expensive for a large percentage of patients, it is hoped that the investment will prevent addiction-related disasters. Third-party payers must accept that it takes time to conduct responsible and proper pain management. While it might take only one minute to write a prescription, it might take as much as 30 minutes to explain why opioids are not in the patient's best interest. Patients should be evaluated in the context of their biological and psychosocial needs, i.e., the physiology of the disease or syndrome in the context of pain and suffering. This can not be achieved in a 10- to 15-minute session; however, if done properly, it can save the industry millions of dollars in unnecessary testing, hospitalizations, and emergency visits.

Cognitive services must be reimbursed consistent with their value to the patient and society. There should be parity in insurance reimbursement in treating pain and addiction consistent with reimbursement for concomitant chronic medical conditions. Access to appropriate medical care for all is society's responsibility.

RESPONSIBILITY OF LAW ENFORCEMENT AND REGULATORS

The regulatory system must strive to embody the central principle of "balance" with regard to the use of controlled substances.[18] The government should establish a system of controls that prevents misuse or diversion of

prescription medications yet ensures availability of opioids for medical, scientific, and clinical purposes. State and federal regulations ensure the safe prescribing of a controlled substance and should not make it difficult to access or practice pain management. New regulations or polices should be coordinated among states. If one state implements an enlightened policy but a neighboring state does not, then the problem is not solved; it just moves next door. In addition, all regulations should be clearly taught to medical students and healthcare practitioners.

Government and private agencies such as the Drug Enforcement Agency, the Food and Drug Administration (FDA), the Center for Substance Abuse Treatment, and private organizations have a responsibility to share data and expertise to determine the weaknesses in the system that lead to the misuse and diversion of prescription medications, including drug diversion from pharmacies, the unlawful procurement of controlled substances from the Internet, counterfeiting of medications, border trafficking of prescription medications, theft from any source, and dishonest patients or healthcare practitioners.

It is difficult to design risk management strategies for opioids, since these drugs can be easily diverted. Data on pharmacy theft have not been made available in nearly a decade, leading to the blaming of drug diversion on doctors and patients. If law enforcement agencies are educated about pain management, they will be able to appreciate patients' need for opioid medicines and understand that prescribing large doses is sometimes necessary for adequate pain management.[19] Some patients are physiological outliers who require high doses. Intractable cases sometimes require unusually high doses. There is tremendous individual diversity in how people respond to opioids. Thus, it is important not to target physicians for writing high-dose prescriptions, tying their hands as they attempt to help patients who do not respond to lower doses. Physicians, however, must educate their communities to be mindful of addiction monitoring in patients predisposed to addiction. High doses should be reserved for patients who otherwise appear to be responsible opioid users.

RESPONSIBILITY OF INDUSTRY

The pharmaceutical companies must develop safe medications for the benefit of society. Their responsibility does not end with the approval of their drugs by the FDA. The pharmaceutical industry should and does conduct post-marketing studies to determine the safety of its products. Priority should be given to improving the efficacy and safety of a product and developing reasonable risk management procedures.

Pharmaceutical companies also have an ethical responsibility to make sure that educational programs they sponsor do not focus solely on selling their products. They must educate program participants on the complexities of pain management. The industry should be commended for its support of continuing medical education programs, especially since there are few courses for healthcare professionals on the prescribing of controlled substances and prevention of addiction following pain management. The industry has also developed CD-ROM and Web-based programs through which healthcare practitioners can receive training on their own time.

Education, not restrictive regulation, is essential to ensure both the appropriate prescribing of controlled substances and prevention of misuse and diversion of these medications. Finally, the industry has the responsibility to train its sales representatives appropriately and then monitor their selling techniques. Inappropriate claims must not be made, and incentives and perquisites must be limited. The sales techniques used for "growing" the market must not interfere with the responsible use of an agent.

RESPONSIBILITY OF THE MEDIA

The media must be committed to responsible journalism based on verifiable facts and basic physiological principles. The media frequently confuses addiction and physical dependence, consequently mislabeling patients. Balanced reporting should include the benefits of pain management, not just the failures in a minority of cases. The majority of chronic pain patients on rational pharmacotherapy have experienced improved quality of life as a result of decreased pain and increased function. While misuse and criminal behavior involving the inappropriate prescribing of controlled substances should be reported, the other side of the story should be told. Focusing on visible targets, such as a high-profile pharmaceutical company, can be misleading. If an approved drug's delivery system has been altered, then the responsibility lies with the person who altered it, not with the pharmaceutical company who manufactured the drug and promoted its use as approved by the FDA.

People who are legitimately treated with pain medication rarely develop problems with addiction, unless they have genetic, social, psychiatric, and spiritual risk factors for addiction. Exposure to potentially addictive drugs does not in itself cause addiction; however, the media often portrays it as doing such. This can frighten patients who use their medications as prescribed and who are at low risk.

SUMMARY

Every American has a stake in this health, economic, and social issue. We are all aging, and many of us will experience pain. Some of us will require treatment for it. Unfortunately, some of us will also know the pain of prescription drug abuse personally or witness it in those we

love. Solutions to this problem must be devised now so that we can enjoy the comfort of knowing that safe and effective pain treatment will be there for us if we require it. It is the responsibility of all to make this a reality.

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REFERENCES

1. Dembe AE, Himmelstein JS, Stevens BA, et al.: Improving workers' compensation health care. *Health Aff.* 1998; 16: 253-257.
2. Osterweis M, Kleinman A, Mechanic D: *Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives.* Report of the Committee on Pain, Disability, and Chronic Illness Behavior, Institute of Medicine, National Academy of Sciences. Washington, D.C.: National Academy Press, 1987.
3. Verhaak PFM, Kerssens JJ, Dekker J, et al.: Prevalence of chronic benign pain disorder among adults: A review of the literature. *Pain.* 1998; 77: 231-239.
4. Glajchen M, Fitzmartin RD, Blum D, et al.: Psychosocial barriers to cancer pain relief. *Cancer Pract.* 1995; 3: 76-82.
5. Ramer L, Richardson JL, Cohen MZ, et al.: Multimeasure pain assessment in an ethnically diverse group of patients with cancer. *J Transcult Nurs.* 1999; 10: 94-101.
6. Ward SE, Goldberg N, Miller-McCoulry V, et al.: Patient-related barriers to management of cancer pain. *Pain.* 1993; 52: 319-324.
7. Colliver JD, Kopstein AN: Trends in cocaine abuse reflected in emergency room episodes reported to DAWN. *Publ Health Rep.* 1991; 106: 59-68.
8. Gfroerer J, Brodsky M: The incidence of illicit drug use in the United States, 1962-1989. *Br J Addict.* 1992; 87: 1345-1351.
9. Regier DA, Meyers JK, Dramer M, et al.: The NIMH epidemiologic catchment area program. *Arch Gen Psychiatry.* 1984; 41: 934-941.
10. Rinaldi RC, Steindler EM, Wilford BB, et al.: Clarification and standardization of substance abuse terminology. *JAMA.* 1988; 259: 555-557.
11. Hancock CM: OxyContin use and abuse. *Clin J Oncol Nursing.* 2002; 6: 109.
12. Hays L, Kirsh KL, Passik SD: Seeking drug treatment for OxyContin abuse: A chart review of consecutive admissions to a substance abuse treatment facility in the bluegrass region of Kentucky. *J Natl Compr Canc Netw.* 2003; 1: 423-428.
13. Joranson D, Ryan K, Gilson A, et al.: Trends in medicaid use and abuse of opioid analgesics. *JAMA.* 2000; 283: 1710-1714.
14. Weinstein SM, Laux LF, Thornby JI, et al.: Medical students' attitudes toward pain and the use of opioid analgesics: Implications for changing medical school curriculum. *South Med J.* 2000; 93: 472-478.
15. Weissman DE: Understanding pseudoaddiction. *J Pain Symptom Manage.* 1994; 9: 74.
16. Schlaepfer TE, Strain EC, Greenberg BD, et al.: Site of opioid action in the human brain: Mu and kappa agonists' subjective and cerebral blood flow effects. *Am J Psychiatry.* 1998; 155: 470-473.
17. Passik SD, Weinreb HJ: Managing chronic nonmalignant pain: Overcoming obstacles to the use of opioids. *Adv Ther.* 2000; 17: 70-83.
18. Joranson DE, Carrow GM, Ryan KM, et al.: Pain management and prescription monitoring. *J Pain Symptom Manage.* 2002; 23: 231-238.
19. Hill CS: Government regulatory influences on opioid prescribing and their impact on the treatment of pain of nonmalignant origin. *J Pain Symptom Manage.* 1996; 11: 287-298.

Pain control for dying patients: Hastening death or ensuring comfort?

Marshall B. Kapp, JD, MPH

Engaging in affirmative acts to intentionally hasten another human being's death may leave a physician open to state prosecution for homicide under the specific legal theories of murder, attempted murder, and/or voluntary manslaughter. Apprehension about the risk of such criminal prosecution has likely inhibited many physicians from responding adequately (in other words, humanely) to the pleas of dying patients for relief from their terrible and unremitting pain. The unfortunate consequence of this legal anxiety-induced inadequacy in medical care has been unnecessary emotional and physical suffering on the part of a substantial number of dying patients and their families, who have watched and shared in that suffering.

A proper understanding of the legal and ethical character of pain control in the end-of-life context should address that negative consequence by encouraging different, more positively responsive behavior on the part of physicians caring for dying patients. In particular, healthcare professionals, state prosecutors and law enforcement officers, and the general public need to better understand the fundamental legal and ethical distinction between proper pain control on the one hand and the prohibited practice of euthanasia on the other.

Euthanasia is the carrying out of an affirmative act, such as the administration of a lethal injection, by one person for the precise purpose of hastening another person's death, with the cognizant expectation and actual result of accomplishing that objective. Whether undertaken with (voluntary euthanasia) or without (involuntary euthanasia) the permission or request of the ultimately euthanized individual, this kind of act is presently legally and ethically condemned in every American jurisdiction and most of the rest of the world. By contrast, providing adequate pain medication for a dying patient is a qualitatively different act than euthanasia. Therefore, it should be treated quite distinctly under the law, for at least two reasons.

First, the purpose of prescribing sufficient pain medication for a suffering patient in the final stage of life is to provide palliation for that patient. Unsurprisingly, physical pain is the primary motivation for patients who ask their physicians to provide relief through prescription drugs.[1] In such cases the patient's death is a foreseeable and expected event, but bringing about that death is not, per se, the physician's goal in prescribing pain medications. Although it is not necessarily unwelcome, the patient's death in this situation is, at most, an accompaniment to or byproduct of humane palliative care. Thus, the philosophical principle of "double effect" (engaging in an act for a morally good purpose even while realizing the act may also contribute to a morally bad effect) would excuse, if not applaud, the prescribing of pain medications for suffering end-of-life patients.

Second, and more importantly, it may not even be necessary for proponents of the prescription of adequate pain medications for dying patients to resort to the double-effect principle for moral vindication and legal protection. This is because the physician's palliating action may not really contribute to a hastening of the patient's death. There is substantial evidence that even when it sedates a patient so deeply as to render him or her unconscious or stuporous until death has occurred, the administration of pain medication may not have any deleterious effect on the patient's life span.

As put by one legal scholar,[2] "Since deep sedation is administered to patients who are gravely deteriorated and unavoidably dying, it may be almost impossible to know whether the underlying disease process or the effects of sedation caused the death." Regarding the administration of pain relievers to a point short of inducing terminal sedation, the same commentator notes, "In the context of a debilitated, fatally afflicted patient, it is difficult to establish whether the analgesics actually hasten death. That evidentiary difficulty helps explain why very few criminal prosecutions [for homicide] have involved physician administration of analgesics."

The medical literature overwhelmingly agrees that "[o]pioids, which are recognized worldwide as the most appropriate drugs to treat severe pain, can be taken in large doses without having a lethal effect" and that "fears over the perceived life-shortening side effects of higher doses of opioids (known as 'opiophobia'), the risk for

abuse of opioids and possible legal consequences" are "probably often unrealistic."[3] Internationally, there appears to be a "growing notion that the effect of opioids on survival might be much smaller than frequently thought"[4] and that "opioids are safe [that is, not death hastening] in the terminally ill when their doses are titrated against the symptom response . . . ."[5]

As is true elsewhere in clinical medicine, maintaining ethical practice while effectively managing legal risks depends on both behaving properly at the time and being able to prove you have done so afterwards. Proper physician behavior in this arena consists of prescribing opioids and other analgesic medications for dying patients only when clinically indicated to treat the effects of specific pain symptoms, and only to the extent (but certainly to the full extent) necessary to alleviate those symptoms.[2] Then, the factual basis for the physician's clinical judgment and conduct should be documented fully and honestly in the patient's medical record, as a safeguard in anticipation of a subsequent challenge to the physician's reasoning. Assuming good professional practice that is properly documented, a compassionate physician should not realistically fear adverse legal consequences for hastening the comfort of patients, even (or perhaps especially) at the ends of their lives.

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REFERENCES

1. Rietjens JAC, van Delden JJM, van der Heide A, et al.: Terminal sedation and euthanasia: A comparison of clinical practices. *Arch Intern Med.* 2006; 166: 749-753.
2. Cantor NL: On hastening death without violating legal and moral prohibitions. *Loyola Univ Chicago Law J.* 2006; 37: 407-431.
3. Bilsen J, Norup M, Deliens L, et al.: Drugs used to alleviate symptoms with life-shortening as a possible side effect: End-of-life care in six European countries. *J Pain Symptom Manage.* 2005; 31: 111-121.
4. Onwuteaka-Philipsen BD, Fisher S, Cartwright C, et al.: End-of-life decision making in Europe and Australia: A physician survey. *Arch Intern Med.* 2006; 166: 921-929.
5. Sykes N, Thorns A: Sedative use in the last week of life and the implications for end-of-life decision making. *Arch Intern Med.* 2003; 163: 341-344.

Modafinil: Is it ready for prime time?

Eric Prommer, MD

ABSTRACT

Psychostimulants have been used to treat many symptoms associated with advanced cancer. The primary role of psychostimulants in such cases is the treatment of symptoms such as cancer-related fatigue, opioid-induced sedation, depression, and cognitive dysfunction associated with malignancies. These uses for psychostimulants came after approval for treatment of disorders such as attention deficit disorder. Modafinil, a new psychostimulant, is following a similar path after its approval for use in attention deficit disorder in 1998. Modafinil has been used to treat fatigue associated with neurodegenerative disorders such as multiple sclerosis and amyotrophic lateral sclerosis. It is now being increasingly used for cancer-related symptoms targeted by psychostimulants. Preliminary evidence from literature review suggests that modafinil is efficacious in improving opioid-induced sedation, cancer-related fatigue, and depression. There is no evidence to support its use in the treatment of cognitive dysfunction related to cancer or to support its having analgesic properties. Well-designed, randomized, controlled clinical trials are still needed to further elucidate the precise role of this drug in the care of patients with cancer. Specifically, large placebo-controlled trials with modafinil must be conducted in patients with cancer, with specific attention paid to pain control, depression, cognitive function, and adverse effects.

Key words: modafinil, reticular activating system, psychostimulants

INTRODUCTION

Modafinil, 2-[(diphenylmethyl)sulphinyl]acetamide, is a schedule IV compound, approved by the Food and Drug Administration (FDA) in December 1998 for treatment of excessive daytime sleepiness in patients with narcolepsy.[1] Its stimulant properties led to its use in treating fatigue due to neurodegenerative disorders.[2,3] Clinical trial data suggest that modafinil has an excellent safety profile and is well tolerated.[4-6] As a stimulant, modafinil has been used increasingly for the palliation of symptoms for which psychostimulants are traditionally used, namely cancer-related fatigue, opioid-induced sedation, and depression. In recognition of modafinil's increasing use, this paper will review the current status of this substance in the treatment of cancer-related symptoms commonly targeted by psychostimulants and will examine whether its use is based on solid clinical evidence. The structure of modafinil is shown in Figure 1.

PHYSIOLOGY OF THE SLEEP–WAKE CYCLE

The neural pathway of the waking process, called the reticular activating system,[7] originates in the brainstem and sends projections from the brainstem and posterior hypothalamus throughout the forebrain.[8] Modern neuroanatomic tracer methods and immunohistochemical techniques have identified several nuclei as contributors to this arousal pathway. Important contributors include the cholinergic pedunculopontine, laterodorsal tegmental nuclei,[9] noradrenergic locus coeruleus, and serotoninergic dorsal and median raphe nuclei, as well as histaminergic projections from the tuberomammillary nucleus (lateral hypothalamus).[7] Cholinergic nuclei project to the thalamus, which then projects to the cortex. Aminergic nuclei project diffusely throughout the forebrain, regulating the activity of cortical and hypothalamic targets directly. Neurotransmitters such as acetylcholine, histamine, serotonin, and norepinephrine are activating. All activating neuronal groups become silent during sleep (both nonrapid eye movement, or NREM, and rapid eye movement, or REM), with the exception of the cholinergic pedunculopontine and laterodorsal tegmental nuclei, which fire intermittently during REM sleep. Table 1 summarizes the important nuclei and neurotransmitters involved in the sleep-wake cycle. Table 2 summarizes the activities of the nuclei important during the sleep-wake cycle.

Neurotransmitters such as γ-amino-butyric acid (GABA) and galanin, which originate in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, antagonize the proawakening influences of these neurotransmitters via inhibitory projections from the VLPO. The VLPO is also innervated in a reciprocal fashion by histaminergic axons from the tuberomammillary nucleus,

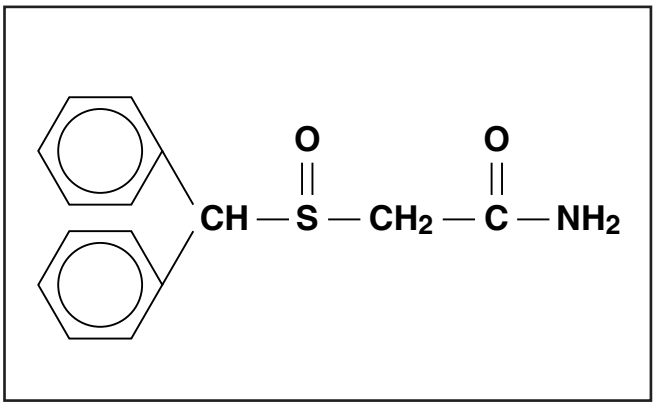

Figure 1. Molecular structure of modafinil.

noradrenergic terminals from the locus coeruleus, and serotoninergic inputs from the midbrain raphe nuclei.[10] In animal models, lesions placed in the VLPO can lead to reductions in both REM and NREM sleep.[11]

More recent discoveries have emphasized the role of the hypocretin/orexin peptides, which originate from the lateral hypothalamus and interact with all components of the arousal pathway. Orexin-containing neurons promote wakefulness. The hypocretin/orexin peptides also play a critical role in other physiological functions, such as activation of the sympathetic nervous system, appetite, and activation of the hypothalamic-pituitary-adrenal axis (directly or indirectly).[12] Their importance in the sleep-wake cycle is supported by their deficiency in the cerebrospinal fluid of patients with narcolepsy.[13]

Most sleep models hypothesize mutual inhibition between the VLPO and the major arousal systems. When VLPO neurons fire rapidly during sleep, they inhibit the monoaminergic cell groups, thus disinhibiting and reinforcing their own firing. Similarly, when monoamine neurons fire at a high rate during wakefulness, they inhibit the VLPO, thereby disinhibiting their own firing. This is analogous to what is described in engineering as a *flip-flop circuit*.[7] The two halves of a flip-flop circuit, by strongly inhibiting each other, create a feedback loop that is bistable, with two possible stable patterns of firing and a tendency to avoid intermediate states; in the case of the sleep-wake cycle, this prevents the inappropriate onset of sleep, which could be disastrous. This stability also offsets other potential influences that could shift transitions from wakefulness to sleep, such as circadian sleep drive. Orexin/hypocretin neurons are postulated to act as a "finger," pressing the flip-flop switch into the wakeful position and preventing inappropriate switching into the sleep position.[7]

MODAFINIL AND OTHER PSYCHOSTIMULANTS: MECHANISMS OF ACTION

Amphetamine, methylphenidate, and pemoline act neuropharmacologically by enhancing the amount of monoamines available within the synaptic cleft by either blocking uptake of dopamine or by facilitating catecholamine release from neurons.[14]

The predominant mode of action of modafinil is that of inhibition of GABA. This inhibition appears to allow release of dopamine, norepinephrine, and serotonin from their cells of origin as opposed to specific actions at the synapse. The alerting effect of modafinil is abolished by the α1-adrenoceptor antagonist prazosin, consistent with a possible role of the ascending noradrenergic system in the wakefulness-promoting effect of modafinil.[15]

Modafinil strongly increases Fos expression in tuberomammillary nuclei and orexin neurons, and activation of these neurons may be an essential component of modafinil's wake-promoting mechanism, resulting in dopaminergic activation of postsynaptic adrenergic receptors.[16] Modafinil may reinforce the action of the orexin nuclei.

PHARMACOLOGY

Pharmacokinetics

Modafinil is a racemic compound, whose l-isomer has a half-life approximately three times that of the d-isomer and accounts for the pharmacologic data available. Modafinil pharmacokinetics have not been studied in cancer patients. Modafinil is available in tablet form only. The half-life of modafinil after multiple doses is about 15 hours.[17] Modafinil exhibits linear kinetics upon multiple dosing of 200 to 600 mg/day in healthy volunteers, and steady state is reached after two to four days of dosing.[18]

Absorption and distribution

Absorption of modafinil tablets is rapid, with peak plasma concentrations occurring at 24 hours. Food may delay absorption. Modafinil is well distributed in body tissue, with an apparent volume of distribution (~ 0.9 L/kg) larger than the total volume of body water (0.6 L/kg). Modafinil is moderately bound to plasma protein (~ 60 percent, mainly to albumin).[19]

Metabolism and elimination

Modafinil is metabolized primarily in the liver (90 percent) through hydrolytic deamidation, S-oxidation, aromatic-ring hydroxylation, and glucuronide conjugation. Metabolites are renally excreted. The metabolites (modafinilic acid) of modafinil are inactive. Less than 10 percent of an administered dose is excreted as the parent compound. Chronic dosing may lead to decreased trough levels, suggesting autoinduction of metabolism. Modafinil pharmacokinetics are not affected by gender. Single-dose

Table 2. Activity of nuclei and neurotransmitters according to sleep stage			
Nuclei	**Awake**	**NREM**	**REM**
LDT/PPT	++	0	++
LC/DR/TMN	++	+	0
VLPO	0	+-++	++
Hypocretin/orexin	++	?	?

Adapted from Saper CB, Chou TC, Scammell TE: The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neurosciences.* 2001; 24(12): 726-731. DR, dorsal raphe nucleus; LC, locus coerulus; LDT, laterodorsal tegmental; NREM, non-rapid eye movement; PPT, pedunculopontine; REM, rapid eye movement; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus.

or laboratory parameters were evident with modafinil treatment. Table 3 summarizes the incidence of adverse effects (> 5 percent) in studies comparing modafinil with placebo (n = 369). Modafinil has not been directly compared to other psychostimulants in clinical trials, so there has been no direct comparison of adverse effects. There are no adequate well-controlled studies in pregnant women. In laboratory mice, no evidence of teratogenicity has been shown.

MODAFINIL FOR THE TREATMENT OF OPIOID–INDUCED SEDATION

Although there have been no large, randomized, controlled trials for treatment of opioid sedation, use of psychostimulants such as methylphenidate can be useful in counteracting the sedative effects of opioids.[23,24] Webster and colleagues[25] retrospectively assessed the responses of patients who had been prescribed modafinil for opioid-induced sedation. These patients were routinely assessed for sedation using the Epworth Sleepiness Scale (ESS), a commonly used sedation scale. When modafinil was prescribed to treat opioid-induced sedation, there was a significant improvement in ESS scores between the first ESS measurement and the final ESS measurement while patients remained on modafinil treatment ($p = 0.023$). The average opioid dose (in morphine equivalents) at which modafinil was started was 536 mg/patient/day, and the average ending opioid dose was 810 mg/patient/day (mean change: + 274 mg/patient/day; $p = 0.027$). The average initial modafinil dose was 264 mg/patient/day, which increased to a final dose of 427 mg/patient/day (mean change: + 164 mg/patient/day; $p = 0.009$). It appears that modafinil can counteract opioid-induced sedation, allowing increments in opioid doses. There were no additive toxicities when modafinil was combined with opioids.

CANCER–RELATED FATIGUE

There is empiric evidence that stimulants such as methylphenidate may have a beneficial effect on cancer-related fatigue in some patients.[26,27] Modafinil has been studied in cancer patients suffering from fatigue that persisted after therapy.[28] Fifty-one women (mean age: 54.5 years) who had completed breast cancer treatment an average of 23.5 months earlier and who were reporting persistent fatigue were enrolled in a one-month open-label trial of modafinil (200 mg with breakfast). The mean fatigue-severity level at baseline for the 51 enrollees was 6.9 on a scale where 0 represented "not present" and 10 was equal to "as bad as you can imagine." After treatment, mean fatigue severity had fallen to a mean of 3.7 ($p < 0.01$). The majority (86 percent) reported at least a 1-point improvement over the course of the one-month study. Patient-reported global effectiveness measured after treatment supported the finding that modafinil was an effective treatment for fatigue; the mean rating was 5.0 (SD = 2.0; with 1 meaning "no benefit" and 7 meaning "great improvement"). Adverse effects such as agitation occurred in three patients and led to their dropping out of the trial. Fifty-one percent of the patients reported improvement in sleep, and 51 percent reported less drowsiness. Additional improvements reported by a majority of patients were an increase in general activity (64 percent), improved mood (63 percent), improved walking ability (63 percent), normal work ability (66 percent), better relations with other people (66 percent), and greater enjoyment of life (61 percent).

MODAFINIL AND PAIN CONTROL

In animal studies, psychostimulant drugs have been shown to possess intrinsic analgesic properties and to have the ability to enhance the analgesic properties of opioids when both types of drugs are given in combination. Studies with human subjects strongly suggest that psychostimulant drugs enhance opioid analgesia, possibly by enhancing alertness, permitting larger doses of opioids, or possessing analgesic properties in their own right.[23,24,27,29]

Table 1. Important nuclei and neurotransmitters important in the sleep/wake cycle				
Reticular activating system nuclei	**Neurotransmitter**	**Function**	**Link**	**Overall function**
PPT, LDT	acetylcholine	activation	hypothalamus/thalamus/BF	maintain wakeful state and REM sleep
DRN	serotonin	activation	hypothalamus/thalamus/BF	maintains wakeful state slows with NREM sleep
LC	noradrenergic	activation	hypothalamus/thalamus/BF	maintains wakeful state slows with NREM sleep
Hypothalamic nuclei				
VLPO	GABA galanin	inhibitory	tuberomamillary nucleus, LC, DRN, LDT, PPT	inhibit and inhibited by RAS nuclei
TMN	histamine	activates hypothalamus	ventrolateral preoptic area	maintains wakeful state slows with NREM sleep
lateral hypothalamus	hypocretic/orexin	activates hypothalamus	LDT, PPT, DRN, TMN, LC, BF	stabilize firing of neurons that maintain REM and wakeful state
thalamus	acetylcholine	maintenance of awake state and NREM sleep	cortex	receives input from RAS to maintain awake state NREM sleep
BF	acetylcholine	activation	cortex	helps maintain awake state with thalamus

BF, basal forebrain; DRN, dorsal raphe nucleus; GABA, γ-aminobutyric acid; LC, locus coerulus; LDT, laterodorsal tegmental; NREM, nonrapid eye movement; PPT, pedunculopontine; RAS, reticular activating system; REM, rapid eye movement; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus.

studies suggest that age can affect the clearance of modafinil (up to 20 percent), with plasma levels in patients (age range: 67 to 87 years) reaching nearly twice those of properly matched younger patients. Severe renal insufficiency (creatinine clearance = 20 mL/min) does not affect the pharmacokinetics of modafinil. Patients with liver failure (Childs B, C) can experience a reduction in clearance of up to 60 percent and should have their dosage reduced (see schedule of administration).[19]

Drug interactions

Modafinil interacts with the cytochrome P-450 system. It reversibly inhibits CYP2C9 and induces CYP3A4, leading to the potential for drug interactions. At this time, the actual pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Inhibition of CYP2C9 can potentially lead to increased retention levels of drugs such as phenytoin, diazepam, propranolol, and warfarin.[19] Thus far, single-dose studies involving healthy volunteers have not resulted in any changes in the known pharmacokinetics of warfarin.[20] Induction of CYP3A4 can lead to decreased levels of triazolam and ethinyl estradiol (at doses of 400 mg).[21] One case report describes a lowering of cyclosporine levels by 50 percent one month after the patient had been started on modafinil (200 mg/day).[22] Coadministration of dextroamphetamine and methylphenidate did not alter the pharmacokinetics of modafinil.[17] Overall, no significant clinical consequences of these interactions have been reported. However, until further information is available, caution should be used when modafinil is administered with other drugs that interact with CYP2C9 and CYP3A4.

Adverse effects

The results of two double-blind phase III trials of modafinil in more than 550 patients with narcolepsy showed a slightly higher incidence of adverse events in the modafinil group than in the placebo group.[19] Headache, nausea, and rhinitis were the only adverse effects experienced by patients in two other double-blind, placebo-controlled studies.[5,6] No clinically significant effects on vital signs, electrocardiographic findings,

Table 3. Adverse effects of modafinil (incidence ≥ 5 percent)			
Organ system	**Adverse effect**	**Placebo (n = 185) (percent)**	**Modafinil (n = 389) (percent)**
Central nervous system	Headache	40	50
	Nervousness	6	8
	Dizziness	4	5
	Insomnia	1	5
Digestive	Nausea	4	13
	Diarrhea	4	8
	Dry mouth	1	5
	Anorexia	1	5
	Dyspepsia	4	5
Respiratory	Rhinitis	6	7
Other	Back pain	6	7
Adapted from package insert.			

Twelve healthy subjects with acute pain (e.g., finger pressure and ischemic pain) were assessed in a randomized, double-blind crossover study of placebo and modafinil (400 mg once daily). The single-dose study failed to demonstrate any analgesic properties of modafinil. Currently, there is no evidence that modafinil has intrinsic analgesic properties. It may enable larger doses of opioids to be given by counteracting sedation.

MODAFINIL FOR THE TREATMENT OF DEPRESSION

The reported prevalence of depression among cancer patients varies from 0 to 38 percent for major depression to 0 to 58 percent for depression spectrum syndromes, depending on the criteria for diagnosis and methodology used to define depression, as well as the populations studied. Depression is highly associated with oropharyngeal (22 to 57 percent), pancreatic (33 to 50 percent), breast (1.5 to 46 percent), and lung (11 to 44 percent) cancers.[30] Depression increases with disease stage and affects compliance and ability to care for one's self. It is also associated with poor symptom control, pain, and fatigue.[31] Psychostimulants have a role in the management of depressed medically ill persons and in cancer patients.[26] In addition, because of their rapid onset of action compared with antidepressants, psychostimulants such as methylphenidate are frequently used to "bridge" patients until antidepressants become effective, especially in patients with a short life expectancy and in patients with depression and fatigue.

Most studies evaluating modafinil in depression have been limited to "augmentation studies" where modafinil was used to alleviate sedation, depression, and fatigue in patients already receiving antidepressants, usually selective serotonin-reuptake inhibitors (SSRIs). These studies did not include cancer patients. One multicenter, placebo-controlled study of modafinil augmentation evaluated 311 patients who had a partial response to SSRI monotherapy (= eight weeks) or had been at a stable dosage for four weeks or longer but still had significant depression, sedation, and fatigue as measured by the 31-item Hamilton Rating Scale for Depression (HAM-D) (scores of 14 to 26), the ESS (scores = 10), and the Fatigue Severity Scale (FSS) (scores = 4). Patients were randomized to augmentation therapy with either modafinil 200 mg/day or with placebo for eight weeks. Assessments of response to modafinil/placebo included scores on the ESS, Clinical Global Impressions of Improvement scale (CGI-I) (assesses magnitude of effect between antidepressants and placebo), 31-item and 17-item HAM-D, FSS, Brief Fatigue Inventory, and Montgomery-Asberg Depression Rating Scale. Modafinil significantly improved patients' overall clinical condition compared with placebo on the basis of CGI-I scores ($p = 0.02$), and there were trends toward greater mean reductions in sedation, depression, and fatigue when compared with placebo.[32]

An earlier study evaluated 136 patients with major depression with partial response to antidepressant therapy given for at least six weeks.[33] Most patients (82 percent) were fatigued, and more than half of the patients (51 percent) felt sedated. Seventy-five percent had been taking SSRIs, and 20 percent had been taking non-SSRIs such as venlafaxine, trazodone, nefazodone, mirtazapine, and bupropion. Again, there were no cancer patients included. Patients received once-daily doses (100 to 400 mg) of modafinil or matching placebo as adjunct treatment to ongoing antidepressant therapy. The

effects of modafinil were evaluated using the HAM-D, the FSS, the ESS, the Clinical Global Impressions of Change (CGI-C), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Modafinil rapidly improved fatigue and daytime wakefulness, with significantly greater mean improvements from baseline when compared with placebo with regard to fatigue (FSS) scores at week two ($p < 0.05$) and sleepiness (ESS) scores at week one ($p < 0.01$); the differences between modafinil and placebo at week six were not statistically significant. It seems that modafinil can have a rapid onset of action, similar to other psychostimulants such as methylphenidate. The effects may wane with continued usage. In summary, modafinil is safe to use in patients with depression. It appears to be useful in treating fatigue and sleepiness associated with depression and antidepressant use and, like other psychostimulants, can rapidly improve fatigue and somnolence.

EFFECTS ON COGNITIVE FUNCTION

Psychostimulants enhance cognitive function. Agents such as methylphenidate have been shown to be beneficial in hypoactive delirium[34,35]; improving cognition problems associated with opioid use[35]; and improving some attentional and social deficits among survivors of childhood ALL, childhood brain tumors,[36] and adult gliomas.[37] So far, understanding of the cognition-enhancing effects of modafinil and its relevant neurobiological mechanisms is incomplete. When tested in normal human hosts who are not sleep deprived, improvements are limited to the span of immediate verbal recall and short-term visual recognition memory, which is insufficient to be considered cognition enhancing.[38] There does not appear to be a dose relationship associated with these cognitive improvements.

ABUSE POTENTIAL

Jasinski and coworkers[39] evaluated the abuse liability of modafinil. Their work showed that modafinil at doses less than 800 mg did not produce the euphoric effects seen with other psychostimulants. The study did demonstrate euphoric psychoactivity typical of amphetamines and other prototypic drugs of abuse at doses of 800 mg/day. Overall, abuse of psychostimulants in medically ill patients has not been reported.

COST COMPARISON WITH METHYLPHENIDATE

Average wholesale prices (AWP) (Red Book 2004) are in US dollars as follows:

Methylphenidate		Modafinil	
5 mg	AWP: 0.33	100 mg	AWP: 6.19
10 mg	AWP: 0.48	200 mg	AWP: 8.55
20 mg	AWP: 0.69		

SCHEDULE OF ADMINISTRATION

The recommended dosage of modafinil is 200 mg given once a day. Dosages up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dosage confers additional benefit beyond that of the 200-mg dosage. Switching from methylphenidate to modafinil was well tolerated with or without a between-treatment washout period or when the methylphenidate dosage was gradually tapered during initiation of modafinil therapy.[13]

CONCLUSION

Modafinil appears to be a well-tolerated medication that has many characteristics of psychostimulants but with a different mechanism of action. Currently, there is no evidence that it has analgesic properties or can benefit cognitive functioning. Studies claiming improvement in opioid-induced sedation and cancer-related fatigue have been retrospective (sedation) or prospective open-label (fatigue). There is evidence that modafinil can be used as a psychostimulant in the treatment of depression to counteract adverse effects of antidepressants and provide improvements in mood and energy before the antidepressants work; however, further testing in cancer patients is warranted. As with other psychostimulants, there is still the need for well-designed, randomized, controlled clinical trials to further elucidate the precise role of this drug in the care of terminally ill patients. Specifically, large, placebo-controlled trials with modafinil must be conducted in patients with cancer, with attention to specific outcomes including pain control, depression, cognitive function, adverse effects, and duration of action. Like methylphenidate, further trials may confirm the preliminary evidence that modafinil can treat opioid-induced sedation, fatigue, depression, or pain. If further trials can establish a comparative efficacy to other psychostimulants and/or fewer adverse effects, modafinil may become an option when other psychostimulants cause adverse effects or when their effects wane. Unfortunately, its cost may be prohibitive for some hospices.

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REFERENCES

1. Price CS, Taylor FB: A retrospective chart review of the effects of modafinil on depression as monotherapy and as adjunctive therapy. *Depress Anxiety.* 2005; 21: 149-153.
2. Rammohan KW, Rosenberg JH, Lynn DJ, et al.: Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: A two centre phase 2 study. *J Neurol Neurosurg Psychiatry.* 2002; 72: 179-183.

3. Carter GT, Weiss MD, Lou JS, et al.: Modafinil to treat fatigue in amyotrophic lateral sclerosis: An open label pilot study. *Am J Hosp Palliat Care.* 2005; 22: 55-59.
4. Bastuji H, Jouvet M: Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Prog Neuropsychopharmacol Biol Psychiatry.* 1988; 12: 695-700.
5. US Modafinil in Narcolepsy Multicenter Study Group: Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol.* 1998; 43(1): 88-97.
6. US Modafinil in Narcolepsy Multicenter Study Group: Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology.* 2000; 54: 1166-1175.
7. Boutrel B, Koob GF: What keeps us awake: The neuropharmacology of stimulants and wakefulness-promoting medications. *Sleep.* 2004; 27: 1181-1194.
8. Moruzzi G, Magoun HW: Brain stem reticular formation and activation of the EEG. 1949. *J Neuropsychiatry Clin Neurosci.* 1995; 7: 251-267.
9. Edley SM, Graybiel AM: The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. *J Comp Neurol.* 1983; 217: 187-215.
10. Chou TC, Bjorkum AA, Gaus SE, et al.: Afferents to the ventrolateral preoptic nucleus. *J Neurosci.* 2002; 22: 977-990.
11. Lu J, Greco MA, Shiromani P, et al.: Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J Neurosci.* 2000; 20: 3830-3842.
12. Martynska L, Wolinska-Witort E, Chmielowska M, et al.: The physiological role of orexins. *Neuro Endocrinol Lett.* 2005; 26: 289-292.
13. Thorpy M: Current concepts in the etiology, diagnosis and treatment of narcolepsy. *Sleep Med.* 2001; 2: 5-17.
14. Homsi J, Walsh D, Nelson KA: Psychostimulants in supportive care. *Support Care Cancer.* 2000; 8: 385-397.
15. Ferraro L, Antonelli T, O'Connor WT, et al.: Modafinil: An antinarcoleptic drug with a different neurochemical profile to d-amphetamine and dopamine uptake blockers. *Biol Psychiatry.* 1997; 42: 1181-1183.
16. Chemelli RM, Willie JT, Sinton CM, et al.: Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell.* 1999; 98: 437-451.
17. Wong YN, King SP, Laughton WB, et al.: Single-dose pharmacokinetics of modafinil and methylphenidate given alone or in combination in healthy male volunteers. *J Clin Pharmacol.* 1998; 38: 276-282.
18. Wong YN, Simcoe D, Hartman LN, et al.: A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol.* 1999; 39: 30-40.
19. Cephalon prescribing information: Provigil (modafinil) tablets. West Chester: Cephalon, Inc., 1999.
20. Robertson P Jr, Hellriegel ET, Arora S, et al.: Effect of modafinil at steady state on the single-dose pharmacokinetic profile of warfarin in healthy volunteers. *J Clin Pharmacol.* 2002; 42: 205-214.
21. Robertson P Jr, Hellriegel ET, Arora S, et al.: Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther.* 2002; 71: 46-56.
22. Le Cacheux P, Charasse C, Mourtada R, et al.: Gelineau syndrome in a patient with renal transplantation. Evidence of cyclosporine-modafinil interaction. *Presse Med.* 1997; 26: 466.
23. Bruera E, Fainsinger R, MacEachern T, et al.: The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. *Pain.* 1992; 50: 75-77.
24. Bruera E, Chadwick S, Brenneis C, et al.: Methylphenidate associated with narcotics for the treatment of cancer pain. *Cancer Treat Rep.* 1987; 71: 67-70.
25. Webster L, Andrews M, Stoddard G: Modafinil treatment of opioid-induced sedation. *Pain Med.* 2003; 4: 135-140.
26. Sarhill N, Walsh D, Nelson KA, et al.: Methylphenidate for fatigue in advanced cancer: A prospective open-label pilot study. *Am J Hosp Palliat Care.* 2001; 18: 187-192.
27. Bruera E, Driver L, Barnes EA, et al.: Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: A preliminary report. *J Clin Oncol.* 2003; 21: 4439-4443.
28. Morrow GR, Gillies LJ, et al.: The positive effect of the psychostimulant modafinil on fatigue from cancer that persists after treatment is completed. *ASCO Annual Meeting Abstract.* 2005; 8012.
29. Dalal S, Melzack R: Potentiation of opioid analgesia by psychostimulant drugs: A review. *J Pain Symptom Manage.* 1998; 16: 245-253.
30. Massie MJ: Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr.* 2004; (32): 57-71.
31. Rozans M, Dreisbach A, Lertora JJL, et al.: Palliative uses of methylphenidate in patients with cancer: A review. *J Clin Oncol.* 2002; 20: 335-339.
32. Fava M, Thase ME, DeBattista C: A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry.* 2005; 66: 85-93.
33. DeBattista C, Doghramji K, Menza MA, et al.: Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: A preliminary double-blind, placebo-controlled study. *J Clin Psychiatry.* 2003; 64: 1057-1064.
34. Morita T, Otani H, Tsunoda J, et al.: Successful palliation of hypoactive delirium due to multi-organ failure by oral methylphenidate. *Support Care Cancer.* 2000; 8: 134-137.
35. Gagnon B, Low G, Schreier G: Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: A prospective clinical study. *J Psychiatry Neurosci.* 2005; 30: 100-107.
36. Mulhern RK, Khan RB, Kaplan S, et al.: Short-term efficacy of methylphenidate: A randomized, double-blind, placebo-controlled trial among survivors of childhood cancer. *J Clin Oncol.* 2004; 22: 4795-4803.
37. Meyers CA, Weitzner MA, Valentine AD, et al.: Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *J Clin Oncol.* 1998; 16: 2522-2527.
38. Randall DC, Viswanath A, Bharania P, et al.: Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? *J Clin Psychopharmacol.* 2005; 25: 175-179.
39. Jasinski DR: An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *J Psychopharmacol.* 2000; 14: 53-60.

ORIGINAL ARTICLE

Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain

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ABSTRACT

Chronic opioid therapy is commonly prescribed for chronic nonmalignant pain. Few published data describe the adverse effects experienced by patients with chronic nonmalignant pain being treated by primary care physicians. A prevalence study was conducted on a sample of 1,009 patients (889 receiving chronic opioids) being treated by 235 primary care physicians. Standardized questionnaires and medical record reviews were used to assess rates of addiction, pain diagnosis and severity, opioid adverse effects, and mental health. The mean daily dose of opioids was 92 mg using a morphine-equivalent conversion. Side effects included constipation (40 percent), sleeping problems (25 percent), loss of appetite (23 percent), and sexual dysfunction (18 percent), with patients on daily opioids experiencing more side effects than subjects on intermittent medication. The Medical Outcomes Study Mental Health Inventory (MOS-MHI) cognitive functioning scale indicated poorer cognitive function in the overall sample of chronic pain patients as compared to a general clinical sample ($\Delta \bar{x}$ 95 percent CI = 9.28, 13.76). However, there were limited differences in MOS scores between chronic pain subjects on daily opioids vs. intermittent opioids vs. no prescription opioids. A regression model suggests that psychological measures and pain severity are more predictive of decrements in cognitive function than specific opioid preparations or daily opioid dose. Physicians should closely monitor patients for adverse effects and adequacy of pain control when using chronic opioid therapy for chronic pain treatment. Psychological health, an important predictor of cognitive dysfunction, is a particularly important measure to actively monitor and manage.

Key words: opioids, adverse effects, chronic nonmalignant pain, primary care physicians

INTRODUCTION

It has been estimated that 50 million Americans suffer from chronic nonmalignant pain (CNMP).[1,2] Opioids are the most effective analgesics available, but their use in CNMP continues to be controversial. While published guidelines advocate the use of long-acting opioid analgesics in the management of CNMP,[3-7] care providers have expressed reluctance in survey-based studies to prescribe these agents chronically due to concern that adverse effects may precipitate functional decline.[8-11]

Opioid adverse effects are generally dose-related, but severity varies between individuals. Systems affected include the central nervous (sedation, respiratory depression, and cognitive impairment), gastrointestinal (nausea, vomiting, and constipation), and the skin (pruritus).[8,12] Though most studies have observed no significant cognitive impairment with long-term opioid use,[13-16] others have raised the concern that adverse effects with long-term use may contribute to serious adverse events, such as falls and hip fractures[17,18] and impairment of judgment and reaction time necessary for safe driving.[19] Randomized clinical trials have found that opioids improve pain relief in the setting of CNMP but with the trade-off of more frequent adverse effects (primarily constipation, sedation, dizziness, and nausea).[20-23]

The findings of previous clinical trials, of 14 weeks or less in duration, may not generalize to clinical settings where opioid analgesics are commonly used over the longer term. The current study sought to determine the prevalence of adverse effects, the level of cognitive dysfunction, and patient factors and prescribing practices associated with these adverse effects in a primary care sample with CNMP patients taking opioid analgesics for three months or more. We hypothesized that, when controlling for important covariates, long-term daily opioid use, particular opioid analgesic preparations, and higher daily doses would not be predictors of greater levels of cognitive dysfunction. We further hypothesized that adverse effects would be more strongly associated with intermittent, or as-needed, use than with daily scheduled use of opioid analgesics.

METHODS

Detailed study methods have been published elsewhere[24] and will be summarized here.

Setting and dates

Subjects were recruited with the help of 235 primary care physicians. These physicians were members of five healthcare systems: the UW Medical Foundation, Dean Clinics, Group Health Cooperative, Aurora Health Care, and Mercy Health Care. Interviews were conducted in a variety of settings including primary care clinics and research offices. The interviews were conducted by one of four researchers. Study recruitment and data collection took place from July 2002 to July 2004.

Procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983. The study protocol was reviewed and approved by the University of Wisconsin—Madison Health Sciences Institutional Review Board.

Sample

An interview study was conducted with a convenience sample of 1,009 subjects being treated for CNMP. Chronicity was defined as pain that has persisted every day for at least three months. Inclusion criteria for the primary group of interest included 1) age between 18 and 81, 2) a diagnosis of CNMP, and 3) current treatment by a primary care physician including chronic opioid therapy.

Overall response rate was over 85 percent, with some variation by physician and clinic. Primary reasons given for nonparticipation included lack of time, employment time conflicts, childcare responsibilities, confidentiality issues related to chronic pain treatment, and transportation problems.

Of the 1,009 recruited subjects, 889 were receiving opioid medications on an intermittent (n = 98) or chronic daily (n = 791) basis. Chronic daily use was defined as having taken prescription opioids for at least 20 days in a 30-day time period in at least one of the previous three months. More than 95 percent of subjects in this group were using prescription opioids daily during the previous three months. Intermittent users were characterized by having taken opioids on fewer than 20 days of any 30-day period during the last three months but having taken opioids for pain at some time during the last six months. Opioid use was determined by an initial screening interview and later confirmed by an inventory of the patient's medication bottles, completed during the interview. Ultimately, all analyses were conducted using opioid-intake information from this medication inventory, as it was assumed to be more current.

Subject recruitment

The first step was to identify patients of individual physicians being treated for chronic pain. Physicians used a number of strategies to identify subjects, including clinic logs of persons on opioids, billing records using ICD-9 codes of chronic pain diagnosis, pharmacy records, and electronic medical record searches. The second step was to mail each potential subject a letter of invitation from his or her primary care physician.

Measurements

Once subjects had completed consent forms, the interview resumed with a medication checklist, the Medical Outcomes Study Mental Health Inventory (MOS-MHI) cognitive functioning scale,[25] the Substance Dependence Severity Scale (SDSS),[26-28] the Addiction Severity Index (ASI),[29,30] the Neighborhood Disorder Scale (NDS),[31] and the Pain Inventory Survey.[32] For further previous studies validating these instruments, the authors refer the reader to the study's primary methodological paper.[24]

The subject and interviewer reviewed all medications and dosages. Patient self-report on the type, dose, and frequency of pain medication was confirmed by medical and pharmacy records when available. Disagreements between these reports were resolved by the PI survey, with patient self-report being the primary source of the data used. Until we have reliable statewide pharmacy-reporting mechanisms, patient self-report of pain medication will be the most valid source of medication usage; physician and pharmacy records are often incomplete and may not reflect what patients are actually using. Medical records were also used for determination of the subjects' pain diagnoses.

The primary outcome of cognitive function was assessed using the MOS-MHI cognitive functioning scale. The scale consists of six questions using a Likert scale to quantify six possible responses, ranging from Never to Always. These items generate a score on a 100-point scale, with a lower score indicating greater dysfunction. Questions address experiences over the last 30 days, such as:

1. How often have you had difficulty reasoning and solving problems?

2. How often have you had difficulty with concentration and thinking?

3. How often have you had episodes of confusion?

4. How often have you had short-term memory problems?

Table 1. Demographics of sample*			
Variable		**n**	**Percent of total subjects (N = 889)**
Gender	Male	277	30.7
	Female	612	69.3
Age (years)	18 to 30	43	4.8
	31 to 40	132	14.8
	41 to 50	329	37.0
	51 to 60	275	30.9
	More than 60	110	12.4
Race	White, non-Hispanic	673	75.7
	Black, non-Hispanic	201	22.6
	American Indian	7	0.8
	Asian/Pacific Islander	1	0.1
	Hispanic - Mexican	3	0.3
	Hispanic - Puerto Rican	2	0.2
	No answer	2	0.2
Marital status	Married	267	30.0
	Remarried	116	13.0
	Widowed	49	5.5
	Separated	53	6.0
	Divorced	227	25.5
	Never married	176	19.8
	No answer	1	0.1
Employment status (usual)	Full time	266	29.9
	Part time regular	75	8.4
	Part time irregular	34	3.8
	Student	9	1.0
	Retired/disability	408	45.9
	Unemployed	96	10.8
	No answer	1	0.1
Substance abuse or dependence present	Yes	116	13
	No	773	87
* Current substance abuse or dependence status (yes/no) is per the Substance Dependence Severity Scale.			

Table 2. Opioid analgesics used by study sample					
Drug	**Frequency of prescription (n)**	**Percentage of subjects (out of 889)**	**Range of dosage***	**Mean dosage***	**Standard deviation**
Oxycodone	441	49.6	3 to 640	66.41	89.96
Hydrocodone	254	28.6	1 to 120	21.89	17.87
Morphine	142	16	1 to 800	123.93	152.48
Codeine	88	9.9	2.51 to 80.16	22.12	18.48
Fentanyl	68	7.6	5 to 800	138.46	141.46
Methadone	61	6.9	30 to 1,020	257.95	208.53
Propoxyphene	51	5.8	5 to 55	15.66	13.02
Demerol	12	1.3	6 to 120	32.14	29.90
Dilaudid	11	1.2	10 to 720	115.45	203.19
Overall	**1,128****		**2 to 1,020**	**92.26**	**136.46**

* All doses and ranges are in morphine milligram equivalents; ** Total prescriptions exceed sample size due to 239 subjects taking more than one opioid analgesic.

5. How often have you had difficulty focusing attention on a single activity? and

6. How often have you had slow reactions to things?

In creating a summary score, each item is weighted equally and rescaled to range from 0 to 100. The item responses are then averaged to create an overall score of 0 to 100.

An Adverse Medication Checklist was developed based on the SAFTEE[33-40] and contains 18 items addressing 18 potential opioid adverse effects. On each item patients indicated 1) whether they had experienced specific side effects and 2) whether they felt that these effects were due to opioid analgesics.

The PI survey includes 16 questions that inquire about pain location, pain diagnosis, pain severity, onset of pain problems, opioid efficacy, and patients' concerns about opioids. Questions assess pain severity on a 0 to 10 scale for worst pain, average pain, and least pain experienced.

The SDSS uses DSM-IV and ICD-10 criteria to give a diagnosis of current alcohol or drug dependence. The schedule specifically asks about alcohol, heroin, cocaine, hallucinogens, sedatives, stimulants, pain killers, and methadone. The SDSS was used rather than other diagnostic schedules (e.g. SCID, CIDI) to try to separate patients with true opioid addiction from patients physically dependent on appropriate doses of prescription opioids.

The ASI is a questionnaire containing seven subscales (medical, employment, alcohol, drugs, legal, social, and psychiatric). The depression and anxiety measurements of this instrument were used to control for the effects of these disorders in regression modeling.

The NDS consists of 14 questions and uses a Likert scale of strongly agree, agree, disagree, and strongly disagree. The instrument was included to assess health disparities due to community-level stressors among patients being treated for chronic pain.

The total daily dose of opioids for each patient in the sample was based on a 24-hour morphine sulfate equivalent. The dose equivalents chosen were based on a number of sources, including American Pain Society guidelines, a recent systematic review of clinical guidelines, primary research, and personal communication with pharmacologists and clinicians with expertise in pain management.[41-47] There have been limited empirical studies comparing opioids in noncancer chronic pain samples. For oral morphine medications such as Kadian, MS Contin, immediate-release (IR) morphine, and sustained-release (SR) morphine, we considered the mg dose of each medication as a 24-hour equivalent—10 mg of MS Contin was considered the same as 10 mg of IR morphine; 3 mg of oxycodone was considered equal to 4 mg of morphine.[46,48] A 50-µg/hour fentanyl patch was considered equal to 140 mg of morphine,

Table 3. Frequencies of primary diagnoses among subjects taking pain medication		
Primary diagnostic category	**Number of subjects**	**Percent of subjects (N = 889)**
Arthritis	212	23.8
Chronic low back disorder	189	21.3
Migraine	81	9.1
Neuropathy NOS	48	5.4
Trauma and other injuries	35	3.9
Fibromyalgia	34	3.8
Cervical spine disease	27	3.0
Diabetic neuropathy	25	2.8
Rheumatoid arthritis	24	2.7
Lupus	23	2.6
Chronic abdominal disorder NOS	20	2.2
Myofascial syndrome	19	2.1
Chronic pancreatitis	17	1.9
Spinal stenosis	17	1.9
Shoulder disorder NOS	11	1.2
Headaches NOS	9	1.0
Herniated lumbar disc	9	1.0
Lumbar disc disease and nerve compression	9	1.0
Reflex sympathetic dystrophy	7	0.8
Sickle cell anemia	7	0.8
Avascular necrosis of hips	6	0.7
Knee disorder NOS	6	0.7
Scoliosis	5	0.6
Restless leg syndrome	4	0.4
TMJ	4	0.4
Carpal tunnel syndrome	3	0.3
Other	38	4.3
Total	**889**	**99.7***
* Total percentage at 99.7 rather than 100.0 due to rounding.		

Table 4. Average scores for MOS-MHI 6-item cognitive functioning subscale and mean differences between groups*				
	Group 1 - Chronic opioids (n = 790)	**Group 2 - Intermittent opioids (n = 98)**	**Group 3 - No opioids (n = 115)**	**General clinic population (n = 2,469)**
Total score - Mean (SD)	70.82 (22.42)	71.33 (21.45)	66.96 (20.72)	82.4 (16.5)
Mean differences, 95% CI				
vs. Group 1		0.51 (-3.86, 4.88)	3.86 (-0.48, 8.20)	11.58 (9.30, 13.86)
vs. Group 2	0.51 (-3.86, 4.88)		4.37 (-1.30, 10.04)	11.07 (7.30, 14.84)
vs. Group 3	3.86 (-0.48, 8.20)	4.37 (-1.30, 10.04)		15.44 (11.92, 18.96)
vs. General population	11.58 (9.30, 13.86)	11.07 (7.30, 14.84)	15.44 (11.92, 18.96)	

The six items on the subscale address experiences over the last 30 days: 1) How often have you had difficulty reasoning and solving problems, 2) How often have you had difficulty with concentration and thinking, 3) How often have you had episodes of confusion, 4) How often have you had short-term memory problems, 5) How often have you had difficulty focusing attention on a single activity, and 6) How often have you had slow reactions to things. Answers are on a 6-point Likert scale ranging from "never" to "always." In creating a summary score, each item is weighted equally and rescaled to range from 0 to 100. The item responses are averaged to create an overall score of 0 to 100.

assuming that 1) 50 µg/hour fentanyl = 2 mg morphine IV, and 2) the oral bioavailability of morphine is 35 percent.[46,49] 10 mg of methadone was treated as equal to 30 mg of morphine. Analysis was also undertaken with a conversion of 1 mg morphine = 10 mg morphine, given controversy surrounding a consistent conversion ratio for all dosage levels of methadone:morphine.[46,50] Tylenol #3 was considered equal to 5 mg of morphine. Similarly, the total daily dose of benzodiazepines for each patient was based on a 24-hour diazepam equivalent[51,52]: diazepam 10 mg = alprazolam 1 mg = lorazepam 2 mg = clonazepam 4 mg.

Analysis

Data were entered into an Access database and transferred to SPSS version 12.0 statistical software for analysis. The data were assessed for skewness and kurtosis. The average daily mg equivalents demonstrated a high degree of rightward skew for both morphine and diazepam mg equivalents. The natural log of these values exhibited near-normal distribution and was used for purposes of regression modeling.

The type of opioid medication was also examined as a potential contributor to cognitive dysfunction in regression modeling. Dummy variables were created for each medication, and the interaction term for medication X average daily dose was created and included in stepwise regression. The log of average daily dose in morphine mg equivalents for each opioid was also used in this portion of the analysis to more closely approximate normal distribution.

Independent sample t-testing was performed comparing the frequency of adverse effects among those taking opioid analgesics only intermittently vs. that among those taking opioids on a scheduled daily basis. Levene's test for equality of variance was performed, and, when appropriate based upon this test, variance was assumed equal between these groups for the purposes of t-testing.

Due to the small number of subjects in ethnic categories other than White and African American/non-Hispanic, race was included in final analyses as a binary variable (White/non-White). Dummy variables were created for the categories of marital status and employment status. These dummy variables were then retained for analysis of nonparametric bivariate correlations and for stepwise regression analysis if statistically significant Spearman correlations were observed.

Regression analysis was hypothesis-driven and proceeded as follows for modeling of cognitive function score. Medication X dose interaction terms for each opioid analgesic were entered into an initial model to examine dose-response effects by medication on cognitive function. Covariates were then entered into the model via stepwise regression after examination of bivariate analysis of covariates and their correlations with cognitive function. Pearson correlation coefficients were used for

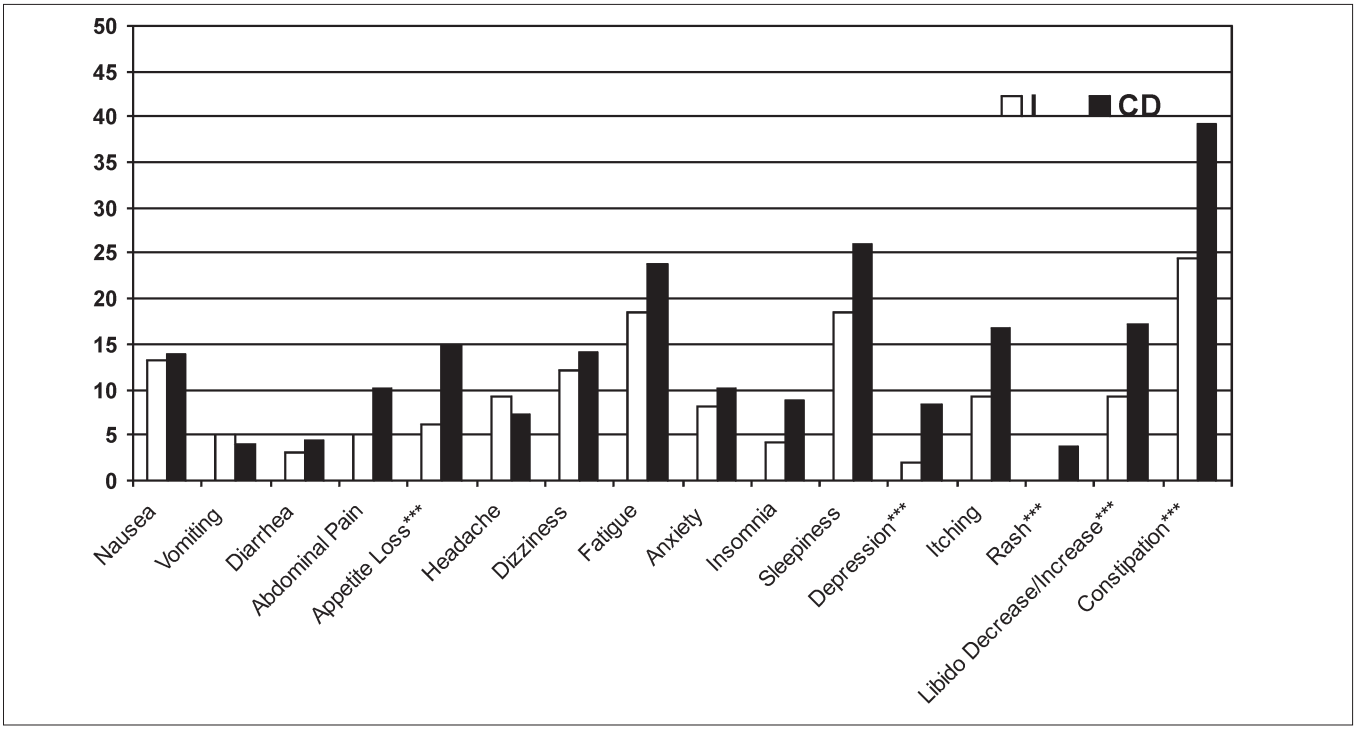

Figure 1: Percentage of subjects reporting side effects due to opioid treatment, by condition. I = intermittent opioids, CD = chronic daily opioids (> three months). * Symptoms with a significant difference between conditions ($p < 0.05$).**

continuous variables and Spearman correlations for categorical variables. Age and gender were retained in the final model for purposes of statistical control for these demographic covariates.

RESULTS

Descriptive statistics

The demographic characteristics of the study sample are detailed in Table 1. As one can see, 30 percent of the sample is male and 22 percent is African American. Other ethnic groups comprised less than 1 percent of the sample, with the next highest category being Native American (0.8 percent). Only 43 percent were currently married, and 20 percent were never married. Thirteen percent of the 889 subjects receiving opioids intermittently or daily met criteria for alcohol or drug dependence.

Table 2 includes relevant information regarding the opioids used by the study population. The most frequently prescribed opioids were the oxycodone family of medications, with nearly half the sample on an oxycodone-based preparation. The second most common were hydrocodones (vicodin and lortabs were the most common preparations). Morphine preparations were third. Prescription methadone was being used by 6.9 percent of the sample for pain control. Propoxyphene continues to be used, with 6 percent of the sample on this medication. The total daily dose in the sample was under 100 mg/day.

Table 3 lists the pain diagnoses for which subjects were being treated. One of the primary challenges in the study was assigning a primary pain diagnosis for each subject. Patient perception and medical records did not always agree, and in some cases it was difficult to find a primary diagnosis in the record. As noted, arthritis and chronic lower back pain were the diagnosis for nearly half the subjects. The next most common diagnoses were migraine headache, trauma, neuropathy, and fibromyalgia.

Means comparisons

Adverse medication effects. Figure 1 reports the frequency of common adverse effects. Constipation was reported as a side effect by 39 percent of the sample on daily opioids. The next most common side effects were fatigue, sleep problems, and loss of appetite. The frequency of adverse effects was much higher in the daily opioid group than in the intermittent medication group. The difference between groups in the overall number of adverse effects experienced also attained statistical significance ($t^{133.6} = -3.047$, $p = 0.003$, equal variances not assumed). While there are multiple other causes for these adverse effects in the sample (e.g. uncontrolled pain, other medications, other chronic medical disorders, lack of exercise) the frequency suggests physicians may want to ask about the effects when using chronic opioids. Six subjects who reported taking opioid medications did not provide information on the adverse

Table 5. Final model of MOS-MHI cognitive functioning score on significant covariates (N = 889)			
	Standardized coefficients β	**t**	**Sig.**
Age in years	-0.06258	-2.2308	0.02594
Gender	0.03568	1.2599	0.20802
ASI Psychiatric Composite	-0.5084	-17.874	< 0.00001
NDS score	-0.1206	-4.2366	< 0.00001
Worst pain level	-0.1015	-3.5637	0.00039

effects they were experiencing and were excluded from this analysis.

Cognitive function

Table 4 compares mean MOS-MHI cognitive functioning scores with 95 percent confidence intervals for the differences between means for the groups in the study and for a general clinical population in prior research.[25] Data on individuals with CNMP taking no opioids are from the current study. The subjects not taking opioids (n = 115) did not complete questionnaires regarding potential opioid adverse effects or opioid dosing. The mean difference in MOS-MHI cognitive functioning score between the overall study population and the general population achieved statistical significance ($\Delta \bar{x}$ 95 percent CI = 9.28, 13.76). Confidence intervals for the differences between the study groups, however, all include 0, and thus do not achieve statistical significance.

Regression modeling

The final model attained via stepwise regression is summarized in Table 5. In addition to the variables listed in Table 5, covariates achieving significance on initial bivariate analysis included monthly income ($p < 0.001$), methadone X dose interaction ($p = 0.022$), and the "least pain" ($p < 0.001$) and "average pain" ($p < 0.001$) measures on the PI survey. The significance of each of these measures, however, disappeared during the course of stepwise regression when covariates were added and partial F-testing performed. The "worst pain" measure provided the greatest statistical significance and the largest effect size of the three pain measures. Formation of a pain index combining the three measures did not improve significance or effect size. The adjusted R-squared for the final model was 0.316.

The final model indicated no significant effect for opioid formulation or dose upon MOS-MHI cognitive functioning score when important covariates were controlled. Though significance was initially observed for a methadone X dose interaction term ($p = 0.022$), the effect size was minimal ($r = -0.077$), and significance disappeared when important covariates were controlled. The presence of a DSM-IV substance-related disorder also failed to achieve statistically significant predictive value for cognitive dysfunction ($p = 0.10$).

DISCUSSION

This paper presents new information on the relationship of opioids to adverse medication effects and cognitive dysfunction in a primary care sample. Chronic daily users of opioid analgesics experienced more medication-associated adverse effects (constipation, depression, sexual dysfunction, rash, and appetite loss) than individuals taking opioids intermittently. This is consistent with the results of previous short-term randomized trials of opioid analgesics in subjects with CNMP.[20-23]

The overall study sample suffered from a greater degree of cognitive dysfunction than general clinical populations.[25] However, we found no significant difference in cognitive function based upon the frequency of opioid use or daily opioid dose. Mental health and stress measures were of greater predictive value. Psychiatric severity accounted for over half of the variation in cognitive function and was followed distantly by neighborhood disorder and pain severity. This finding is consistent with previous studies failing to uncover significant cognitive impairment when daily opioid doses are stable over the long term.[13-15]

With a small negative effect for increasing age ($\beta = -0.06$, $p = 0.026$) on cognitive function, our findings are also consistent with research indicating a potential for some impairment among older individuals with CNMP taking chronic daily opioids.[17,18]

The current study was nonrandomized and cross-sectional. Thus, inferences regarding causality must be made with caution. Unmeasured factors that predate the subjects' pain diagnoses and psychiatric comorbidities may

explain the predictive value of mental health and stress measures for cognitive dysfunction. Associations certainly provide a strong argument, however, for clinical follow-up and concurrent management of these psychosocial issues when managing patients with CNMP.

Strengths of the study include a large sample from a primary care population with prevalent painful conditions and the measurement of and control for numerous potentially important covariates.

These findings present several implications for clinical practice in the primary care management of CNMP. First, adverse effects of long-term opioids are common and should be actively monitored and managed. Primary among these are constipation, depression, sexual dysfunction, loss of appetite, and rash. An appropriate bowel regimen should be routinely recommended to patients on chronic daily opioid analgesics. Patients with CNMP should be routinely assessed for the presence of depression, and appropriate pharmacotherapy and consultation should be arranged. Providers should also assess for sexual dysfunction and initiate an appropriate evaluation. Potential causes include diabetes, atherosclerotic cardiovascular disease, medications (such as antihypertensives and antidepressants), smoking, and psychological causes.[53-55] The presence of decreased libido warrants laboratory evaluation, including measurements of thyroid-stimulating hormone, prolactin, lipids, testosterone, and hemoglobin A1C.

Second, inadequately controlled pain may be of greater concern than opioid prescription when considering the potential impact on cognitive function. Titration of opioid dosing, however, may require greater care in older individuals (over age 60) to reduce what may be an increased risk for impairment, albeit an increase of apparently small magnitude.

This study also confirms the strong associations between psychological well-being and poorly controlled pain. Depression was particularly common in the sample, and psychiatric morbidity was strongly associated with decrements in cognitive function. Additionally, significant association was discovered for community-level stress and cognitive dysfunction. These findings point toward the importance of psychosocial factors in the well-being of patients with CNMP. Clinicians should carefully assess their CNMP patients for psychiatric comorbidity and initiate appropriate management, consultation, and ancillary care.

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REFERENCES

1. Brookoff D: Chronic pain: A new disease? *Hosp Pract (Hosp Ed).* 2000; 7: 1-18.
2. Christo PJ: Opioid effectiveness and side effects in chronic pain. *Anes Clin North Am.* 2003; 21 (December): 699-713.
3. Collett BJ: Chronic opioid therapy for non-cancer pain. *Br J Anaesth.* 2001; 87 (July): 133-143.
4. Evans P: Opioids for chronic musculoskeletal pain. In: Kalso E, McQuay H, Wiesenfeld-Hallin Z (eds.): *Opioid Sensitivity of Chronic Non-Cancer Pain*: IASP Press, 1999.
5. Graven S, De Vet H, van Kleefe M, et al.: Opioids in chronic non-malignant pain: A criteria based review of the literature. Paper presented at: Ninth World Congress on Pain, Progress in Pain Research and Management, 2000.
6. Marcus DA: Treatment of nonmalignant chronic pain. *Am Fam Physician.* 2000; 61: 1331-1338.
7. McCarberg BH, Barkin RL: Long-acting opioids for chronic pain: Pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001; 8 (May-June): 181-186.
8. Bannwarth B: Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Saf.* 1999; 21 (October): 283-296.
9. Coniam S: Prescribing opioids for chronic pain in non-malignant disease. Paper presented at the Edinburgh Symposium on Pain Control and Medical Education, London, 1989.
10. Potter M, Schafer S, Gonzalez-Mendez E, et al.: Opioids for chronic nonmalignant pain. Attitudes and practices of primary care physicians in the UCSF/Stanford Collaborative Research Network. University of California, San Francisco. *J Fam Pract.* 2001; 50: 145-151.
11. Reid MC, Engles-Horton LL, Weber MB, et al.: Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002; 17: 173-179.
12. Reisine T, Pasternak G: Opioid analgesics and antagonists. In: Hardman J, Limbird L (eds.): *Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 9th ed.* New York: McGraw-Hill, 1996.
13. Bruera E, Macmillan K, Hanson J, et al.: The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain.* 1989; 39: 13-16.
14. Sjogren P, Olsen AK, Thomsen AB, et al.: Neuropsychological performance in cancer patients: The role of oral opioids, pain and performance status. *Pain.* 2000; 86: 237-245.
15. Sjogren P, Thomsen AB, Olsen AK: Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. *J Pain Symptom Manage.* 2000; 19: 100-108.
16. Byas-Smith MG, Chapman SL, Reed B, et al.: The effect of opioids on driving and psychomotor performance in patients with chronic pain. *Clin J Pain.* 2005; 21: 345-352.
17. Cumming RG: Epidemiology of medication-related falls and fractures in the elderly. *Drugs Aging.* 1998; 12: 43-53.
18. Shorr RI, Griffin MR, Daugherty JR, et al.: Opioid analgesics and the risk of hip fracture in the elderly: Codeine and propoxyphene. *J Gerontol.* 1992; 47: M111-M115.
19. Vainio A, Ollila J, Matikainen E, et al.: Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet.* 1995; 346: 667-670.
20. Arkinstall W, Sandler A, Goughnour B, et al.: Efficacy of controlled-release codeine in chronic non-malignant pain: A randomized, placebo-controlled clinical trial. *Pain.* 1995; 62: 169-178.
21. Dhaliwal HS, Sloan P, Arkinstall WW, et al.: Randomized evaluation of controlled-release codeine and placebo in chronic cancer pain. *J Pain Symptom Manage.* 1995; 10: 612-623.

22. Peloso PM, Bellamy N, Bensen W, et al.: Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol.* 2000; 27: 764-771.
23. Peloso PM, Fortin L, Beaulieu A, et al.: Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: A multicenter, outpatient, randomized, double blind, placebo controlled trial.[see comment]. *J Rheumatol.* 2004; 31: 2454-2463.
24. Fleming MF, Mundt MP, Balousek S, et al.: Chronic pain, addiction and opioids in a primary care sample; Submitted to *JAMA.* September 2005.
25. Stewart A, Ware J, Sherbourne C, et al.: Psychological distress/well-being and cognitive functioning measures. In: Stewart A, Ware J (eds.): *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach.* Durham, NC: Duke University Free Press, 1992.
26. Miele GM, Carpenter KM, Cockerham MS, et al.: Substance Dependence Severity Scale: Reliability and validity for ICD-10 substance use disorders. *Addict Behav.* 2001; 26: 603-612.
27. Miele GM, Carpenter KM, Smith Cockerham M, et al.: Concurrent and predictive validity of the Substance Dependence Severity Scale (SDSS). *Drug Alcohol Depend.* 2000; 59: 77-88.
28. Miele GM, Carpenter KM, Smith Cockerham M, et al.: Substance Dependence Severity Scale (SDSS): Reliability and validity of a clinician-administered interview for DSM-IV substance use disorders. *Drug Alcohol Depend.* 2000; 59: 63-75.
29. Leonhard C, Mulvey K, Gastfriend D, et al.: The Addiction Severity Index: A field study of internal consistency and validity. *J Subst Abuse Treat.* 2000; 18: 129-135.
30. McLellan AT, Kushner H, Metzger D, et al.: The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment.* 1992; 9: 199-213.
31. Ross CE, Mirowsky J: Neighborhood disadvantage, disorder, and health. *J Health Soc Behav.* 2001; 42: 258-276.
32. Adams NJ, Plane MB, Fleming MF, et al.: Opioids and the treatment of chronic pain in a primary care sample. *J Pain Symptom Manage.* 2001; 22: 791-796.
33. Rabkin JG, Markowitz JS, Ocepek-Welikson K, et al.: General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research.[see comment]. *J Clin Psychopharmacol.* 1992; 12: 3-10.
34. Jacobson AF, Goldstein BJ, Dominguez RA, et al.: Interrater agreement and reliability measures of SAFTEE: General inquiry vs. systematic inquiry. *Psychopharmacol Bull.* 1987; 23: 97-101.
35. Guy W, Wilson WH, Brooking B, et al.: Intra-interrater reliability of SAFTEE using videotape interviews and clinical trial data. *Psychopharmacol Bull.* 1987; 23: 93-96.
36. Markowitz JS, Rabkin JG, Stewart J, et al.: Validity assessment of SAFTEE: A preliminary report. *Psychopharmacol Bull.* 1987; 23: 102-105.
37. Guy W, Wilson WH, Brooking B, et al.: Reliability and validity of SAFTEE: Preliminar analyses. *Psychopharmacol Bull.* 1986; 22: 397-401.
38. Rabkin JG, Markowitz JS: Side effect assessment with SAFTEE: Pilot study of the instrument. *Psychopharmacol Bull.* 1986; 22: 389-396.
39. Jacobson AF, Goldstein BJ, Dominguez RA, et al.: Interrater agreement and intraclass reliability measures of SAFTEE in psychopharmacologic clinical trials. *Psychopharmacol Bull.* 1986; 22: 382-388.
40. Levine J, Schooler NR: SAFTEE: A technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull.* 1986; 22: 343-381.
41. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed.* Glenview, IL, 1999.
42. Dahl J: Personal communication. 2005.
43. Fleming M: Personal communication. 2005.
44. Krause C: Personal communication. 2005.
45. Foley KM, Houde RW: Methadone in cancer pain management: Individualize dose and titrate to effect. [comment]. *J Clin Oncol.* 1998; 16: 3213-3215.
46. Pereira J, Lawlor P, Vigano A, et al.: Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. *J Pain Symptom Manage.* 2001; 22: 672-687.
47. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed.* Glenview, IL, 2003.
48. Bruera E, Belzile M, Pituskin E, et al.: Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain.[see comment]. *J Clin Oncol.* 1998; 16: 3222-3229.
49. Watanabe S, Pereira J, Hanson J, et al.: Fentanyl by continuous subcutaneous infusion for the management of cancer pain: A retrospective study. *J Pain Symptom Manage.* 1998; 16: 323-326.
50. Bruera E, Pereira J, Watanabe S, et al.: Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer.* 1996; 78: 852-857.
51. Ballenger J: Benzodiazepines. In Schatzberg A, Nemeroff C (eds.): *The American Psychiatric Press Textbook of Psychopharmacology, 2nd Edition.* Washington DC: American Psychiatric Press, 1998.
52. Charney D, Mihic J, Harris R: Hypnotics and Sedatives. In Hardman J, Limbird L (eds.): *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed.* New York: McGraw-Hill, 2001.
53. Bodie J, Lewis J, Schow D, et al.: Laboratory evaluations of erectile dysfunction: An evidence based approach. *J Urol.* 2003; 169: 2262-2264.
54. Johnson A, III, Jarow J: Is routine endocrine testing of impotent men necessary? *J Urol.* 1992; 147: 1542.
55. Lue TF. Male sexual dysfunction—how little do we know? *J Urol.* 2003; 169: 2265.

ORIGINAL ARTICLE

Opioids and brain imaging

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ABSTRACT

Since the introduction of the gate-control theory, a plethora of evidence to support the spinal processing of pain signals has come to light. Cognitive and affective aspects of the pain experience indicate the importance of supraspinal structures, but the biological mechanisms have remained inadequately explored. Within the past decade, imaging techniques have emerged that enable in vivo assessment of the central opioidergic system and the central processing of pain. The two most important imaging modalities to this end are functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). This article will describe the underlying principles of these techniques and explain their importance in determining the loci of opioidergic pathways and their neuromodulatory influence on acute and chronic pain conditions, role in placebo effects, implication in drug dependence, and potential role in studying the analgesic efficacy of new drugs.

Key words: brain imaging, fMRI, PET, central opioid pathways, central pain processing

INTRODUCTION

The development of modern imaging techniques has allowed clinical researchers and other scientists to better appreciate the functional organization of the central nociceptive system and its modulation by opioids. Cognitive and affective aspects of the pain experience indicate that the brain is one of the most potent centers for modulation of pain signals.[1,2] Prior to the advent of functional neuroimaging technologies, these mechanisms had been studied only cursorily.[3] Regional cerebral blood flow (CBF), as a reflection of the activity of regional synapses, can be quantified with radiographic techniques. Pain intensity-related hemodynamic changes have been identified in a widespread, bilateral brain system that includes the parietal, insular, cingulate, and frontal cortical areas. Changes have also been noted in the thalamus, amygdala, and midbrain.

Neuroimaging studies have also contributed to our knowledge of the role of endogenous opioids in the placebo effect and of the effects of substance misuse and abuse on the brain. We now understand that the mechanism of action of opioids is more complex than simple inhibition of neural activation. Recent technology has allowed for demonstrations of opioid receptor distribution, neurophysiology at the receptor level, delineation of neurochemical pathologies in disease states, and changes in neurotransmission.[4] The hope is that, based on information gained from brain imaging, pathway-targeted interventions will be developed.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is the only neuroimaging technology that allows three-dimensional determination of the central opioid receptor distribution in fully conscious humans. The first human opioid receptor imaging study using PET was conducted on May 24, 1984,[5] and the first PET report on human pain was published in 1991.[6] The basic underlying principle of the technique is that neurons within active areas of the brain require more glucose and oxygen compared to neurons at a baseline condition within the same area. Thus, in response to the increase in metabolism in the active neurons, regional cerebral blood flow (CBF) increases. Radiolabeled glucose, such as ^{18}F fluorodeoxyglucose (F-18 FDG), is readily taken up by neurons, even more so by active neurons. Gamma rays released from the interactions of these radiolabeled molecules with electrons within the body are detected and processed by external sensors, and this external equipment produces an image.[7] PET scanners can map the concentration of the radiolabeled molecule and the binding of pharmacological agents over time. However, PET as a tool for assessing task-related brain activity is restricted by its relatively long measuring time.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The first functional magnetic resonance imaging

(fMRI) report on human pain was published in 1995,[8] and the experiment used electrical stimulation of an extremity to demonstrate activation of the somatosensory cortex. MRI measures the different magnetic spins between oxygenated and deoxygenated hemoglobin, the levels of which change with neuronal oxygen consumption. In the original studies, longer periods of painful stimulus were used for brain imaging studies. This introduced confounding factors to the study of pain, due to the effects of skin damage, subject compliance, interstimulus interaction, etc. It was proven that the changes in signal intensity during periods of short, repetitive stimuli and longer periods of painful stimuli were similar.[9] Consequently, more tolerable, shorter stimuli that do not have the desensitizing effects of longer stimuli are now used in these neuroimaging studies.

While PET can be used to measure available receptors and uptake sites, fMRI measures the indirect effects of drugs on the brain through their effects on CBF.[10] Compared to PET, fMRI has greater temporal (seconds vs. minutes) and spatial (about 1 mm vs. 4 mm) resolution, allowing for better localization of brain activity during complex event-related tasks.[11] Recently, novel approaches using a combination of fMRI and PET used to measure concurrent changes in CBF and regional cerebral metabolic rate during human brain activity have been reported.[12]

HYBRID IMAGING

PET/CT

A frequent complaint in receptor binding investigations is the lack of accuracy in determining the location of ligand-receptor binding in the brain.[13,14] Accuracy in determining brain regions of interest with PET signals is better accomplished by combining PET images with computed tomography (CT) images.[13,15] Early experiments required that the subjects/patients be imaged in a PET scanner first and in a CT scanner later. This necessitated moving the patient from one machine to another and sometimes making a second appointment. Furthermore, the separate images had to be either visually compared side by side or co-registered using software that merged the images. The software method did not always result in perfectly co-registered images, making analyses somewhat unreliable.

Within the last few years, dual PET/CT scanners have been developed.[14] Essentially, they are a combination of dedicated PET and dedicated CT scanners within the same chassis. Thus, even though patients can be scanned by PET and CT in a single experiment without having to move to a different machine, the scans will still be sequential as opposed to simultaneous. The advantage of dual PET/CT scanners is that inaccuracies due to repositioning are minimized. That being said, the bed on which the patient is lying does move so that the body part of interest is positioned in the right place for the chosen scan. Consequently, there is still some repositioning artifact, but the results are vastly preferable to those obtained by independent machines.

There are exciting possibilities for opioid research with combination PET/CT scanners. However, to date little has been done in opiate receptor or pain research with this hybrid technology. A dedicated PET scanner on its own is still the machine of choice for opiate imaging research because of its relatively low cost and the fact that PET/CT scanners are relegated mostly to clinical diagnostic work, often for use in cancer staging.

PET/MRI

As mentioned, current PET/CT machines do not allow for simultaneous PET and CT images. Simultaneous imaging using separate modalities is key for a machine to be a true hybrid. MRI uses strong magnetic fields for imaging purposes, and these fields may negatively interact with the detectors used in most PET scanners. Nevertheless, there are prototypes of PET/MRI hybrids being built today that may be the predecessors of better machines to come. Advantages of such technology include better soft-tissue images from MRI (compared to CT) in combination with simultaneous PET images that can be co-registered with greater accuracy. There are no repositioning artifacts, as the patient would not be moved to another machine or have the bed shifted when a different scanning modality was enacted. So far, only mouse images have been acquired in this way, using small-bore PET/MRI machines.[16] But this technology is promising and eagerly anticipated by the imaging community.

OPIATE RADIOLIGANDS

A tracer is a high affinity ligand that has a slow receptor dissociation rate and thus prolonged retention at the receptor. Derivation of the mathematical model that determines receptor-ligand binding properties for opioid receptors has been very helpful in PET imaging. In pain studies, commonly the μ-opioidergic agonist ^{11}C-carfentanil and the nonspecific opioid receptor antagonist ^{11}C-diprenorphine are utilized. Diprenorphine is a higher-affinity ^{3}H opiate ligand developed for visualizing opioid receptors. It lacks opiate receptor subtype specificity and has similar affinity for the μ, δ, and κ subtypes.[17] Diprenorphine also shows variability in its in vivo and in vitro binding characteristics because of the presence of sodium. Earlier studies used a highly potent μ-selective opioid agonist, lofentanil, but since it was not easily amenable to radiolabeling, it has been replaced by carfentanil.[18] Unlike diprenorphine, carfentanil, and newer

potent opiate agonists show similar in vivo and in vitro binding characteristics.

Radiotracers based on ^{11}C have a half-life of about 20 minutes and are suitable only for short imaging protocols lasting less than one hour after a bolus injection. For longer imaging requirements, an infusion is necessary following the bolus. This increases the total dose of opiate radioligands, imposing safety concerns. Compared to ^{11}C, an ^{18}F-labeled μ-selective ligand with a half-life of about 110 minutes improves signal quality and can be used for long-lasting imaging protocols, even with a single bolus injection. The recently developed ^{18}F-sufentanil is a promising tracer for extended protocols in μ-opioid mapping and quantification with PET.[19]

Discovery of a newer radioligand for the κ-opioid system, GR 103545,[20] now provides a unique opportunity to assess the opioidergic system in drug-dependent humans and in some neuropsychiatric disorders.

APPLIED NEUROANATOMY

Familiarity with basic neuroanatomy is essential in order to appreciate the importance of brain structures identified with functional brain imaging (Table 1). μ-receptor-mediated neurotransmission has been observed in both higher-order and subcortical brain regions. The prominent endogenous opioid transmission and μ-receptor populations are present in the prefrontal, cingulate, temporal, insular cortex, thalamic, hypothalamic, amygdala, basal ganglia, and brain stem regions.

The limbic system is a collective name for the structures involved in emotions, emotional responses, hormonal secretions, mood, motivation, pain, and pleasure sensations. It includes cortical and subcortical brain structures. The cortical structures include the prefrontal, anterior cingulate, and insular cortices. The subcortical structures include the thalamus, hypothalamus, amygdala, and hippocampus.

The nuclei that make up the basal ganglia are the striatum, globus pallidus, subthalamic nuclei, and substantia nigra. The striatum is further subdivided into the putamen, caudate nucleus, and nucleus accumbens. Although there is no clearly identified role for the basal ganglia, it may be important for motor function and learning. In particular, the nucleus accumbens, also called the ventral striatum, is rich in opioid receptors and is implicated in emotion and behavior.

OPIOID RECEPTORS AND ENDOGENOUS OPIOIDS

The endogenous opioid system is implicated not only in pain processing but in neuroendocrine function and immune modulation. In 1973, the receptors were first demonstrated in nervous tissue by the use of radioligand binding assay.[21] Bencherif et al.[22] studied the role of the supraspinal endogenous opioid system in pain processing using PET imaging of ^{11}C-carfentanil in eight healthy volunteers. They applied topical capsaicin to inflict acute pain and found that the supraspinal μ-opioid system was activated. They hypothesized that endogenous opioid peptides such as beta-endorphin, metenkephalin, endomorphin, or other opioid peptides are released in response to pain.

The contralateral insula is consistently one of the most significantly active regions involved in pain processing in studies using fMRI.[23] The medial nucleus of the thalamus projects to the anterior cingulate and prefrontal cortices. These areas partly comprise the median pain system that is thought to mediate affective-motivational aspects of pain perception.[24] The PET ligand studies of Zubieta et al.[25] revealed increases in μ-opioid receptor availability with advancing age in neocortical regions and the putamen. They also observed that women had higher opioid binding potential than men during the reproductive years, but binding decreased below that of men after menopause. Investigations regarding opioid receptors in the adult human cerebellum have been limited, but one PET study with ^{11}C-diprenorphine has provided strong evidence for opioid circuitry in the cerebellum.[26]

OPIOID AGONISTS

Neuroimaging technology is proving that opioid receptor activation has complex effects. The PET study conducted by Adler et al.[27] challenged the commonly believed hypothesis that, given the inhibitory effects of opioids on neuronal activity, there will be suppression of pain-evoked responses in distinct brain areas. They observed both decreases and increases in regional brain activity with fentanyl. The decrease in activity was noted bilaterally in the thalamus and posterior cingulate, while activation was observed in the anterior cingulate and contralateral motor cortex. The particular sector of the anterior cingulate that was activated by fentanyl has been implicated in attentional and affective processes in the past.[28] Thus, the mechanism of action of fentanyl analgesia is more than simple inhibition of regional cerebral neuronal activation. The modulation of attentional and affective processes may also contribute to fentanyl analgesia. Similarly, blood flow increases reflecting increased neuronal activity were detected in the orbitofrontal and medial prefrontal regions and the anterior cingulate cortex (ACC).[29] These brain regions are known to contribute to the processing of painful stimuli, as well as of attention and emotions.

Some fMRI studies have shown robust pain-related activity in the insular cortices that is significantly modulated by steady-state infusion of remifentanil. Wise et al.[30] were the first to use fMRI to calculate pharmacokinetic parameters describing the time of onset and offset of

Table 1. Applied neuroanatomy		
Structure	**Location**	**Role**
Prefrontal cortex	Anterior part of the frontal lobes of the brain; divided into lateral, orbitofrontal, and medial prefrontal areas	Implicated in planning complex cognitive behaviors; orbitofrontal cortex involved in decision making
Anterior cingulate cortex (ACC)	Located in middle of brain, just behind prefrontal cortex	Attention, cognitive modulation
Insular cortex	Buried deep in the lateral sulcus	Anterior part: emotion Posterior part: ascending visceral symptoms
Thalamus	Large, dual-lobed mass of gray-matter cells, located at top of brain stem	Receives auditory, visual, and somatosensory signals and relays them to the cerebral cortex
Hypothalamus	Posterior to optic chiasma, below the thalamus	Autonomic and endocrine functions, homeostasis, emotions, motor function; regulates food and water intake, sleep-wake cycle
Amygdala	Almond-shaped mass of nuclei, located deep within temporal lobes; lies medial to hypothalamus and adjacent to hippocampus	Arousal, aggression, fear, emotional responses, hormonal secretions
Hippocampus	Horseshoe shaped; located within temporal lobes, adjacent to amygdala	Consolidation of new memories, emotions, navigation, and spatial orientation
Nucleus accumbens	Lateral to septum pellucidum	Reward, pleasure, and addiction

remifentanil action based on changes in pain-related brain function.

OPIOID ANTAGONISTS

In 1975, Snyder and co-workers[17] demonstrated that opiate receptors could be labeled in vivo following an intravenous injection of an opiate antagonist, ^{3}H-naloxone. This was a landmark study, the first to investigate in vivo labeling of any receptor. The effects of naloxone on experimental and clinical pain have been widely reported. Naloxone enhances baseline clinical pain and diminishes the analgesic effectiveness of placebo.[31]

Borras et al.[32] conducted a study to determine the effect of naloxone on brain activity as measured by fMRI. They assessed the effects of naloxone on endogenous opioid systems and also evaluated its effect on central nervous system response to noxious heat. They observed that naloxone-specific activation changes were found in a number of cortical and subcortical regions and in the cerebellum. Cortical activation was induced in regions including the cingulate, prefrontal cortex, and insula. Subcortical regions showing increased signal change included the thalamus, hippocampus, and entorhinal cortex. These activated areas are the sites of action of endogenous opioid pathways involved in regulating central nervous system response to aversive stimuli.

PLACEBO ANALGESIA

There is overwhelming evidence that the endogenous opioid system is involved in placebo analgesia. In an elegant, widely cited PET study, Petrovic et al.[33] analyzed the brain regions that are affected both by placebo analgesia and remifentanil. In both cases, regional CBF changed in similar areas of the anterior cingulate, lateral orbitofrontal cortex, and brain stem, suggesting that placebo activates the same opioid receptor system to which remifentanil binds. However, this study did not include an anticipation period and so could not discriminate neural responses during anticipation from changes associated with the painful stimulus itself.

Amanzio and Benedetti[34] investigated the mechanism underlying the activation of endogenous opioids in placebo analgesia in humans by using a model of experimental ischemic arm pain. In their study, they produced different types of placebo response that could be totally blocked, partially blocked, or totally unaffected by naloxone. They speculated that placebo analgesia can be dissected into opioid and nonopioid components, depending on

the procedure used to induce the placebo response. By adding expectation cues, an opioid component is observed. The two fMRI experiments conducted by Wager et al.[35] found that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and ACC, and was associated with increased activity during anticipation of pain in the prefrontal cortex, providing evidence that placebos alter the experience of pain.

More recently, Zubieta and colleagues[36] provided the first direct evidence that the administration of a placebo with implied analgesic properties activated the endogenous opioid system. They observed that neurotransmitter activity took place directly in higher-order brain regions, namely the rostral ACC; the dorsolateral, prefrontal, and insular cortices; and the nucleus accumbens. With the exception of the nucleus accumbens, these findings are similar to those of the fMRI studies of Wager et al.[35] It should be noted that nucleus accumbens signals are difficult to obtain with fMRI techniques.

ACUTE AND CHRONIC PAIN

There are differences in brain images acquired during acute and chronic pain states. Studies with ^{11}C-carfentanil revealed reduced μ-opioidergic binding, following induction of acute pain in masseter muscles, in the dorsal ACC, insula, thalamus, hypothalamus, amygdala, and lateral prefrontal cortex. It was also noted that with activation of the opioidergic system in the amygdala, thalamus, and nucleus accumbens, sensory pain scores were lower. Similarly, there was a negative correlation with affective pain ratings with activation of the ACC, thalamus, and nucleus accumbens.[37]

In chronic pain, PET studies have shown a decrease in radioligand-opiate receptor binding. Rheumatoid arthritis, trigeminal neuralgia, and central poststroke pain all lead to decreased ligand binding in pain-processing regions during painful periods in comparison to pain-free intervals or in healthy subjects. Willoch et al.[38] presented a case report of central pain following pontine infarction that was associated with changes in opioid receptor binding. Jones et al.[39] were the first to systematically demonstrate reduction in opioid receptor binding capacity in neurons within the human nociceptive system in four patients with central neuropathic pain. These findings may explain why certain patients with central pain require high doses of synthetic opiates to achieve optimum analgesia.

Although the decrease in ligand-opiate receptor binding is a common factor in acute and chronic pain, the underlying mechanisms may be different. In chronic pain, the decrease may be due to a combination of the following factors: increased endogenous opioid release, receptor internalization, receptor down-regulation, decrease in affinity of opioid receptors for radioligands, or loss of neurons carrying these receptors.[4] In contrast, in acute pain, the decrease in radioligand binding observed in healthy controls is more likely to be due to endogenous peptide release, or possibly agonist-induced internalization and recycling of μ-opioid receptors, than to receptor down-regulation and changes in affinity.[22]

ADDICTION AND DRUG DEPENDENCE

The presence and quantity of μ-opioid receptors have been suggested to indicate opioid abuse potential.[40] Zubieta and co-workers[41] were the first to observe increased μ-opioid binding, using PET with ^{11}C-carfentanil, in certain brain regions of cocaine addicts; these increases correlated with the severity of cocaine craving experienced at the time.

Different drugs stimulate dopamine release in the nucleus accumbens, part of the ventral striatum. Striatal dopamine release is stimulated by μ-opioid receptor activation but inhibited by striatal κ-opioid receptors. In view of the current interest in the opioid system in neuropsychiatric disorders, recent studies have focused on identifying the ideal radioligands for brain imaging of the κ-opioid system.[42] The newer radioligand for κ-receptors, GR 103545, now provides an opportunity to assess the opioidergic system in drug-dependent humans, though the application of this knowledge in management of addiction is still in its infancy.

Brain imaging has been used to investigate opioid dependence. PET imaging in methadone-maintained addicts failed to demonstrate widespread reduced uptake of tracers in the brain, as would be expected if methadone were occupying opioid receptors.[43,44] This suggests that the efficacy of methadone may not depend upon receptor blockade or reduction; instead, it may act by desensitizing receptors to opioids.[10] On the other hand, PET studies in patients on buprenorphine clearly show that μ-opioid receptors are occupied in a dose-dependent fashion. Hence, receptor blockade may contribute to the effectiveness of buprenorphine.[45]

LIMITATIONS

The sensation of pain is the result of an intricate interaction of peripheral chemical and electrical signaling, central modulation, emotion, and behavior. This partly explains why effective relief of persistent pain can not be achieved by neurosurgical ablative procedures.[46] It is unrealistic to expect brain imaging technology to accurately quantify the source or intensity of pain, as there is interindividual variability. Review of PET/fMRI neuroimaging shows only 50 to 85 percent consistency on the sites, sides, and intensities.[7] Nevertheless, in the past

decade, neuroimaging studies in humans have formed the basis for our understanding of the brain's processing of pain.

In most brain imaging studies, the observed effects were assumed to be a direct consequence of the administered drug. Since there have been no concurrent pharmacokinetic studies to verify it, this assumption could be erroneous. Similarly, when investigating relative regional CBF changes using PET or fMRI, it is assumed that global CBF and arterial oxygen and carbon dioxide tensions do not change across the investigated conditions. But intense pain can increase sympathetic activity and hyperventilation, both of which can potentially alter these parameters.[47]

The basic mechanisms of ligand activation are yet to be completely understood. Although the changes in ligand binding observed with PET are currently assumed to be related to competition of the ligand with the endogenous transmitters, the underlying mechanism may be more complex.[4]

CONCLUSION

The development of noninvasive brain imaging technologies has led to exciting discoveries regarding central opioidergic function and dysfunction. This has opened up new possibilities in the diagnosis and treatment of painful conditions. The opportunity afforded by fMRI to compare time courses of drug effects in different brain regions has helped to identify the neural networks essential for analgesia. This knowledge will aid in designing treatments to target specific brain systems for maximum therapeutic effect. The altered opioid receptor binding noted in patients with chronic pain conditions raises the possibility of new pharmacological approaches to treatment.

More exploration of opioidergic circuitry and opioid receptor distribution within the cerebellum will promote better appreciation of the role of opioids in cerebellar function.[26,48] The future will witness more-focused treatment for conditions that remain poorly treated, such as substance abuse. Physicians must gain a basic understanding of these technologies in order to take advantage of their clinical implications.

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REFERENCES

1. Melzack R, Casey KL: Sensory, motivational and central control determinants of pain. In Kenshalo DR (ed.): *The Skin Senses*. Springfield: Thomas, 1968.
2. Weisenberg M, Schwarzwald J, Tepper I: The influence of warning signal timing and cognitive preparation on the aversiveness of cold-pressor pain. *Pain*. 1996; 64: 379-385.
3. Petrovic P, Ingvar M: Imaging cognitive modulation of pain processing. *Pain*. 2002; 95: 1-5.
4. Sprenger T, Berthele A, Platzer S, et al.: What to learn from in vivo opioidergic brain imaging? *Eur J Pain*. 2005; 9(2): 117-121.
5. Frost JJ, Wagner HN Jr, Dannals RF, et al.: Imaging opiate receptors in the human brain by positron tomography. *J Comput Assist Tomogr*. 1985; 9(2): 231-236.
6. Talbot JD, Marrett S, Evans AC, et al.: Multiple representations of pain in human cerebral cortex. *Science*. 1991; 251: 1355-1358.
7. Chen AC: New perspectives in EEG/MEG brain mapping and PET/fMRI neuroimaging of human pain. *Int J Psychophysiol*. 2001; 42(2): 147-159.
8. Davis KD, Wood ML, Crawley AP, et al.: fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *Neuroreport*. 1995; 7(1): 321-325.
9. Davis KD, Kwan CL, Crawley AP, et al.: Event-related fMRI of pain: Entering a new era in imaging pain. *Neuroreport*. 1998; 9(13): 3019-3023.
10. Lingford-Hughes A: Human brain imaging and substance abuse. *Curr Opin Pharmacol*. 2005; 5: 42-46.
11. Tracey I: Prospects for human pharmacological functional magnetic resonance imaging (phMRI). *J Clin Pharmacol*. 2001; 41: 21S-28S.
12. Newberg AB, Wang J, Rao H: Concurrent CBF and CMRG1c changes during human brain activation by combined fMRI-PET scanning. *Neuroimage*. 2005; 28: 500-506.
13. Schulthess GK: Positron emission tomography versus positron emission tomography/computed tomography: From "unclear" to "new-clear" medicine. *Mol Imaging Biol*. 2004; 6(4): 183-187.
14. Beyer T, Antoch G, Müller S, et al.: Acquisition protocol considerations for combined PET/CT imaging. *J Nucl Med*. 2004; 45: 25S-35S.
15. Vogel WV, Oyen WJG, Barentsz JO, et al.: PET/CT: Panacea, redundancy, or something in between? *J Nucl Med*. 2004; 45: 15S-24S.
16. Pichler BJ, Judenhofer MS, Catana C, et al.: Performance test of an LSO-APD detector in a 7-T MRI scanner for simultaneous PET/MRI. *J Nucl Med*. 2006; 47(4): 639-647.
17. Frost JJ: PET imaging of the opioid receptor: The early years. *Nucl Med Biol*. 2001; 28(5): 509-513.
18. Dannals RF, Ravert HT, Frost JJ, et al.: Radiosynthesis of an opiate receptor binding radiotracer: [11C]carfentanil. *Int J Appl Radiat Isot*. 1985; 36(4): 303-306.
19. Henriksen G, Platzer S, Hauser A: ^{18}F-labeled sufentanil for PET-imaging of μ-opioid receptors. *Bioorg Med Chem Lett*. 2005; 15: 1773-1777.
20. Talbot PS, Narendran R, Butelman ER, et al.: 11C-GR103545, a radiotracer for imaging kappa-opioid receptors in vivo with PET: Synthesis and evaluation in baboons. *J Nucl Med*. 2005; 46(3): 484-494.
21. Pert CB, Snyder SH: Opiate receptor: Demonstration in nervous tissue. *Science*. 1973; 179(77): 1011-1014.
22. Bencherif B, Fuchs PN, Sheth R, et al.: Pain activation of human supraspinal opioid pathways as demonstrated by [11C]-carfentanil and positron emission tomography (PET). *Pain*. 2002; 99(3): 589-598.
23. Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of

brain responses to pain. A review and meta-analysis. *Neurophysiol Clin.* 2000; 30(5): 263-288.
24. Albe-Fessard D, Berkley KJ, Kruger L, et al.: Diencephalic mechanisms of pain sensation. *Brain Res.* 1985; 356(3): 217-296.
25. Zubieta JK, Dannals RF, Frost JJ: Gender and age influences on human brain mu-opioid receptor binding measured by PET. *Am J Psychiatry.* 1999; 156(6): 842-848.
26. Schadrack J, Willoch F, Platzer S, et al.: Opioid receptors in the human cerebellum: Evidence from [11C]diprenorphine PET, mRNA expression and autoradiography. *Neuroreport.* 1999; 10(3): 619-624.
27. Adler LJ, Gyulai FE, Diehl DJ: Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *Anesth Analg.* 1997; 84: 120-126.
28. Corbetta M, Miezin FM, Dobmeyer S, et al.: Selective and divided attention during visual discriminations of shape, color, and speed: Functional anatomy by positron emission tomography. *J Neurosci.* 1991; 11(8): 2383-2402.
29. Sprenger T, Wagner K, Willoch F, et al.: Hot-spots of opioid receptor activation by μ-agonists—a fusion study of [11C]-diprenorphine and H215O-PET. *J Cereb Blood Flow Metab.* 2003; 23(suppl. 1): 715.
30. Wise RG, Williams P, Tracey I: Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. *Neuropsychopharmacology.* 2004; 29(3): 626-635.
31. Grevert P, Albert LH, Goldstein A: Partial antagonism of placebo analgesia by naloxone. *Pain.* 1983; 16(2): 129-143.
32. Borras MC, Becerra L, Ploghaus A, et al.: FMRI measurement of CNS responses to naloxone infusion and subsequent mild noxious thermal stimuli in healthy volunteers. *J Neurophysiol.* 2004; 91: 2723-2733.
33. Petrovic P, Kalso E, Petersson KM, et al.: Placebo and opioid analgesia—imaging a shared neuronal network. *Science.*2002; 295: 1737-1740.
34. Amanzio M, Benedetti F: Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci.* 1999; 19(1): 484-494.
35. Wager TD, Rilling JK, Smith EE, et al.: Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science.* 2004; 303(5661): 1162-1167.
36. Zubieta JK, Bueller JA, Jackson LR, et al.: Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *J Neurosci.* 2005; 25(34): 7754-7762.
37. Zubieta JK, Smith YR, Bueller JA, et al.: Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science.* 2001; 293(5528): 311-315.
38. Willoch F, Tolle TR, Wester HJ, et al.: Central pain after pontine infarction is associated with changes in opioid receptor binding: A PET study with 11C-diprenorphine. *AJNR Am J Neuroradiol.* 1999; 20(4): 686-690.
39. Jones AK, Watabe H, Cunningham VJ, et al.: Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. *Eur J Pain.* 2004; 8(5): 479-485.
40. Roache JD: Performance and physiological measures in abuse liability evaluation. *Br J Addict.* 1991; 86(12): 1595-1600.
41. Zubieta JK, Gorelick DA, Stauffer R, et al.: Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. *Nat Med.* 1996; 2(11): 1225-1229.
42. Machulla HJ, Heinz A: Radioligands for brain imaging of the kappa-opioid system. *J Nucl Med.* 2005; 46(3): 386-387.
43. Kling MA, Carson RE, Borg L, et al.: Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. *J Pharmacol Exp Ther.* 2000; 295(3): 1070-1076.
44. Melichar JK, Hume SP, Williams TM, et al.: Using [11C]-Diprenorphine to image opioid receptor occupancy by methadone in opioid addiction: Clinical and preclinical studies. *J Pharmacol Exp Ther.* 2005; 312(1): 309-315.
45. Greenwald MK, Johanson CE, Moody DE, et al.: Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* 2003; 28: 2000-2009.
46. Xu X, Fukuyama H, Yazawa S, et al.: Functional localization of pain perception in the human brain studied by PET. *Neuroreport.* 1997; 8(2): 555-559.
47. Porro CA: Functional imaging and pain: Behavior, perception, and modulation. *Neuroscientist.* 2003; 9(5): 354-369.
48. Bucher SF, Seelos KC, Oertel WH, et al.: Cerebral generators involved in the pathogenesis of the restless legs syndrome. *Ann Neurol.* 1997; 41(5): 639-645.

CORRECTION

Journal of Opioid Management 2.2, March/April 2006, pp 105-112

The article "Effect of drug and medical treatment on wide geographic variations in repeated emergency department use by HIV-infected drug users" was headed as a Literature Review in error. It is an original article using a database that the authors assembled themselves. We apologize for the error.

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ORIGINAL ARTICLE

The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA®) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin®) for the treatment of chronic, moderate to severe low back pain

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ABSTRACT

This large, open-label, randomized, parallel-group, multicenter study compared two oral sustained-release opioids (SROs)—AVINZA® (A-MQD), morphine sulfate extended-release capsules given once a day, and OxyContin® (O-ER), oxycodone modified-release tablets given twice a day—in SRO-naive subjects ages 30 to 70 with chronic, moderate to severe low back pain. Of the 392 subjects enrolled and randomized, 266 (132 in the A-MQD group and 134 in the O-ER group) completed the opioid dose titration phase and entered an eight-week evaluation phase. During the evaluation phase, A-MQD achieved significantly better pain control than O-ER, as demonstrated by a greater decrease from baseline in pain scores obtained four times daily during weeks one, four, and eight ($p = 0.002$). The number of breakthrough-pain rescue medication doses adjusted for the number of patient days was significantly lower in the A-MQD group ($p < 0.0001$). Better pain control with A-MQD was achieved with a significantly lower daily opioid dose than with O-ER (mean 69.9 mg and 91 mg morphine equivalents, respectively; $p = 0.0125$). Quality of sleep was significantly better with A-MQD for the entire evaluation phase ($p = 0.0026$). The incidence and severity of elicited opioid side effects were similar in the two groups. This trial demonstrated that once-daily A-MQD provides consistent around-the-clock pain relief in patients with low back pain. In patients who completed opioid dose titration, A-MQD was significantly better than O-ER for reducing pain and improving sleep, while requiring a lower daily opioid dose.

Key words: AVINZA, OxyContin, chronic low back pain

INTRODUCTION

Chronic pain is defined as pain lasting at least six months and/or pain duration longer than the expected time for normal tissue healing.[1] It is estimated that approximately 50 million Americans live with chronic pain caused by disease or accident.[2] One of the most prevalent types of chronic pain is low back pain. Andersson[3] estimated that the annual prevalence of low back pain in the United States ranges from 12 percent to 30.2 percent, and the lifetime incidence ranges from 48.8 percent to 69.9 percent. The socioeconomic impact of chronic low back pain is considerable. It was estimated that total healthcare expenditures incurred in 1998 by individuals with low back pain in the United States were $90.7 billion, and total incremental expenditures attributable to back pain reached approximately $26.3 billion.[4] Treatment of low back pain consists of pharmacological and nonpharmacological approaches, including nonsteroidal anti-inflammatory drugs, muscle relaxants, single-entity opioids, and combinations of nonopioid and opioid analgesics.

Recent clinical studies have demonstrated that opioid pharmacotherapy is effective for the management of

chronic low back pain.[1,5-9] In a recent position paper, the American Pain Society (APS) stated that oral sustained-release opioids (SROs) are one of the most important innovations in the management of moderate to severe cancer-related pain and that they are usually preferred over short-acting opioids because their longer duration of action may lessen the frequency and severity of end-of-dose pain.[1] Over the last several years, SROs have emerged as the most commonly prescribed pharmacological therapy for chronic, moderate to severe pain, and their usage has been steadily increasing.[5]

Several oral SROs are available, characterized by type of opioid and modified-release technology. Because opioids are rapidly absorbed in the gastrointestinal tract, the pharmacokinetic and analgesic properties of an SRO are highly dependent on the technology employed to release the opioid from its carrier. Thus, two different modified-release formulations of the same opioid may result in different analgesic profiles, even if dosed at the same frequency. Among the opioids, morphine has the longest history in the treatment of pain, has a well-defined safety and efficacy profile,[5-9] and is available in several modified-release formulations. The first modified-release morphine formulation to be available for oral administration, MS Contin® (MSC, Purdue Pharma LP, Stamford, CT), was approved for dosing every 12 hours. More recently, AVINZA® (A-MQD, Ligand Pharmaceuticals Inc., San Diego, CA), a morphine-containing SRO with a novel modified-release technology, was approved for once-daily dosing. The technology employed in A-MQD capsules was developed specifically for once-daily use. The capsules are made of hard gelatin shells containing small beads 1 to 2 mm in diameter; 10 percent of the beads release their morphine content rapidly upon ingestion, and the other 90 percent are composed of an inert core surrounded by a morphine layer enclosed in a matrix of soluble and insoluble polymers and release their morphine content over 24 hours. This dual-release formulation allows targeted plasma morphine concentrations to be attained rapidly after ingestion and to be sustained throughout the 24-hour dosing interval.

Caldwell et al.[10] conducted a double-blind, double-dummy, four-arm, Phase III study comparing A-MQD given once in the morning, A-MQD given once in the evening, MSC given every 12 hours, and placebo in opioid-naïve patients with chronic, moderate to severe pain due to osteoarthritis. Designed for regulatory registration, this study was powered as a noninferiority trial to demonstrate that A-MQD is at least as effective as MSC. Results from weekly efficacy assessments confirmed the noninferiority hypothesis and showed that both A-MQD and MSC were significantly better than placebo for improving pain. This trial, however, did not include multiple pain assessments throughout the day to document that the A-MQD formulation provides constant pain relief over 24 hours with a single daily dose. A comparison of the pharmacokinetics of A-MQD given every 24 hours and MSC given every 12 hours showed that both SROs provided similar total systemic exposures, but A-MQD had less fluctuation of morphine concentrations during a 24-hour period.[11]

The formulation used for OxyContin® tablets (O-ER, Purdue Pharma LP, Stamford, CT) delivers approximately 38 percent of its content rapidly upon ingestion and the remaining content over a more extended period.[12] In a randomized double-blind study conducted in patients with chronic, moderate to severe low back pain, O-ER given every 12 hours was shown to have comparable safety and efficacy to short-acting oxycodone given four times daily.[13]

A trial comparing the pharmacokinetics of A-MQD and O-ER has shown fewer and narrower peak-to-trough fluctuations with A-MQD.[14] Prior to the present trial, no trial had been conducted to compare the efficacies of A-MQD and O-ER. In addition, no randomized trials have been published comparing the long-term use of different SROs in patients with chronic low back pain. Therefore, we conducted this randomized, multicenter study with multiple pain assessments throughout the day to demonstrate that A-MQD given once daily provides continuous pain relief over 24 hours and to compare the efficacy and safety of once-daily A-MQD to that of twice-daily O-ER in patients with chronic, moderate to severe low back pain.

METHODS

Study design

The ACTION (AVINZA Comparator Trials in Opioid Naive) study was an open-label, randomized, parallel-group, multicenter trial designed to evaluate and compare the efficacy and safety of A-MQD and O-ER for the treatment of chronic, moderate to severe low back pain. The study protocol was reviewed and approved by a central institutional review board, and the study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. Informed consent was obtained from each patient before enrollment in the study. The study was cofunded by Ligand Pharmaceuticals Inc. (San Diego, CA) and Organon Pharmaceuticals USA Inc. (Roseland, NJ).

Participants

Subjects between the ages of 30 and 70 were candidates for the study if they had persistent, moderate to severe, chronic low back pain that was judged by the investigator as appropriate for chronic opioid therapy. To be eligible for the study, subjects had to have had suboptimal analgesic response to nonsteroidal anti-inflammatory

drugs, acetaminophen, and/or immediate-release opioids. Subjects were required to have a pain score > 4 on an 11-point numerical scale, where 0 = "no pain" and 10 = "pain as bad as you can imagine." Subjects with neuropathic back pain were allowed in the trial provided that no surgical or pharmacological intervention was anticipated to be required in the next three months. To be eligible for enrollment, subjects had to be willing to be treated with the study drug to which they were randomized, be able to read and understand English, and be willing and capable to input study-specific assessments using a hand-held patient electronic diary (PED).

Subjects were excluded from the study if they were treated with an SRO, had used an SRO within the previous six months, or were previously unresponsive or intolerant to opioids. Other exclusion criteria included a serious diagnosed medical condition that would interfere with the ability to complete the study, back surgery in the past six months, more than two surgeries for back pain, or an expected need for back surgery or steroid injection during the first 12 to 14 weeks of the trial.

Interventions

Eligible patients were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER dosed every 12 hours. Subjects were instructed to take their study medication at the same time of the day ± 30 minutes. The branded formulations of both SROs and ibuprofen were provided free of charge throughout the study. Ibuprofen (200-mg tablets) was the only rescue medication permitted for breakthrough pain and could be used in doses up to 2,400 mg a day. Subjects were instructed not to take an additional dose of their SRO for breakthrough pain. The study protocol provided detailed guidelines for opioid dose escalation. Measures to prevent opioid-induced constipation were recommended but not mandatory.

Titration phase. The subjects underwent opioid dose titration for three to six weeks to establish a patient-specific daily dose that provided an optimal balance between efficacy and safety. The study protocol specified that the opioid dose was considered stabilized when all the following criteria were met: 1) same dose of study medication for seven consecutive days, 2) pain scores consistently = 4 for all scheduled assessments on three consecutive days, and 3) an average of two or fewer ibuprofen doses per day during these three days.

Evaluation phase. Upon completion of the titration phase, subjects entered an eight-week evaluation phase divided in two four-week periods. In the first period, the SRO daily dose attained at the end of the titration phase was to remain fixed for four weeks, and in the event of worsening pain ibuprofen rescue could be used as needed. In the second period, the SRO daily dose could be modified as needed to optimize pain control.

Extension phase. Following completion of the eight-week evaluation phase, the subjects were given the option to continue the study for an additional four months (extension phase). The aim of this extension was to objectively evaluate the long-term efficacy and pattern of SRO use.

Objectives

The objectives of the eight-week evaluation phase of the trial were: 1) to compare the efficacy and safety of A-MQD and O-ER in SRO-naive patients with chronic, moderate to severe low back pain; 2) to evaluate the efficacy of A-MQD in this patient population; and 3) to demonstrate that the modified-release formulation used in A-MQD delivers continuous 24-hour pain relief with a single daily dose.

Patient evaluation

Subjects were requested to assess their pain levels and rescue medications daily. Self-reported scores of the "pain right now" component of the Brief Pain Inventory[15] (BPI), a validated 11-point visual analog scale, were collected every morning prior to the morning dose for the duration of the study. The number of ibuprofen rescue doses used in the preceding 24 hours was also collected daily for the duration of the study. In addition, to provide a detailed evaluation of the extent and duration of pain relief achieved with each SRO, subjects were requested to document their pain scores and rescue medication usage during weeks one, four, and eight of the evaluation phase at four specific times during the day: immediately before taking the morning dose, and then six, nine, and 12 hours after taking the morning dose. In the O-ER group, the 12-hour time point had to be assessed before taking the evening dose. Except for on day one, the pain scores obtained immediately before taking the morning opioid dose correspond to the trough opioid plasma concentration for both drugs and thus represent the end-of-dose pain score. The pain scores obtained 12 hours after taking the morning dose correspond to another trough opioid plasma concentration in the O-ER group only.

Sleep parameters were evaluated monthly using the Pittsburgh Sleep Quality Index (PSQI), a validated multidimensional sleep scale developed for use in clinical trials.[16] Other efficacy assessments consisted of the Short-Form 12 (SF-12) Questionnaire, a validated multipurpose quality-of-life instrument consisting of a 15-item ordinal scale, and the Work Limitations Questionnaire, a validated instrument that measures the physical and mental impact of pain on work-related activities.

Daily for the duration of the study, subjects were asked to answer the Elicited Opioid Side Effect

Table 1. Patient disposition			
	Total (percent)	**A-MQD (percent)**	**O-ER (percent)**
Number of subjects randomized (AST)	392 (100)	203 (100)	189 (100)
Titration phase			
Subject withdrawals during titration	126 (32.1)	71 (35.0)	55 (29.1)
Subjects completing titration	266 (67.9)	132 (65.0)	134 (70.9)
Eight-week evaluation phase			
Subjects entering the evaluation phase (ITT)	266 (100)	132 (100)	134 (100)
Subject withdrawals during evaluation phase	46 (17)	22 (17)	24 (18)
Subjects completing evaluation phase	220 (83)	110 (83)	110 (82)
Discontinuations			
Number of discontinuations	172 (43)	93 (45.8)	79 (41.8)
Reason for discontinuation			
Adverse reactions	65 (37.8)	38 (40.9)	27 (31.2)
Adverse event	60	36	24
Serious adverse event	5	2	3
Subject withdrew consent	37 (21.5)	18 (19.4)	19 (24.1)
Subject lost to follow-up	19 (11.0)	12 (12.9)	7 (7.5)
Lack of efficacy/persistent pain	16 (9.3)	10 (10.8)	6 (7.6)
Noncompliance	11 (6.4)	6 (6.4)	5 (6.3)
Opioid dose not stabilized	9 (5.2)	5 (5.4)	4 (5.1)
Investigator withdrew patient	6 (3.5)	1 (1.1)	5 (6.3)
Protocol violation	5 (2.9)	1 (1.1)	4 (5.1)
Other	4 (2.3)	2 (2.1)	2 (2.5)

Questionnaire, which captures the occurrence of seven adverse reactions commonly reported with opioid use (constipation, nausea, vomiting, dizziness, drowsiness, dry mouth, and itchiness) and their severity using a scale from 0 to 10, where 0 = "no event" and 10 = "an awful lot." Serious adverse events (SAEs), which included any documented or suspected episode of opioid misuse or abuse, were recorded by the investigators and reported to the clinical research organization (CRO) that managed the trial.

As nearly all efficacy, safety, and dosing information was derived from data entered by subjects into their PEDs (PHT Corp., Charlestown, MA), one researcher at each study site was given thorough training in the proper use of the PED and served as trainer for other site personnel and for subjects treated at that site. To enhance compliance with treatment and schedule of assessments, each PED was programmed to sound an alarm at the anticipated times of study medication dosing and data input. Subjects were instructed to submit the data they had entered in their PED daily, by phone, and were contacted by the study-site personnel if they neglected to do so.

Sample size, randomization, and statistical analyses

The number of patients to enroll in the study was determined prospectively, with the intent of having

Table 2. Patient demographics in the all-subjects-treated (AST) and intent-to-treat (ITT) populations

		AST population		ITT population	
		A-MQD (n = 203) (percent)	O-ER (n = 189) (percent)	A-MQD (n = 132) (percent)	O-ER (n = 134) (percent)
Gender	Male	74 (36.5)	79 (41.8)	48 (36.4)	61 (45.5)
	Female	129 (63.5)	110 (58.2)	84 (63.6)	73 (54.5)
Age (years)	Median	50	50	49	51
	Range	28 – 70	29 – 73	28 – 68	30 – 73
Race*	Black/African American	47 (23.2)	32 (16.9)	41 (31.1)	21 (15.7)
	Caucasian	154 (75.9)	156 (82.5)	90 (68.2)	112 (83.6)
	Other	2 (1)	1 (0.5)	1 (0.8)	1 (0.7)
Weight	Median	87 kg	91 kg	87 kg	93 kg
Height	Median	168 cm	168 cm	167 cm	169 cm
Back pain history	Median	7 years	6 years	8 years	7 years
Cause of back pain**	Mechanical	155 (76.4)	160 (84.7)	102 (77.3)	115 (85.8)
	Nonmechanical	48 (23.6)	29 (15.3)	30 (22.7)	19 (14.2)
Nerve involvement***	Yes	75 (36.9)	51 (27)	54 (40.9)	38 (28.4)
	No	128 (63.1)	138 (73.0)	78 (59.1)	96 (71.6)

* p not significant (NS) for AST and $p < 0.02$ for ITT; ** $p < 0.04$ for AST and NS for ITT; *** $p < 0.04$ for AST and $p = 0.03$ for ITT.

approximately 120 subjects enter the extension phase of the study, a cohort size deemed adequate to provide useful information on the long-term use of SROs. We empirically assumed drop-out rates of 30 percent during the titration phase, 10 percent/month during the eight-week evaluation phase, and 10 percent during the transition from the evaluation to the extension phase. With these assumptions, we determined that 400 subjects had to be enrolled in the study, 280 of whom would enter the eight-week evaluation phase; of those, 120 would continue into the extension phase. We also verified that a sample size of 140 subjects/arm entering the evaluation phase would provide an 80 percent power to detect an increase in the proportion of patients achieving pain relief, from 70 percent in the O-ER arm to 85 percent in the A-MQD, using a two-sided test and an alpha error of 0.05.

Randomization was performed centrally for all study sites, with no stratification factors. Because the number of subjects withdrawn from study during titration could differ between the two study groups, an interactive voice response system was used for subject registration and randomization, and this system was programmed to calibrate the randomization ratio as needed to achieve an equal number of subjects from each group at the start of the evaluation phase.

For data analysis, two populations were distinguished: the "all subjects treated" (AST) population, defined as all randomized subjects who received at least one dose of either study drug; and the "intent to treat" (ITT) population, defined as subjects who entered the eight-week evaluation phase. Standard descriptive statistics were used to report baseline demographic variables. Comparison between groups was performed by the Wilcoxon two-sample test for continuous variables and the Pearson's chi-square test for categorical variables.

Efficacy variables (raw scores from BPI, PSQI, and a brief sleep questionnaire) were analyzed for the ITT population only. These variables were analyzed and compared between groups for predefined assessment time

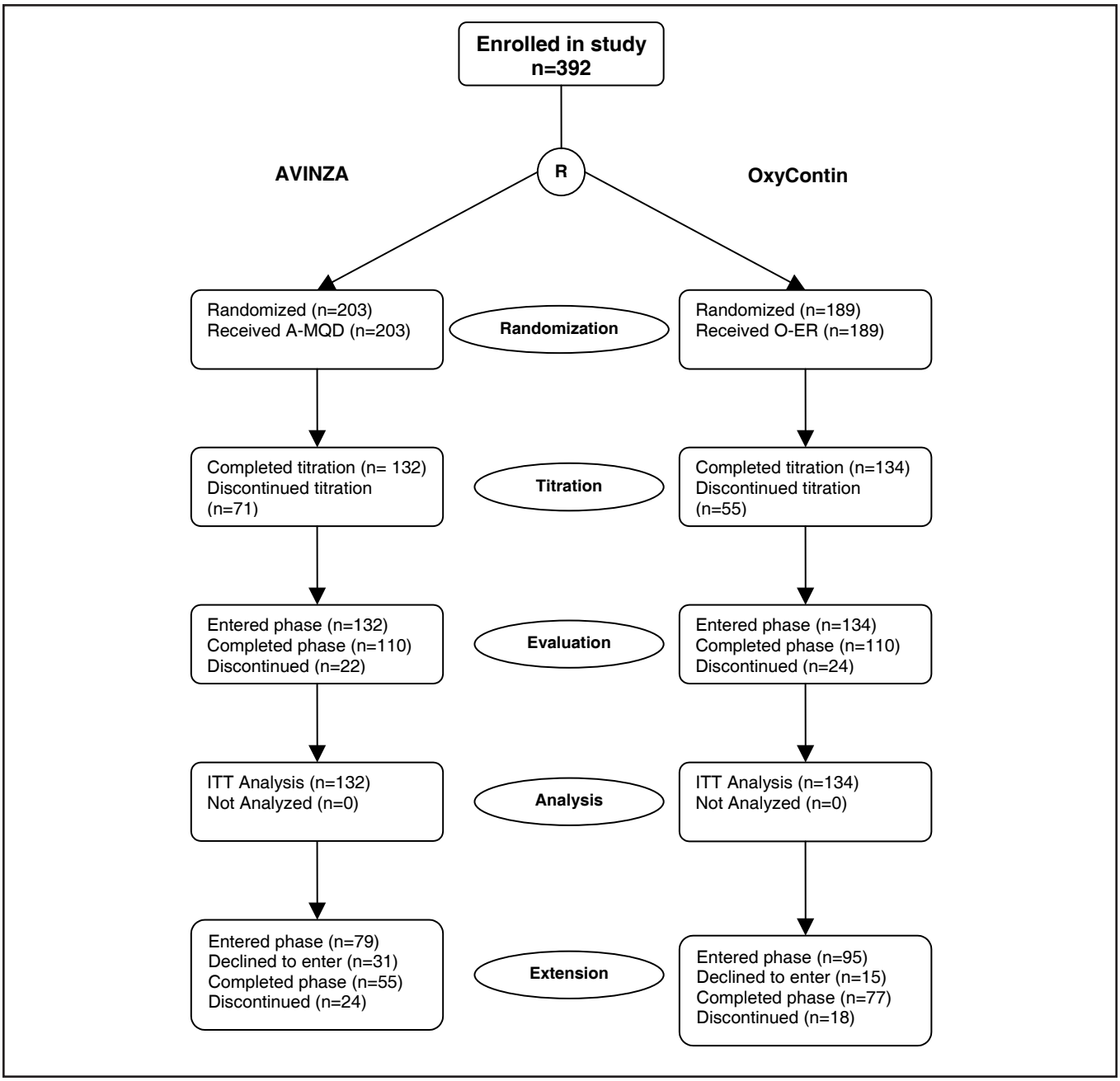

Figure 1: Patient disposition diagram.

points and presented both as absolute values and as relative changes from baseline, defined as the values obtained at enrollment. Daily and weekly averages during the eight-week evaluation phase were computed. Baseline scores were compared between the two groups using the Wilcoxon two-sample test. Categorical efficacy variables were compared using the Cochran-Mantel-Haenzel test. Within-group continuous efficacy variables were compared by the paired t-test or the Wilcoxon signed rank test. Differences between treatments and 95 percent confidence intervals for predefined pain assessment time points were compared by ANOVA, with patient baseline characteristics tested as covariates. All comparisons between groups were two-sided and considered significant for p values < 0.05. No adjustment was made for multiple comparisons or for one interim analysis, as the penalty spent for the latter was deemed negligible.

Safety information was analyzed for the AST and ITT populations. Standard descriptive statistics were used to describe the incidence and severity of the elicited opioid-related side effects. In the case of multiple occurrences of the same event within the same subject, the event was only counted once, and the highest reported severity grade was counted. In tables where severity or relationships were

Table 3. Exposure to study medication

		AST population		ITT population	
		A-MQD (n = 203)	O-ER (n = 189)	A-MQD (n = 132)	O-ER (n = 134)
Days to dose stabilization	Mean	28.6	30.6	28.6	30.6
	Median (range)	28 (6 – 50)	29 (12 – 56)	28 (6 – 50)	29 (12 – 56)
Days on study medication	Mean	62.9	64.2	83.8	82.2
	Median (range)	76 (2 – 134)	78 (0 – 114)	83 (17 – 134)	85 (17 – 114)
Total daily opioid dose (mg)	Mean	63.7	53.3	69.9	60.7
	Median (range)	56 (30 – 360)	40 (16 – 233)	58 (30 – 360)	56 (16 – 233)
Daily dose in morphine-equivalents* (mg)	Mean**	63.7	80	69.9	91
	Median (range)	56 (30 – 360)	60 (24 – 349)	58 (30 – 360)	84 (24 – 349)

* Using American Pain Society conversion factor 1:1.5 for oxycodone:morphine; ** p = 0.001 for ATT, p = 0.0125 for ITT by ANOVA.

tabulated, the adverse event with the greatest severity or strongest relationship to study drug was the event counted.

This report presents the final results of the first part of the study, i.e., the titration and evaluation phases. An interim analysis of the evaluation phase for the first 329 subjects enrolled in the study has been previously presented.[17] As extensive quality-of-life data were collected in the study, these analyses will be the subject of a future report. A preliminary analysis of the data from the extension phase of the study was presented recently and will also be the subject of a future report.[18]

RESULTS

Between May and November 2004, 392 eligible subjects were enrolled at 35 study sites and randomized to treatment with A-MQD (n = 203) or O-ER (n = 189). During the dose-titration phase, 126 subjects (32.1 percent) left the study, 71 (35 percent) in the A-MQD arm and 55 (29 percent) in the O-ER arm. The remaining 266 subjects met the criteria for stabilized opioid dose and entered the evaluation phase, with 132 in the A-MQD group and 134 in the O-ER group. These 266 subjects correspond to the ITT population that served to evaluate and compare the efficacy and safety of the two study drugs during the evaluation phase. Forty-six subjects (17.3 percent of the ITT population) left the study before completing the eight-week evaluation phase, 22 in the A-MQD group and 24 in the O-ER group, and the remaining 220 subjects (110 per group) completed the evaluation phase. Subject disposition is shown in Figure 1, and reasons for leaving the study are shown in Table 1.

Baseline characteristics

Subject demographics and baseline characteristics for the AST and ITT populations are shown in Table 2. The demographics of the two study groups were comparable except for the number of African Americans in the ITT population (31.1 percent in the A-MQD group vs. 15.7 percent in the O-ER group, $p < 0.02$), nonmechanical back pain in the AST population (23.6 percent in the A-MQD group vs. 15.3 percent in the O-ER group, $p < 0.04$), and back pain associated with nerve involvement, which was higher in the A-MQD group both in the AST population (36.9 percent vs. 27 percent, respectively, $p < 0.04$) and the ITT population (40.9 percent vs. 28.4 percent, respectively, $p = 0.03$).

Exposure to study drug

Table 3 summarizes the exposure to study medication in the AST and ITT population. There were no differences in the number of days of opioid use between the two treatments, both in terms of total length of therapy (mean in the ITT of 83.8 and 82.2 days for A-MQD and O-ER, respectively) and of the length of the titration phase (mean in the ITT of 28.6 and 30.6 days for A-MQD and O-ER,

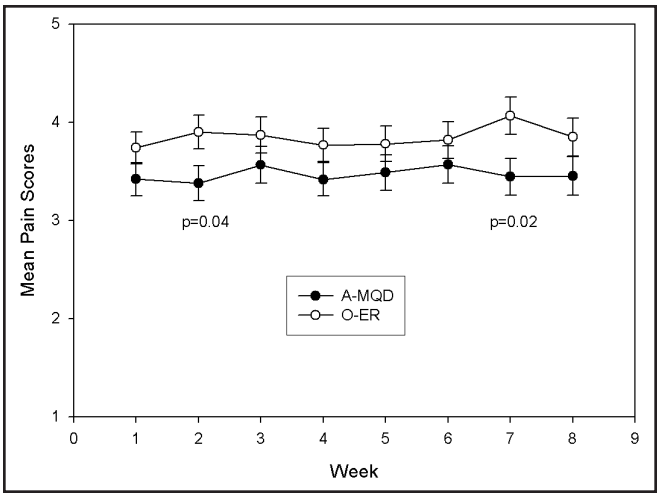

Figure 2. Mean weekly BPI pain scores during the evaluation phase for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

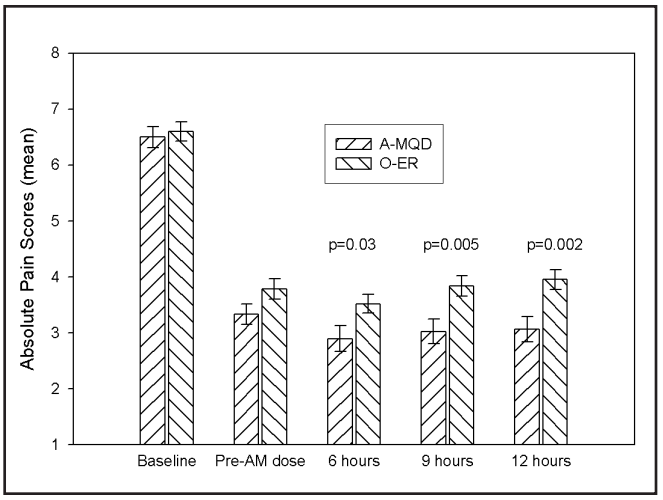

Figure 3. Mean weekly BPI pain scores averaged for the evaluation phase weeks one, four, and eight for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

respectively). For the ITT population, the mean total daily opioid dose was 69.9 mg of morphine (range, 30 to 360 mg) in the A-MQD group and 60.7 mg of oxycodone (range, 16 to 233 mg) in the O-ER group. When converting the oxycodone dose into an equianalgesic morphine dose using the ratio of 1:1.5 (i.e., 1 mg oxycodone equivalent to 1.5 mg morphine) recommended by the APS,[1] the morphine-equivalent dose used by the O-ER group in the ITT population was significantly higher (mean = 91 mg) compared to the morphine dose used in the A-MQD group (mean = 69.9 mg, p = 0.0125).

Pain assessments

The mean pain scores at baseline (i.e., at enrollment) were comparable in the two groups (6.5 in the A-MQD group and 6.6 in the O-ER group). Pain scores had decreased to 4 or less in all subjects who entered the evaluation phase as required by study design. During the eight-week evaluation phase, the weekly average BPI pain scores remained at less than 4 in both groups (Figure 2)—with mean weekly scores consistently lower in the A-MQD group compared to the O-ER group—for the full duration, with the difference reaching significance at weeks two (p = 0.04) and seven (p = 0.02). The BPI pain scores obtained four times a day for seven consecutive days on weeks one, four, and eight were averaged for all three weeks and were found to be significantly lower in the A-MQD group compared to the O-ER group at six hours (p = 0.03), nine hours (p = 0.005), and 12 hours (p = 0.002) after the morning dose (Figure 3).

There was a difference between the two groups in the pain score profiles observed over 24 hours (Figure 3). In the A-MQD group, the mean pain scores six, nine, and 12 hours after the morning dose were consistently lower than the mean pain scores prior to the morning dose, suggesting that pain relief was maintained or further improved throughout the day. By contrast, in the O-ER group, only the mean pain score six hours after the morning dose was lower than the mean pain score prior to the morning dose, whereas the mean pain scores nine and 12 hours after the morning dose were higher than the mean pain score prior to the morning dose, suggesting a gradual loss of the analgesic effect.

Figure 4 reports the mean absolute change in the BPI pain scores between the first assessment at entry on study (baseline) and the pain scores averaged for weeks one, four, and eight and shows a significant difference in favor of the A-MQD group for the six-hour (p = 0.038), nine-hour (p = 0.005), and 12-hour (p = 0.002) time points after the morning dose.

A responder analysis was performed for the ITT population, with a responder defined as a subject whose average weekly pain score had improved by at least 2 points from entry on study at week one to week eight of the evaluation phase or the week of the last visit. In the A-MQD group, 73 of 132 subjects (55.3 percent) were identified as responders, compared to 59 of 134 subjects (44.0 percent) in the O-ER group (p = 0.03).

Sleep assessments

Both treatments resulted in improved sleep scores as assessed by the PSQI assessments, evaluated every four weeks, with improvement noted by the end of titration and continuing during the eight-week evaluation phase. As shown in Figure 5, the relative changes in PSQI scores from entry on study were significantly better in the A-MQD group compared to the O-ER group at week four (30 percent

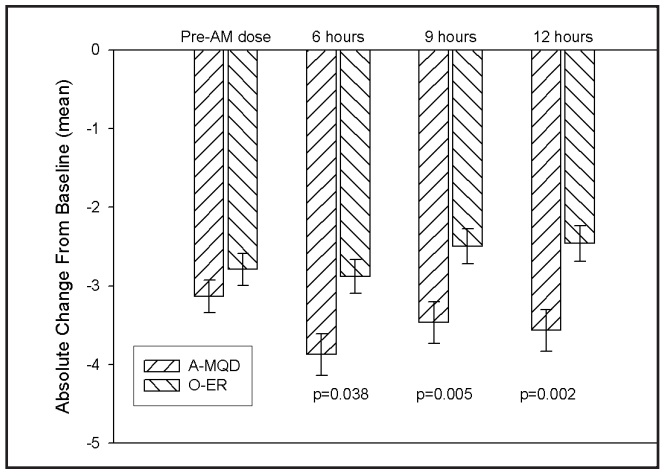

Figure 4. Mean absolute change from baseline in BPI pain scores averaged for the evaluation phase weeks one, four, and eight for the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

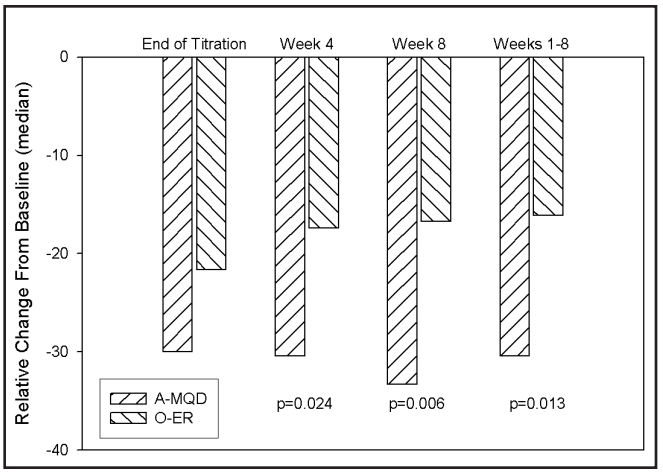

Figure 5. Median relative change in PSQI scores from baseline in the ITT population. Comparison between groups was performed by the Brown-Mood test, and only significant p values for comparison between treatment groups are shown

improvement vs. 17 percent, p = 0.024), week eight (33 percent vs. 17 percent, p = 0.006) and weeks one, four, and eight combined (30 percent vs. 16 percent, p = 0.013).

Rescue medications

Ibuprofen (200-mg capsules) was the only analgesic permitted as rescue medication for breakthrough pain. Ibuprofen use during the eight-week evaluation phase was low in both groups, with a mean of four to six doses/patient/week (Figure 6). There were fewer total rescue doses in the A-MQD group (2,595 doses) compared to the O-ER group (3,154 doses), and the difference was significant ($p < 0.0001$) when ibuprofen doses were normalized to the number of patient days on study (A-MQD = 83,124 and O-ER = 81,268).

Safety assessments

The incidence and severity of elicited opioid side effects were comparable between the two groups both in the AST and ITT populations, as shown in Table 4. Sixteen SAEs were reported (seven from A-MQD and nine from O-ER). Eight of these 16 SAEs were considered probably or possibly related to study drug, two in the A-MQD group (one case each of hypersensitivity and hypoxia) and six in the O-ER group (one case each of intestinal obstruction and respiratory failure and four cases of drug abuse or diversion). Drug abuse or diversion was described by the investigator as intentional misuse (n = 1), drug abuse (n = 1), or theft (n = 2). No cases of drug abuse or diversion were reported in the A-MQD group.

DISCUSSION

The ACTION study, a randomized, two-arm, open-label, multicenter trial, was conducted to compare the effectiveness of two SROs, each with a unique modified-release profile, and to evaluate the pattern of SRO use over several months in patients with chronic, moderate to severe low back pain. Our aims in conducting this trial were: 1) to verify that A-MQD provides 24-hour around-the-clock pain relief with a single daily dose, and 2) to compare the clinical benefits of A-MQD given once a day to those of O-ER given twice a day. Our working hypothesis was that, as A-MQD dosed once daily provides plasma concentrations with narrower fluctuations and with a single "peak and trough" profile over 24 hours compared to O-ER dosed twice daily, it is better at maintaining morphine concentrations within a patient-specific effective therapeutic range, resulting in superior pain relief, fewer breakthrough pain episodes, and possibly less dose increase over the long term.

We conducted this trial in subjects with chronic low back pain because it is the single most common reason for SRO prescriptions in the United States. In addition, as subjects with low back pain are usually younger and healthier than subjects with chronic pain due to cancer or osteoarthritis, the risk of confounding factors due to comorbidities was expected to be lower. To our knowledge, this is the largest randomized trial comparing two SROs and also the first trial to compare the efficacy and safety of A-MQD and O-ER in treating low back pain.

Our goal was also to design a pragmatic trial consistent with the clinical management of low back pain in the general population; specifically, the protocol 1) allowed up to six weeks for opioid dose titration to increase the proportion of subjects continuing into the evaluation phase; 2) extended the evaluation period to eight weeks instead of four weeks as seen in most other studies; 3) offered an optional four-month extension phase to replicate "real world" treatment conditions; and 4) selected

Table 4. Incidence and severity score of elicited opioid side effects during the titration plus evaluation phase								
	ITT population				AST population			
	Incidence (percent)		Mean severity score*		Incidence (percent)		Mean severity score*	
	A-MQD (n = 113)	O-ER (n = 115)	A-MQD (n = 113)	O-ER (n = 115)	A-MQD (n = 175)	O-ER (n = 164)	A-MQD (n = 175)	O-ER (n = 164)
Constipation	87	89	3.3	2.9	92	90	3.8	3.2
Dizziness	58	64	0.9	1.0	67	71	1.3	1.1
Drowsiness	85	84	2.0	1.9	85	88	2.3	2.0
Dry mouth	82	76	2.2	2.0	85	81	2.6	2.1
Itchiness	65	57	1.2	1.3	67	62	1.4	1.4
Nausea	50	47	0.8	0.7	60	564	1.1	0.9
Vomiting	24	19	0.3	0.2	28	23	0.5	0.2
* Using a scale from 0 to 10 where 0 = "not at all" to 10 = "an awful lot".								

commonly used scales to measure pain, sleep, quality of life, and functional status. Because double-blinded, double-dummy clinical trials are difficult to manage and execute, we opted for an open-label design for this Phase IV trial. We assumed that the large size of the trial, the multiplicity of study sites, the matching of the number of subjects entering the evaluation phase, and the use of an independent CRO to manage the study would largely offset any potential bias resulting from the open-label design. In fact, the similarity of baseline characteristics between the two groups argues against a systematic bias introduced in patient selection. That unmasking study drugs led to differences between the two groups in early discontinuations cannot be ruled out.

The large number of study sites and the diversity of practices represented led to the enrollment of a study population fairly representative of the general population of subjects with chronic low back pain about to switch to a SRO. This population was characterized by a preponderance of women (60 percent) and middle-aged patients (median of 50 years), a protracted history of back complaints (median of six to seven years), and back problems due to mechanical causes (75 to 85 percent) and with moderate to severe symptoms (pain scores 6 to 7). The two study groups had comparable characteristics at enrollment, except for a higher percentage of Black/African-American patients, back pain of nonmechanical origin, and back pain with nerve involvement in the A-MQD group. Differences in some baseline characteristics sometimes occur when central randomization is performed without stratification by study site, as was the case in this study. These few imbalances in patient demographics, however, do not account for the differences in efficacy perceived between the two SROs, as the superior efficacy of A-MQD over O-ER persists with or without covariate adjustment.

Of the 392 patients enrolled, a sizeable proportion (32 percent) withdrew prematurely from study, mostly during the titration phase (73 percent). The three most frequent reasons cited for early withdrawal add up to 70 percent of the total, with adverse reactions being the most common (37.8 percent), followed by withdrawal of consent (21.5 percent) and refusal to follow-up (11 percent), the last two reflecting an active decision on the part of the subject (32.5 percent combined). In contrast, persistent pain was cited as the cause for early discontinuation in only 9.3 percent of the cases. These drop-out rates are not unique to this trial and are consistent with those observed in patients treated with SROs outside clinical trials as well as in those enrolled in other randomized and single-arm studies of various SROs.[19-21] This substantial drop-out rate may reflect: 1) the low acceptance of subjects suffering from pain, with or without functional disability, of the demands of clinical trials, particularly when the study involves drugs readily available without participation in a clinical trial; 2) the poor tolerability profile of SROs in some patients; and 3) the failure of these drugs to meet overall patient expectations. Reducing patient attrition from SRO therapy might be achieved by better preparing them to accept the early, but usually reversible, opioid-related adverse reactions and by tailoring opioid dose titration according to individual patient needs and characteristics of the SRO.

Two-thirds of subjects (67.9 percent) enrolled in this trial completed the titration phase, and a large majority (57 percent) completed the eight-week evaluation phase. These patients clearly benefited from taking their prescribed SRO dose, as their pain scores significantly decreased from entry on study to completion of titration, with a 49 percent improvement (from a mean score of 6.5 to 3.4) in the A-MQD group and a 43 percent improvement (from a mean score of 6.6 to 3.7) in the O-ER group. In both groups, the mean pain scores remained low during the evaluation phase. In addition, these patients had few episodes of breakthrough

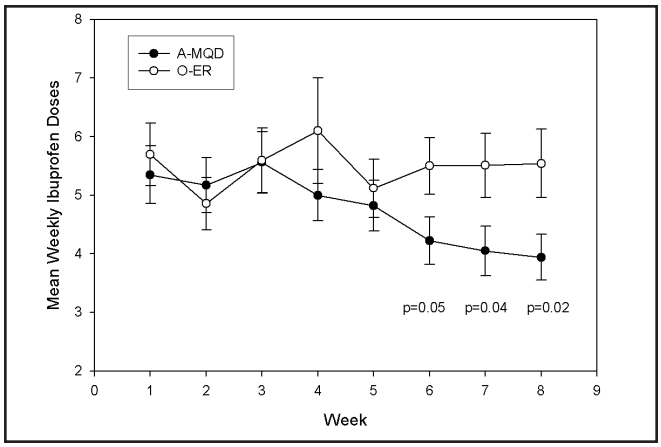

Figure 6. Mean weekly number of ibuprofen rescue doses in the ITT population. Error bars represent standard error (SE) calculations. Only significant p values for comparison between treatment groups are shown.

pain, as suggested by the average of less than one daily ibuprofen rescue, and reported better quality of sleep. This was accomplished with an acceptable safety profile. Thus, SROs represent an effective approach for the symptomatic treatment of the majority of patients with chronic, moderate to severe low back pain, with the prerequisite that the titration phase be conducted carefully and the patients are properly supervised for the duration of their therapy.

This study also confirmed our hypothesis that A-MQD given once every 24 hours provides significantly better pain management compared to O-ER given once every 12 hours. When we designed this study, we were aware of data suggesting that two-thirds of subjects treated with O-ER for chronic pain required more than twice-daily dosing to achieve pain control, with dosing every eight hours reported as the most common method.[22] To avoid variations in dosing intervals between patients within each treatment group, we required that A-MQD and O-ER be administered according to their approved doses. Since we did not compare the pharmacokinetics of A-MQD and O-ER in this trial, we cannot prove that the superior efficacy results are correlated to more uniform opioid plasma concentrations and fewer fluctuations over 24 hours. The clinical evidence, however, strongly supports this explanation, as patients in the A-MQD group showed around-the-clock pain relief consistently throughout the evaluation period, with lower mean pain scores six, nine, and 12 hours after the morning dose compared to the pre-morning dose mean pain scores, with no rebound in mean pain scores 24 hours later. Furthermore, prior pharmacokinetic studies have already documented that A-MQD has a reduced fluctuation index (i.e., less difference between peak and trough plasma concentrations) than twice-daily O-ER despite being administered only once daily.[14] Our study extends the findings of pharmacokinetic studies and documents, in a large number of patients, the added benefits in terms of better pain relief, improved sleep, and lower daily opioid dose over those achieved with an SRO given twice daily.

A significant finding of this trial is that patients in the A-MQD group had better pain relief and at the same time required a lower daily opioid dose compared to patients in the O-ER group (when the dose in the latter group was converted into morphine equivalents). One possible explanation is that the conversion factor recommended by the APS of 1:1.5 for oxycodone:morphine does not apply to sustained-release opioids. Another possible explanation is that for patients to achieve consistent pain control over 24 hours with A-MQD dosed once daily, they are likely to have had uniform morphine plasma concentrations within the therapeutic range throughout 24 hours, possibly leading to slower development of tolerance to morphine.

Another key study finding was the beneficial effect on sleep noted with both SROs. We believe that improved sleep quality was due to less frequent awakenings from breakthrough pain episodes. Improved sleep could also be ascribed to subjects' not needing to wake up in the night to take additional doses of analgesic, as is observed with short-acting opioids or nonopioid analgesics. Patients in the A-MQD group had significantly better sleep scores compared to patients in the O-ER group in week four, week eight, and weeks one through eight of the evaluation phase. Improved sleep in the A-MQD group confirms and extends the sleep findings reported by Caldwell et al.[10] A recently reported polysomnography study confirmed these subjective sleep findings and provided objective measurements of the effects of A-MQD on various sleep parameters, including decreased latency to persistent sleep, number of night awakenings, and total wake time.[23] This study also demonstrated increased sleep efficiency, total sleep time, and Stage 2 sleep duration, with no significant decrease in REM duration from baseline.

It has been argued that SROs' only advantage over short-acting opioids is convenience, and that the abuse liability negates the value of SROs. In our opinion, the results of the ACTION trial refute this assertion. The convenience of SRO dosing may improve the compliance with the prescribed SRO dosing schedule. Fewer peak-to-trough fluctuations over 24 hours result in more uniform pain control, which in turn lead to more normalization of daily activities, better sleep, and less potential for overshooting of medication secondary to poor pain control. Lastly, fewer daily doses simplifies the assessment of a patient's compliance with therapy as a result of easier pill counts.

In conclusion, the ACTION trial demonstrated that SROs are effective agents for the symptomatic management of the majority of patients with chronic, moderate to severe low back pain. Furthermore, the study clearly documented that A-MQD provides 24-hour around-the-clock pain relief with a once-a-day dose and results in better pain control, better quality of sleep, a lower daily opioid dose, and a comparable safety profile compared to patients receiving twice-daily O-ER.

DISCLOSERS

The source of funding for the study was provided by Ligand Pharmaceuticals Inc. and Organon Pharmaceuticals USA, Inc. in equal parts. Dr. Rauck is a consultant to Medtronic Inc., Elan Pharmaceuticals, Advanced Bionics, and Organon Pharmaceuticals USA Inc. Dr. Bookbinder reports no conflicts of interest. Dr. Bunker reports no conflicts of interest. Dr. Alftine reports no conflicts of interest. Dr. Ghalie is an employee of Ligand Pharmaceuticals Inc. Dr. Negro-Vilar is an employee of Ligand Pharmaceuticals Inc. Dr. de Jong is an employee of Organon Pharmaceuticals USA Inc. Dr. Gershon reports no conflicts of interest.

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REFERENCES

1. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain.* Glenview: American Pain Society; 2003.
2. Gallup Organization (for Merck and Co., Inc.): *Pain in America: A Research Report.* New York: Ogilvy Public Relations, 2000.
3. Andersson G: Epidemiological features of chronic low-back pain. *Lancet.* 1999; 354: 581-585.
4. Luo X, Pietrobon R, Sun SX, et al.: Estimates and pattern of direct health care expenditures among individuals with back pain in the United States. *Spine.* 2004; 29: 79-86.
5. Chou R, Clark E, Helfand M: Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. *J Pain Symptom Manage.* 2003: 26: 1026-1048.
6. Desphande AA, Atlas S, Furlan AD, et al.: Opioids for chronic low back pain. *The Cochrane Database of Systematic Reviews 4.* Art. no. CD004959, 2004.
7. Kalso E, Edwards JE, Moore RA, et al.: Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain.* 2004; 112: 372-380.
8. McNicol E, Horowicz-Mehler N, Fisk RA, et al.: Management of opioid side effects in cancer-related and chronic non-cancer pain: A systematic review. *J Pain.* 2003; 4: 231-2567.
9. Watson CP, Watt-Watson JH, Chipman ML: Chronic noncancer pain and the long term utility of opioids. *Pain Res Manag.* 2004; 9: 19-24.
10. Caldwell JR, Rapoport RJ, Davis JC, et al: Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage.* 2002;23(4):278-291.
11. Portenoy RK, Sciberras A, Eliot L, et al.: Steady-state pharmacokinetics comparison of a new, extended-release, once-daily morphine formulation, AVINZA, and a twice-daily controlled-release morphine formulation in patients with chronic moderate-to-severe pain. *J Pain Symptom Manage.* 2002; 23(4): 292-300.
12. Mandema JW, Kaiko RF, Oshlack B, et al.: Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. *Br J Clin Pharmacol.* 1996; 42: 747-756.
13. Hale ME, Fleischmann R, Salzman R, et al.: Efficacy and safety of controlled-release versus immediate-release oxycodone: Randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain.* 1999; 15: 179-183.
14. Eliot L, Geiser R, Loewen G: Steady-state pharmacokinetic comparison of a new, once-daily, extended-release morphine formulation (Morphelan™) and Oxycontin® twice daily. *J Oncol Pharm Practice.* 2001; 7: 1-8.
15. Keller S, Bann CM, Dodd SL, et al.: Validity of the brief pain inventory for use in documenting the outcomes of patients with non-cancer pain. *Clin J Pain.* 2004; 20: 309-318.
16. Buysse DJ, Reynolds CF III, Monk TH, et al.: Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep.* 1991; 14: 331-338.
17. Rauck R, Bookbinder S, Bunker T, et al.: Randomized multicenter study of oral once-a-day AVINZA (morphine sulfate extended-release capsules) vs. twice-daily OxyContin (oxycodone hydrochloride controlled-release) for the treatment of chronic moderate-to-severe low back pain. *J Pain.* 2005; 6(suppl. 1, abstr. 747).
18. Rauck R, Bookbinder S, Bunker T, et al.: Randomized multicenter, open-label extension (Part II) to the ACTION Trial (AVINZA vs. OxyContin Trial in opioid-naive patients) for the treatment of chronic moderate to severe low back pain. *Proced Am Acad Pain Med*: annual meeting. Poster #54. 2006
19. Hale M, Dvergsten C, Gimbel J: Efficacy and safety of oxymorphone extended release in chronic low back pain: Results of a randomized, double-blind, placebo-controlled and active-controlled Phase III study. *J Pain.* 2005; 6: 21-28.
20. Hale MF, Rauck R, Ma T, et al.: Open-label titration of oxymorphone extended release in opioid-experienced patients with chronic low back pain. *Proced Am Acad Pain Med*: annual meeting. Poster #138. 2006.
21. Markenson JA, Croft J, Zhang PG, et al.: Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *Clin J Pain.* 2005; 21: 524-535.
22. Marcus DA, Glick RM: Sustained-release oxycodone dosing survey of chronic pain patients. *Clin J Pain.* 2004; 20: 363-366.
23. Rosenthal M, Spinweber C, Dziewanowska Z, et al.: Once-a-day AVINZA® effects on sleep quality measurements (polysomnographic and subjective) in patients treated for chronic moderate and sever osteoarthritis (OA) pain. American Pain Society: annual meeting. Poster #746. 2005.

ORIGINAL ARTICLE

A Phase II, multicenter, randomized, double-blind, placebo-controlled crossover study of CJC-1008—a long-acting, parenteral opioid analgesic—in the treatment of postherpetic neuralgia

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ABSTRACT

Introduction: *CJC-1008 is a chemical modification of the opioid peptide dynorphin A (1-13) (Dyn A) that promotes dynorphin's covalent attachment to human serum albumin in vivo after administration, thus prolonging its duration of action. The primary objective of this study was to evaluate the preliminary efficacy and safety of CJC-1008 as compared with placebo in patients with postherpetic neuralgia (PHN).*

Methods: *Patients with PHN were assigned 1:1 to receive active study medication or placebo. After dosing, measurements were made every 15 minutes for the first hour; at two, three, four, six, and eight hours postdose; and during return visits to the study site after two, seven, and 28 days (as necessary), as well as during precrossover and exit visits. These measurements examined: 1) overall pain intensity, 2) pain intensity for each individual PHN type, 3) categorical overall pain intensity, 4) categorical pain relief, and 5) adverse events (AEs). When PHN pain intensity returned to baseline and/or at patients' first request for rescue analgesia other than acetaminophen (typically around 28 days after dosing but sometimes as soon as two days postdose), patients were to cross over to the alternative treatment and be monitored on the same schedule.*

Results: *A substantial placebo response was observed, but the analgesic effect observed in the active group was greater than that in the placebo group for the first eight hours. By 24 hours, the difference was not significant. A total of 29 out of 30 patients (96 percent) experienced at least one treatment-emergent AE during active drug treatment, while 14 of 27 patients (52 percent) reported such AEs during placebo treatment. Of the AEs occurring within the first eight hours after dosing, 97 percent were reported during treatment with active drug and 3 percent were reported during treatment with placebo. The majority of these AEs were mild in intensity.*

Discussion: *This study provides evidence of a greater analgesic effect when using CJC-1008 compared to placebo in patients with PHN. However, the effect only lasted through eight hours postdose and diminished by 24 hours. This study provides evidence of a peripheral action of dynorphin, since CJC-1008 does not cross the blood-brain barrier.*

Key words: CJC-1008, dynorphin, postherpetic neuralgia, placebo response

Conflict of interest: This study was funded by ConjuChem, Inc.

INTRODUCTION

Postherpetic neuralgia (PHN), the result of a complication from herpes zoster infection, is a common neuropathic pain syndrome that is easily diagnosed. There are typically three types of pain described in association with PHN: I) constant, deep, aching, steady, burning pain; II) spontaneous, intermittent, recurrent, "neuralgic," shooting or electric-shock-like pain; and III) superficial, sharp, radiating, burning, tender, dysesthetic, or itch-like sensation evoked by light pressure on the skin (allodynia).[1] Because of the stability of the pain of PHN, it is frequently used as a model for the evaluation of drugs' analgesic efficacy.

Dynorphin A (Dyn A) is a potent opioid agonist with morphine-like activity, but it is limited in its clinical utility

by a short half-life of several minutes.[2-4] CJC-1008 (ConjuChem Inc., Montreal, Quebec, Canada) is a chemical modification of the opioid peptide Dyn A(1-13) that promotes dynorphin's covalent attachment to human serum albumin (HSA) in vivo after administration. A chemical modification, using maleimidopropionic acid, to the core therapeutic moiety of Dyn A enables bonding to the free thiol on circulating HSA without interfering with the therapeutic activity of the Dyn A molecule. By bonding to circulating HSA, CJC-1008 has a significantly longer duration of action than free Dyn A, and its ability to cross the blood-brain barrier may be restricted, thus potentially limiting the side effects typically observed with opioids.

CJC-1008 has been demonstrated to be effective in a variety of animal models of pain, including the mouse acetic acid writhing test, mouse paw formalin test, and rat neuropathic pain test. However, no effect was seen in the mouse tail-flick study or rat tail radiant-heat test, suggesting restriction of the compound to peripheral circulation (data on file, ConjuChem, Inc.).[5] Accessibility of CJC-1008 to peripheral nerves is anticipated to depend upon albumin permeation, according to studies reported by Allen and Kiernan.[6]

Safety and tolerability of intravenous (IV) doses of CJC-1008 up to 3 mg/kg was demonstrated in a Phase I study in normal volunteers (data on file, ConjuChem, Inc.). Some subjects experienced hypotension that rapidly returned to normal after stopping the infusions. In addition, some reported urticaria and injection-site irritation that resolved shortly after completion of the infusions.

It is hypothesized that CJC-1008 will provide relief of PHN pain, with an improved safety profile and extended duration of action as compared to conventional opioids. The primary objective of this study was to evaluate the preliminary efficacy of a single dose of CJC-1008 as compared with placebo by measuring change in overall pain intensity over time (up to 28 days) in patients with PHN.

METHODS

This study was approved by the Human Subjects Committee at each participating institution. This was a Phase II, randomized, double-blind, placebo-controlled crossover study comparing the efficacy of a single IV dose of 3 mg/kg CJC-1008 to placebo in patients with PHN. Accepted patients met the following criteria: 1) men and women over the age of 18, 2) weight between 45 and 110 kg, 3) PHN for a minimum of three months following shingles (rash healing), and 4) minimum overall pain intensity of 45 out of 100 mm on the visual analog scale (VAS) at baseline. If overall pain intensity on the VAS was not at least 45 mm, a patient could still be eligible if the pain intensity for at least one of the three individual PHN pain types was at least 45 mm (see introduction for description of pain types). This qualifying pain type was designated as the "Index VAS" for that patient and would be used for further study assessments. Exclusion criteria included: 1) anesthetic nerve block within two weeks of study entry or any previous neurolytic nerve block in the area of PHN pain; 2) Karnofsky score < 60; 3) use of any nonopiate analgesic, unless taking a stable dose for at least 30 days prior to study entry; and 4) use of any psychoactive drug within 72 hours prior to study entry.

After meeting all eligibility criteria at screening (Visit 1), patients who were taking opiate analgesics entered a two-to-seven-day opiate-washout period. Following the washout period, patients with a minimum pain intensity score of 45 mm for overall pain intensity or at least one of the three types of PHN pain and who continued to meet all other eligibility requirements at the time of Visit 2 (baseline visit) were assigned 1:1 to receive either a) active study medication during the first treatment period, followed by blinded placebo during the second crossover treatment period; or b) the same two treatments in the reverse order.

Following randomization, patients received an infusion of study medication or placebo over 30 minutes in a monitored setting. After dosing, evaluations took place every 15 minutes for the first hour; at two, three, four, six, and eight hours postdose; and during return visits to the study site after two, seven, and 28 days (as necessary), as well as precrossover and exit visits. Evaluations performed at these time points included: 1) vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation), 2) overall pain intensity (100-mm VAS), 3) pain intensity (100-mm VAS) for each individual PHN type, 4) categorical overall pain intensity (6-point Likert), 5) categorical pain relief (6-point Likert), 6) AEs, 7) physical examination (selected time points), and 8) blood and urine samples for laboratory evaluations and pharmacokinetic assessments (selected time points). In addition, on day one (for both initial treatment and crossover), one 12-lead electrocardiogram (ECG) was obtained between 30 minutes and an hour after dosing, and blood was collected for coagulation panel two hours after dosing.

During the first week following dosing, AEs and general status were assessed by daily telephone follow-up on days when no study-site visit was scheduled. In addition, efficacy assessments (VAS and Likert) were made daily by the patient in a diary on days when no visit was scheduled.

When PHN pain intensity returned to baseline (typically around 28 days after dosing but sometimes as soon as two days postdose) and/or at patients' first request for rescue analgesia other than acetaminophen, patients were to cross over to the alternative treatment and be monitored on the same schedule.

The intent-to-treat (ITT) population consisted of all patients randomized in the study, whether or not they

Table 1. Demographic and baseline characteristics			
Trait	**Postherpetic pain population**		
	ITT, n = 32	**Safety, n = 30**	**Evaluable, n = 26**
Gender			
Female	14	12	9
Male	18	18	17
Age (years)			
Mean	69	69	70
SD	12	11	12
Minimum	39	39	39
Maximum	83	83	83
Baseline Index VAS score (mm)			
Mean	65.0	65.0	64.7
SD	15.9	15.9	15.9
Minimum	25.0	25.0	25.0
Maximum	96.0	96.0	96.0
Baseline pain intensity Likert score			
Mean	3.0	3.0	3.0
SD	0.7	0.7	0.6
Minimum	1.0	1.0	1.0
Maximum	4.0	4.0	4.0

received any study drug. The safety population consisted of all patients who received any dose of the double-blind study medication. The efficacy-evaluable population consisted of patients who met the crossover criteria after the first treatment period, received the crossover treatment, and had at least one post-treatment efficacy assessment in each treatment period. Patients who failed to meet crossover criteria or left the study after the first treatment were included in the ITT population but not the evaluable population. The statistical analyses for the primary efficacy variable (Index VAS pain intensity score) were performed for both ITT and evaluable populations. Only the evaluable population was used in the statistical analysis of the secondary efficacy variables (overall VAS pain intensity score, pain intensity VAS for each of the three PHN pain types, pain intensity Likert score, pain relief Likert score, and time to Index VAS score (predose) or first request for opioid rescue analgesia, whichever was shorter).

Demographic and other baseline characteristics were summarized by treatment sequence group using descriptive statistics. The analysis of variance (ANOVA) model was used to analyze VAS scores. Least-square means for change from predose scores by treatment was determined, and 95 percent confidence intervals were calculated. Pain intensity and pain relief Likert scores were analyzed using the Wilcoxon Signed-Rank test. Time to Index VAS score (predose) or first request for opioid rescue analgesia, whichever was shorter, was analyzed using the Kaplan-Meier survival analysis and log-rank test. The "last observation carried forward" approach was used for inputting sporadic missing values.

RESULTS

A total of 32 patients entered the study and were randomized to treatment from the four study centers (12 from Wallace, eight from Moulin, seven from Clark, and five from Wasserman). Thirty patients received study treatment, and 26 patients completed the study. The 30 patients who received the initial randomized study treatment were included in the safety analysis. The 26 patients who received the initial treatment followed by the crossover

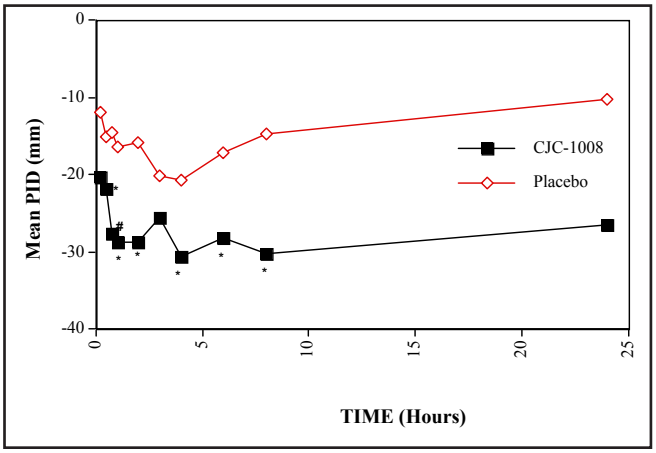

Figure 1. Line graph of the mean Index pain intensity difference (PID), in mm, from baseline through treatment period (0.25 to 24 hours); * p < 0.05, # P < 0.01.

treatment were included in the evaluable population. Demographic descriptions are summarized in Table 1.

The primary efficacy variable was the Index VAS score, which was the PHN pain score that qualified the patient for the study. Index VAS scores decreased immediately following treatment infusion and progressed through 24 hours postdose in both CJC-1008 and placebo groups. A substantial placebo response was observed during this period, but the analgesic effect observed in the active group (decrease of 21 to 31 mm) was greater than that observed with placebo (decrease of 11 to 21 mm). Other than the three-hour postdose time point, the reduction in the Index VAS scores was significantly greater following CJC-1008 administration than following placebo from predose through eight hours postdose. By 24 hours postdose, the difference between CJC-1008 and placebo was not significant. Most patients had pain intensity returning to baseline within 24 hours postdose and elected to cross over or exit within two days of treatment (Figure 1). A similar response was seen with the overall-pain intensity VAS scores (data not shown).

A similar postdose trend was present in VAS scores for both overall and Types I-III PHN. VAS scores for types I-III PHN exhibited very similar treatment effects as that observed in the Index VAS scores. With the exception of VAS scores at three hours postdose, CJC-1008 was significantly more effective at reducing the Type III PHN scores eight hours postdose (Figure 2C). A similar, but somewhat delayed, treatment effect was noted for Type I PHN scores (Figure 2A). Excluding the three-hour postdose time point, CJC-1008 was significantly more effective than placebo at reducing the patients' Type I PHN scores from 30 minutes postdose through the eight-hour postdose time point. CJC-1008 was significantly more effective than placebo in reducing Type II PHN pain intensity at 45 minutes and one hour postdose (Figure 2B). Despite these differences, no individual pain type was significantly more susceptible to the analgesic effects of CJC-1008.

The reduction in categorical pain intensity following administration of CJC-1008 was slightly greater than following placebo, with significant differences observed only at two and eight hours postdose. Patients reported slightly larger mean pain relief Likert scores following CJC-1008 than placebo, but the differences did not reach statistical significance (Figure 3). There were no significant treatment differences on the improvement of pain relief Likert scores between the two treatment groups.

PHN patients who reported drug-infusion-related AEs did not have pain intensity VAS or Likert scores significantly different from those who did not report these AEs.

Postdose time for first request of analgesia other than acetaminophen was analyzed using Kaplan-Meier techniques. Although the length of time to first request was longer following CJC-1008 (3.9 days) than placebo (2.3 days), no significant treatment effect was present, and the median length of time was not different between the two groups. Three patients reported complete and sustained pain relief for 28 days following treatment with CJC-1008, while no patients did so in the placebo group.

A total of 29 of the 30 patients in the study-drug group (96 percent) experienced at least one treatment-emergent AE during active drug treatment, while 14 of 27 patients (52 percent) reported such AEs during placebo treatment. Fifty-two percent of the AEs occurred within the first eight hours after dosing. Of the AEs occurring within the first eight hours, 97 percent were reported during treatment with active drug and 3 percent during treatment with placebo. The majority of these AEs were mild in intensity. Injection-site AEs were commonly reported during this study and were experienced exclusively by the active group (47 percent). Injection-site AEs included pain (30 percent), erythema (20 percent), burning (13 percent), pruritis (7 percent), coldness, paresthesias, and urticaria.[7] Other events reported in 10 percent or more of patients during CJC-1008 administration included dry mouth (67 percent), flushing (20 percent), headache (17 percent), erythema (13 percent), limb pain (13 percent), pruritis (13 percent), nausea (10 percent), conjuctival hyperemia (10 percent), and feeling hot (10 percent). After the first eight hours following infusion of CJC-1008, AEs reported in 10 percent or more of patients included dizziness (30 percent), headache (23 percent), nausea (23 percent), dry mouth (20 percent), constipation (17 percent), abdominal distension (10 percent), back pain (10 percent), influenza-like illness (10 percent), and limb pain (10 percent). No clinically significant abnormalities or trends were noted in the laboratory, vital sign, ECG, or physical examination findings.

DISCUSSION

PHN is a debilitating neuropathic pain syndrome that

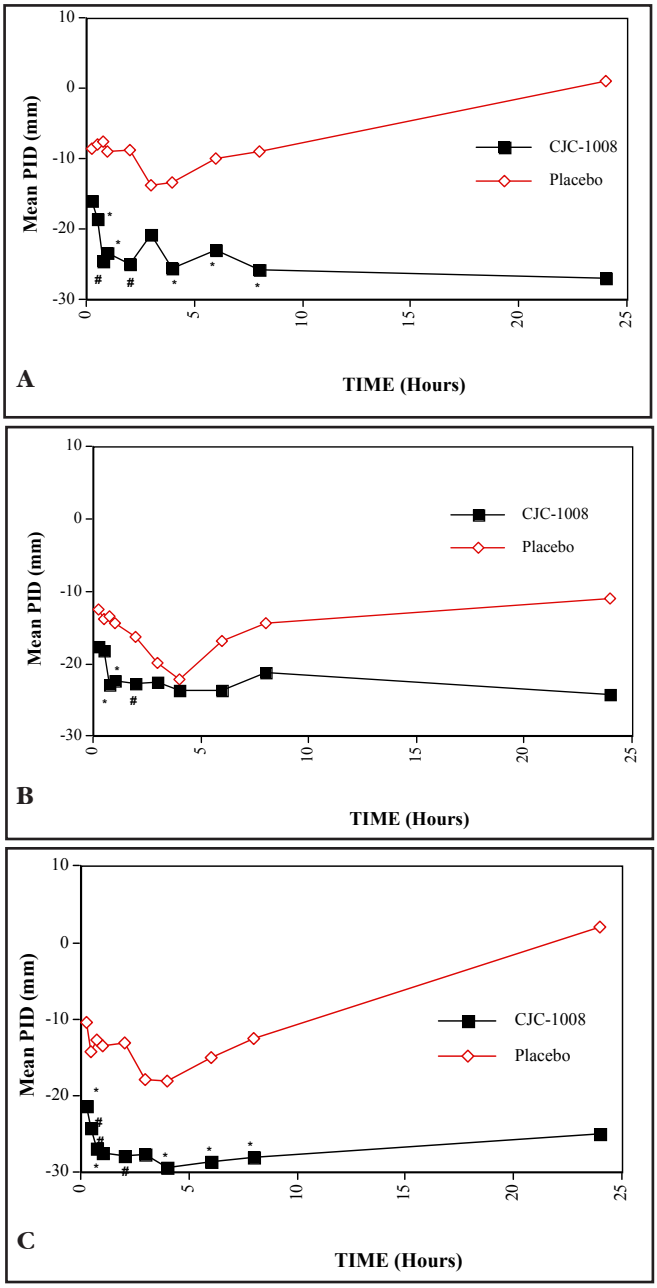

Figure 2. Line graph of the mean pain intensity difference (PID), in mm, of PHN Type I (A), Type II (B), and Type III (C) pain from baseline through treatment period (0.25-24 hours); * $p < 0.05$, # $P < 0.01$.

is often resistant to multiple therapies.[8] As such, it is often used for investigating new therapeutic interventions because it is a common pain syndrome that is readily distinguishable from other neuropathic pain conditions. Autopsy data from PHN patients have demonstrated chronic peripheral inflammation, as well as reduction of both axons and myelin in affected nerves.[9] Therefore, peripheral treatments may be effective. There are few treatments with proven efficacy, including gabapentin, pregabalin, lidoderm, and the tricyclic antidepressants.[10-13] However, there is emerging evidence that the opioids are effective in the treatment of this syndrome and can manage the pain chronically.[14]

Dyn A is an endogenous opioid peptide with both antinociceptive and pronociceptive properties. Dyn A was originally identified as an endogenous antinociceptive and analgesic molecule with activity at the kappa receptor.[15,16] However, more recent studies indicate that dynorphin has significant pronociceptive activity that is not mediated by opioid receptors.[17,18] This has led to mixed results when dynorphin is delivered into the central nervous system.[19,20]

Because of the mixed results with centrally delivered dynorphin, attention has been directed to the effect of endogenous ligands of peripheral opioid receptors. Many preclinical studies have demonstrated the presence of peripheral opioid receptors that, when occupied, decrease the excitability of sensory nerves by decreasing the release of excitatory substances from sensory nerves.[21,22] In addition, opioid peptides, including dynorphin, have been detected in immune cells within inflamed tissue in animals and humans.[22-24] It has been demonstrated that, when released, dynorphin can occupy opioid receptors on nerve endings and effect analgesia.[24] In addition, preclinical models on nociception have demonstrated a peripheral mechanism of action of dynorphin.[25,26] Therefore, there is reason to believe that dynorphin can exert analgesia through a peripheral mechanism.

This is the first clinical study to suggest that dynorphin has a peripheral analgesic action. Although we did not reach our primary efficacy endpoint of extended analgesia, we were able to demonstrate that conjugated dynorphin was analgesic and effected a prolonged analgesia of up to 24 hours. There are several explanations for the lack of extended analgesia. Well-known side effects of the opioids, mediated centrally, include respiratory depression, dependence, sedation, itching, nausea, and dysphoria. By limiting the opioid to the periphery, these side effects should be averted. However, on review of the side effects observed in our study, dizziness (30 percent) and nausea (23 percent) appeared after the first eight hours of the infusion. Side effects reported in the literature during treatment with Dyn A include paresthesia, dizziness, pruritis, headache, nausea, depression, somnolence, dry mouth, and chest palpitations.[27-30] Many of the side effects of Dyn A are thought to be mediated by histamine release, a known effect of opioids.[31,32] Therefore, the side effects observed in our study could result without central nervous system penetration. However, it is possible that, over time, the conjugated Dyn A molecule may penetrate into the central nervous system as albumin slowly equilibrates between the two compartments. If this occurs, then the central pronociceptive effects of dynorphin could counteract the peripheral antinociceptive

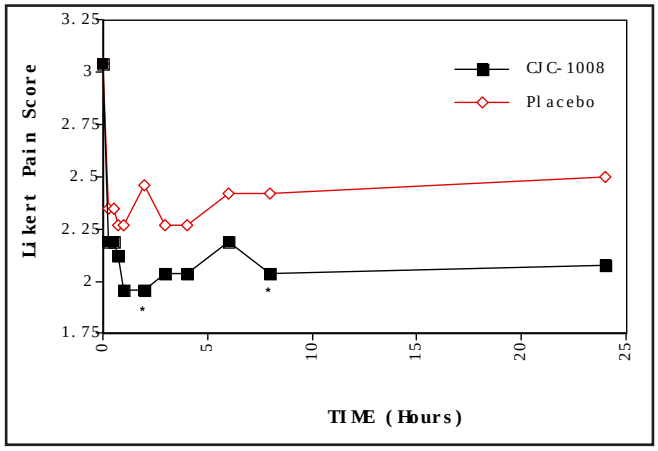

Figure 3. Line graph of the mean pain intensity Likert scale during treatment period (0-24 hours); * p < 0.05.

effects, accounting for the loss of analgesia at 24 hours. In addition, there are recent reports of acute tolerance to short-term delivery of potent opioid agonists, which could also explain the short duration of action.[33] It is unlikely that the dynorphin molecule was released from the albumin complex, since the free dynorphin would be broken down within minutes before it could penetrate the central nervous system. Given the side effects that we observed with CJC-1008, it is unlikely that the duration can be extended by increasing the dose, though the possibility exists to enhance efficacy through delivery of additional doses that may have a cumulative effect.

Another possible explanation for lack of extended duration is the study population we chose. Although PHN patients share a common etiology of pain, it has been suggested that there are actually three categories of pain mechanism.[1] Some patients have an "irritable nociceptor" and report pain relief with local infiltration, suggesting a peripheral mechanism. The other two categories are patients with deafferentation with and without allodynia. These patients do not respond to local infiltration, suggesting a central mechanism. The Type III patients in our study all suffered from allodynia; therefore, they would most likely correlate with the irritable-nociceptor theory. Although there was a trend for these subjects to report more pain relief than those of Types I and II, there was no statistical significance. In addition, there was no correlation between pain type and response seen in the three subjects who experienced sustained pain relief.

This was a proof-of-concept study that sought to demonstrate a prolonged analgesia with conjugated Dyn A. Although the duration of analgesia seen with CJC-1008 (between eight and 24 hours) was not as long as predicted, the duration of analgesia was much longer than that seen with free Dyn A (minutes). This study confirms that an albumin-conjugated drug-affinity complex can lead to sustained circulation without loss of parent pharmacologic activity.

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REFERENCES

1. Fields HL, Rowbotham M, Baron R: Postherpetic neuralgia: Irritable nociceptors and deafferentation. *Neurobiol Dis*. 1998; 5(4): 209-227.
2. Greenwald MK, Stitzer ML, Haberny KA: Human pharmacology of the opioid neuropeptide dynorphin A (1-13). *J Pharmacol Exp Ther*. 1997; 281: 1154-1163.
3. Chou JZ, Chait BT, Wang R, et al.: Differential biotransformation of dynorphin A (1-17) and dynorphin A (1-13) peptides in human blood, ex vivo. *Peptides*. 1996; 17: 983-990.
4. Muller S, Hochhaus G: Metabolism of dynorphin A 1-13 in human blood and plasma. *Pharm Res*. 1995; 12: 1165-1170.
5. Irwin S, Houde RW, Bennett DR, et al.: The effects of morphine, methadone and meperidine on some reflex responses of spinal animals to nociceptive stimulation. *J Pharmacol Exp Ther*. 1951; 101: 132-143.
6. Allen DT, Kiernan JA: Permeation of proteins from the blood into peripheral nerves and ganglia. *Neuroscience*. 1994; 59: 755-764.
7. Lynch JJ III, Jarvis MF, Kowaluk EA: An adenosine kinase inhibitor attenuates tactile allodynia in a rat model of diabetic neuropathic pain. *Eur J Pharmacol*. 1999; 364(2-3): 141-146.
8. Portenoy RK, Duma C, Foley K: Acute herpetic and postherpetic neuralgia: Clinical review and current management. *Ann Neurol*. 1986; 20: 651-664.
9. Portenoy RK: Neuropathic pain. In Portenoy RK, Kanner RM (eds.): *Pain Management: Theory and Practice*. Philadelphia: FA Davis Co., 1996.
10. Galer BS, Rowbotham MC, Perander J, et al.: Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: Results of an enriched enrollment study. *Pain*. 1999; 80: 533-538.
11. Dworkin RH, Corbin AE, Young JP Jr, et al.: Pregabalin for the treatment of postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology*. 2003; 60: 1274-1288.
12. Rowbotham M, Harden N, Stacey B, et al.: Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA*. 1998; 280: 1837-1863.
13. Max MB: Treatment of post-herpetic neuralgia: Antidepressants. *Ann Neurol*. 1994; 35: S50-S53.
14. Pappagallo M, Campbell JN: Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. *Ann Neurol*. 1994;

35: S54-S56.
15. Herz A: Multiple opiate receptors and their functional significance. *J Neural Transm Suppl*. 1983; 18: 227-233.
16. Przewlocki R, Stala L, Greczek M, et al.: Analgesic effects of mu-, delta- and kappa-opiate agonists and, in particular, dynorphin at the spinal level. *Life Sci*. 1983; 33(suppl. 1): 649-652.
17. Vanderah TW, Ossipov MH, Lai J, et al.: Mechanisms of opioid-induced pain and antinociceptive tolerance: Descending facilitation and spinal dynorphin. *Pain*. 2001; 92(1-2): 5-9.
18. Ossipov MH, Kovelowski CJ, Wheeler-Aceto H, et al.: Opioid antagonists and antisera to endogenous opioids increase the nociceptive response to formalin: Demonstration of an opioid kappa and delta inhibitory tone. *J Pharmacol Exp Ther*. 1996; 277(2): 784-788.
19. Knox RJ, Dickenson AH: Effects of selective and non-selective kappa-opioid receptor agonists on cutaneous C-fibre-evoked responses of rat dorsal horn neurones. *Brain Res*. 1987; 415: 21-29.
20. Willcockson WS, Kim J, Shin HK, et al.: Actions of opioids on primate spinothalamic tract neurons. *J Neuroscience*. 1986; 6: 2509-2520.
21. Stein C: Peripheral mechanisms of opioid analgesia. *Anesth Analg*. 1993; 76(1): 182-191.
22. Hassan AH, Przewlocki R, Herz A, et al.: Dynorphin, a preferential ligand for kappa-opioid receptors, is present in nerve fibers and immune cells within inflamed tissue of the rat. *Neurosci Lett*. 1992; 140(1): 85-88.
23. Stein C, Hassan AH, Przewlocki R, et al.: Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proc Natl Acad Sci U S A*. 1990; 87(15): 5935-5939.
24. Cabot PJ, Carter L, Schafer M, et al.: Methionine-enkephalin- and Dynorphin A-release from immune cells and control of inflammatory pain. *Pain*. 2001; 93(3): 207-212.
25. Beyer A, Schafer M, Stein C: Antinociceptive effects of dynorphin peptides in a model of inflammatory pain. *Pain*. 1997; 70(2-3): 141-147.
26. Shibata M, Ohkubo T, Takahashi H, et al.: [Peripheral analgesic actions of opioid peptides and morphine analogues]. *Nippon Yakurigaku Zasshi*. 1986; 88(2): 101-107.
27. Kreek MJ, Schluger J, Borg L, et al.: Dynorphin A1-13 causes elevation of serum levels of prolactin through an opioid receptor mechanism in humans: Gender differences and implications for modulation of dopaminergic tone in the treatment of addiction. *J Pharmacol Exp Ther*. 1999; 288: 260-269.
28. Wen HL, Ho WK: Suppression of withdrawal symptoms by dynorphin in heroin addicts. *Eur J Pharmacol*. 1982; 82: 183-186.
29. Specker S, Wananukul W, Hatsukami D, et al.: Effects of dynorphin A(1-13) on opiate withdrawal in humans. *Psychopharmacology*. 1998; 137: 326-332.
30. Gambus PL, Schnider TW, Minto CF, et al.: Pharmacokinetics of intravenous dynorphin A(1-13) in opioid naive and opioid-treatment human volunteers. *Clin Pharmacol Ther*. 1998; 64: 27-38.
31. Barke KE, Hough LB: Simultaneous measurement of opiate-induced histamine release in the periaqueductal gray and opiate antinociception: An in vivo microdialysis study. *J Pharmacol Exp Ther*. 1993; 266: 934-942.
32. Barke KE, Hough LB: Opiates, mast cells and histamine release. *Life Sci*. 1993; 53: 1391-1399.
33. Gustorff B, Nahlik G, Hoerauf KH, et al.: The absence of acute tolerance during remifentanil infusion in volunteers. *Anesth Analg*. 2002; 94(5): 1223-1228, table of contents.

CASE REPORT

Morphine toxicity in renal failure

Ferraz Gonçalves, MD

INTRODUCTION

A 60-year-old female with a plasmacytoma of the right clavicle, diagnosed in March 2000, was treated surgically. The follow-up revealed a multiple myeloma of K light chains. The patient was treated with chemotherapy (melphalan and prednisolone) and later with the VAD regimen (vincristine, adriamycin, and dexamethasone). In June 2003 she underwent a bone marrow autotransplantation. In March 2005 a relapse was detected, with concurrent renal failure and hypercalcemia. She was treated with intravenous fluids, furosemide, calcitonin, and pamidronate, and following that she began treatment with thalidomide and cyclophosphamide.

In September 2005 she was admitted to the hematology-oncology service, again with renal failure and hypercalcemia. As she also had osseous lower back pain, she was started on tramadol in increasing doses, which was later changed to modified-release morphine (30 mg every 12 hours). A few days later she was referred to palliative care.

On admission to the palliative care unit, she was diagnosed with mild lower back pain and mild somnolence. She maintained the morphine treatment she had been subject to for the previous few days. She also continued with the other drugs she had been using, including antidepressants (amitriptyline 50 mg and trazodone 100 mg at bedtime) and bromazepam (3 mg at bedtime); she had been on all of the sedative medications for months. On the second day, she had no pain and was mildly somnolent. On the third day she was very drowsy, opening her eyes only when strongly stimulated; respiratory rate was eight to nine breaths/minute, hemoglobin saturation (SaO_2) was 83 percent, body temperature was 39°C, and on physical examination there were widespread rhonchi. Serum creatinine was 2.8 mg/dL (normal range: 0.6 to 1.2 mg/dL), and ionized calcium was 3.8 mEq/L (normal range: 2.3 to 2.8 mEq/L). She was treated with naloxone 0.4 mg (1 mL) diluted in 9 mL of normal saline solution (total volume 10 mL), with 1 mL delivered every two minutes until SaO_2 greater than or equal to 90 percent was achieved. She needed to be given naloxone four times—6 mL, 4 mL, 9 mL, and 6 mL, respectively—over a period of 12 hours. She was also hydrated and was started on intravenous antibiotics and 90 mg of pamidronate after hydration; the morphine and all oral medications were suspended. The following day she was somnolent but responsive, with SaO_2 greater than or equal to 90 percent and with no fever. On the fifth day she was awake but confused, with the pain controlled and SaO_2 greater than or equal to 90 percent; creatinine was measured at 2.4 mg/dL and ionized calcium at 3.5 mEq/L. Cognitive function recovered quickly afterwards, and calcium normalized slowly after the patient was started on dexamethasone. After the patient was discharged, the pain was controlled by a daily oral dose of 400 mg of tramadol, with normal-release morphine prescribed 10 mg orally as needed. In the follow-up at the outpatient clinic, she needed to change to a moderate-to-severe-pain opioid, and she started transdermal fentanyl 25 µg/h; this was gradually increased to 75 µg/h without toxicity.

DISCUSSION

There are several reasons for why this patient developed deep sedation and respiratory depression. She had renal failure, hypercalcemia, and an infection, and she was taking sedative medication and morphine, all of which can cause sedation. However, the improvement with administration of naloxone suggests that morphine was the main culprit behind the respiratory depression.

Morphine is primarily metabolized in the liver, and the most important metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), are excreted in the urine. Minor metabolites are normorphine, morphine-3,6-diglucuronide, and morphine sulfate. In renal failure there is a decrease in the clearance of morphine metabolites, resulting in a rise in their plasma concentrations. The increase in the plasma concentration of morphine is typically small, since morphine continues to be metabolized.[1] The role and effect of the M3G is still unclear, but it is not believed to be a significant analgesic. M6G, on the other hand, is a more potent analgesic than morphine. There has been particular interest in the role of M6G in the analgesic and adverse properties of morphine,[1-5] especially in cases of renal failure. The accumulation of M6G

has been seen as the main cause for morphine toxicity in renal failure.[2,4] However, there are many patients with high concentrations of M6G due to renal failure who do not show signs of toxicity. The explanation could be the existence of protective genetic factors or the development of tolerance. There also might be other risk factors that contribute to toxicity, such as drug interactions or disease states.[5] Another factor could be the roles of other morphine metabolites. Therefore, the exact mechanism of morphine toxicity in renal failure is not yet fully understood.

As occurred with the case described above, the toxicity of morphine generates a vicious cycle initiated by somnolence and decreased liquid intake, leading to further deterioration of renal function and then a decrease in respiratory rate; this is eventually followed by respiratory infection and, if this cycle is not interrupted, death.

On the occurrence of renal failure, alternative opioids (for moderate to severe pain) to morphine can be considered. Methadone or its metabolites do not accumulate in renal failure because they are excreted almost exclusively via the feces; therefore, methadone can be a very useful drug in patients with renal failure.[6] Hydromorphone also seems to be safe, even in end-stage renal failure, as was concluded in a recent retrospective study[7]; however, high doses of hydromorphone in patients with renal failure can be associated with nausea and delirium.[8] Buprenorphine is a partial agonist that can be administered by parenteral, sublingual, and transdermal routes; it is another opioid that can be useful in selected cases of pain in patients with renal failure, for whom it appears to be a safe drug.[9] Fentanyl, which can be administered by intravenous, subcutaneous, and transdermal routes, also seems to be safe in such patients[10,11]; however, life-threatening respiratory depression can occur in patients with severe renal failure who are administered transdermal fentanyl.[12] Alfentanil and sufentanil are also safe drugs for patients in renal failure; however, they must be used intravenously or subcutaneously.

Although there are a number of alternatives to morphine for patients with renal failure, for various reasons they are not an option in certain circumstances. If we consider this in a worldwide context, we will find that not all the options described above are always available. For example, in relation to oral opioids, in Portugal methadone is available for treating drug addicts but not for pain control, and hydromorphone and sublingual buprenorphine are not available at all; transdermal buprenorphine and fentanyl are available, but these formulations are not flexible enough for dose titration, and we can easily think of countries in which these drugs are unavailable because they are too expensive. Injectable drugs can be useful in inpatients, but they are usually not suited for an outpatient clinic, although syringe drivers can be used in this setting. The point is that although morphine is not the ideal drug for pain control in renal failure, there are circumstances in which useful alternatives to morphine are not available. Morphine can be used in patients with renal failure, although it must be used carefully. A normal-release preparation is preferred to a modified-release one because, as it has a shorter half-life, it is more flexible and can be reduced or suspended if significant toxicity develops, with effects that are not as prolonged. In this situation, low dosages and schedules that are broader than the usual four-hour one can be used, with extra doses as required and with close monitoring; it is a prudent way of using morphine in renal failure. Alternatively, the dose titration can be done with a normal-release preparation administered every three to four hours as required until the pain is controlled, and then changed, with the same total 24-hour dose, to a regime of every six, eight, or 12 hours. If extra doses are still needed, the dose can be increased by about a third approximately every three or four days.

The goal of the treatment of respiratory depression due to chronic use of morphine or other opioids is to prevent death. If that danger is not present, though, because the patient can ventilate adequately, there is no need to intervene beyond careful observation and reducing or temporarily withdrawing the dose of the opioid and starting later on with a lower dose. In more severe cases, naloxone can be used via intravenous, subcutaneous, and/or intramuscular routes.[13] It can be used as both a bolus and a continuous infusion, but I favor the intravenous use of naloxone in small boluses. The reason is that the goal, in patients chronically using opioids, is to mitigate the risk of death due to respiratory failure, as stated above, and not to immediately normalize the level of consciousness; if a complete reversal of adverse effects is attempted, pain, withdrawal syndrome, and the activation of the sympathetic system, with tachycardia, arrhythmias (including ventricular fibrillation), and high blood pressure may ensue. Therefore, what must be done in these cases is to provide small boluses of naloxone, as described in this case report, under close surveillance. If an oximeter is available, attempts should be made to ensure SaO_2 greater than or equal to 90 percent; if such equipment is not available, then the goal is to attain a respiratory rate greater than or equal to 10 breaths/minute and the reversal of cyanosis. The action of naloxone is short-lived, with a serum half-life of about one hour[13]; therefore, repeated doses may be necessary.

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REFERENCES

1. Mercadante S: "The role of morphine glucuronides in cancer pain." *Palliat Med.* 1999; 13: 95-104.
2. Lötsch J: Opioid metabolites. *J Pain Symptom Manage.* 2005; 29: S10-S24.
3. Portenoy RK, Foley KM, Stulman J, et al.: Plasma morphine and morphine-6-glucuronide during chronic morphine therapy for cancer pain: Plasma profiles, steady-state concentrations and the consequences of renal failure. *Pain.* 1991; 47: 13-19.
4. Osborne RJ, Joel SP, Slevin M: Morphine intoxication in renal failure: The role of morphine-6-glucuronide. *BMJ.* 1986; 292: 1548-1549.
5. Lötsch J,. Zimmermann M, Darimont J, et al.: Does the A118G polymorphism at the μ-opioid receptor gene protect against morphine-6-glucuronide toxicity? *Anesthesiology.* 2002; 97: 814-819.
6. Fainsinger R, Schoeller T, Bruera E: Methadone in the treatment of cancer pain: A review. *Pain.* 1993; 52: 137-147.
7. Lee MA, Leng MEF, Tiernan EJJ: Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. *Palliat Med.* 2001; 15: 26-34.
8. Murray A, Hagen NA: Hydromorphone. *J Pain Symptom Manage.* 2005; 29: S57-S66.
9. Johnson RE, Fudala PJ, Payne R: Buprenorphine: Considerations for pain management. *J Pain Symptom Manage.* 2005; 29: 297-326.
10. Dean M: Opioids in renal failure and dialysis patients. *J Pain Symptom Manage.* 2004; 28: 497-504.
11. Mercadante S, Caligara M, Sapio M, et al.: Subcutaneous fentanyl infusion in a patient with bowel obstruction and renal failure. *J Pain Symptom Manage.* 1997; 13: 241-244.
12. Radbruch L, Sabatowski R, Petzke F, et al.: Transdermal fentanyl for the management of cancer pain: A survey of 1005 patients. *Palliat Med.* 2001; 15: 309-321.
13. Martin WR: Naloxone. *Ann Intern Med.* 1976; 85: 765-768.

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