Journal of Opioid Management™

A medical journal for proper and adequate use

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Official Journal of Opioid Management Society

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AD

OPIOID CERTIFICATION PROGRAM

Presented by

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

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

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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).

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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—

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

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

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

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

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OPIOID MANAGEMENT SOCIETY
470 Boston Post Road
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Dear Colleagues,

As many of you know, there is a substantial and growing body of research that indicates that physicians are underprescribing opioids for the treatment of pain. The primary reasons suggested by this research are twofold. First, clinicians are reluctant to prescribe opioid analgesic medicines for fear that doing so will invite regulatory scrutiny. Secondly, many physicians are simply not comfortable prescribing opioids because they feel they don't have the proper training and education for prescribing and managing them. As a result, this country is in the midst of an epidemic of undertreatment of acute and chronic pain.

To address this problem, the publishers of the *Journal of Opioid Management* have recently launched the **Opioid Management Society**—a professional organization dedicated to educating physicians in the proper and adequate use of these powerful painkillers.

As head of the Educational Advisory Board for the Society, I am proud to announce the Society's inaugural **Opioid Certification Program**, taking place at the Conference Center at Harvard Medical on April 22-23, 2006. This program, led by a renowned group of pain and regulatory specialists, is designed to inform opioid prescribers in the myriad uses, abuses, and legal ramifications of opioids. We believe this program will be highly instructive for all attendees, and will serve as the pilot program for many more such programs that we will organize across the country.

For more information about this program, I invite you to review the enclosed brochure or visit *www.opioidmanagementsociety.org*. I hope you'll consider joining us in Boston in April. Thank you.

Very truly yours,

Robert E. Enck, MD

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

CALENDAR

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37th Annual Meeting and
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May 4-7, 2006
San Diego Sheraton Hotel and Marina
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For registration information, contact:
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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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NIH ANNOUNCES NEW REQUEST FOR GRANT APPLICATIONS

Opioids are the most powerful analgesics available for the treatment of most pain conditions; however, opioid treatment of pain can result in negative health consequences such as intoxication and physical dependence (i.e., tolerance and withdrawal) and sometimes leads to opioid abuse and addiction. The purpose of this new request for grant applications from the National Institutes of Health is to solicit applications to support research on the intersection of the use of opioids in the treatment of pain and the abuse and addiction to opioids. Research examining the rates of physical dependence, abuse, and addiction to opioids when they are given for pain is sought. Also, research elucidating factors (including pain itself) that predispose or protect pain patients from opioid abuse and addiction is encouraged. Furthermore, research on the treatment of pain in the context of opioid abuse and addiction, as well as the prevention or treatment of opioid abuse and addiction in pain patients is encouraged. Because of the diverse nature of the issue, this request is designed to encourage a broad range of research including epidemiology, neuroscience, developmental, prevention and treatment (behavioral, pharmacological, and services approaches), and research, and will support both animal and human studies.

Participating institutes are the National Institute on Drug Abuse (NIDA), National Institute on Aging (NIA), and National Institute of Dental and Craniofacial Research (NIDCR). More information can be found at the official Web site for the request, which is *http://grants1.nih.gov/grants/guide/rfa-files/RFA-DA-06-005.html*. (Source: NIH Web site, December 15, 2005.)

UPDATE ON 2006 AAOP SCIENTIFIC MEETING LOCATION

Due to the unfortunate circumstances in New Orleans, a decision has been made to relocate the American Academy of Orofacial Pain (AAOP) 2006 Scientific Meeting, which was to be held there from April 27 through April 30, 2006. A new site selection search is underway and as soon as the hotel is confirmed, it will be posted. Since the majority of our speakers for the program have already committed to the April 2006 dates, every attempt is being made to retain those same dates.

The AAOP Council did not make this decision in haste; after thoroughly investigating the possibility of keeping the program in New Orleans, it was determined that the damage to the city was so devastating and widespread that it was best to relocate the meeting.

AAOP is currently in contract negotiation with the Red Rock Resort-Spa-Casino in Las Vegas, NV. As soon as the contract is executed, all information pertaining to the conference (i.e., room reservation procedure, registration information, activities) will be posted on the AAOP Web site (*http://www.aaop.org*).

Attendees with any questions or concerns should contact AAOP Headquarters at *aaopco@talley.com* or 856-423-3629. (Source: AAOP Web site, December 15, 2005.)

NEW PROTOCOL FOR MEDICATION–ASSISTED TREATMENT OF OPIOID ADDICTION

US federal officials now are aiming to improve opioid-addiction treatment through the release of a comprehensive guide to medication-assisted treatment. To begin the process, the Substance Abuse and Mental Health Services Administration (SAMHSA) released a new Treatment Improvement Protocol (TIP 43) for medication-assisted treatment of opioid addiction. One goal of the protocol is to encourage more psychiatrists to provide such treatment.

The SAMHSA treatment protocol, which is 43rd in a series, was released in late October 2005 to describe best practices for the use of methadone, buprenorphine, and naltrexone to combat opioid addiction. It includes information on appropriate doses, medically supervised withdrawal, medication maintenance, medication tapering, and treatment for multiple substance use.

The TIP was based on a review of clinical and health services research findings and the experiences of a panel of nonfederal researchers, clinicians, program administrators, and patient advocates. It combines and updates information provided in previous protocols on similar topics and complements TIP 40, "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction," released in the summer of 2004.

Treatment of opioid addiction, including the fast-spreading addiction to prescription painkillers, was expanded beyond the traditional approach of large public clinics to the more convenient offices of qualified physicians by the Drug Addiction Treatment Act of 2000, which allows office-based dispensing and prescribing of Schedule III drugs for opioid addiction treatment.

An estimated 150,000 patients have been treated for opioid addiction since buprenorphine hydrochloride/

naloxone hydrochloride (Suboxone) and buprenorphine hydrochloride (Subutex) were introduced in early 2003, according to Rickett and Colman Pharmaceuticals Inc., the manufacturer.

The TIP authors said they hope the consensus document will provide opioid addiction treatment professionals at what panel members described as 1,150 locations in 45 states with the empirical data and best-practices support they need to treat the 2,450 such patients under their care each day. SAMHSA also plans to develop quick guides from the TIP to allow physicians to access the information more easily.

The TIP's practical information includes suggestions such as that physicians who prescribe buprenorphine for prescription narcotics or heroin addiction need to integrate it with counseling and other support services to ensure comprehensive care. The TIP highlights the importance of matching patients with the specific treatment that will work best for them, such as treating solitary homeless patients versus those with a stable residence and family members, or younger versus older patients. The TIP also suggests changing some past practices that have been found less effective, such as that physicians replace the previous use of "arbitrary" ceilings on buprenorphine use in patients with evidence-based dosing guidelines. Finally, the TIP encourages physicians to no longer terminate treatment of such patients but instead intensify the medication treatment for those who have difficulty abstaining.

TIP 43 is available online at *http://ncadi.samhsa.gov/media/Prevline/pdfs/bkd524.pdf*. (Source: Psychiatric News Web site, December 2, 2005.)

DRUG DISPENSING LAW IN NEW YORK STATE

As of April 19, 2006, doctors in New York will be required under a new law to use state-issued forms to dispense drugs as part of a plan to combat rising abuse of prescription medicines such as OxyContin and Vicodin. Providers will be issued unique serial numbers, which will allow dispensing pharmacies to verify prescriptions more easily, and security measures will be taken to ensure that the forms will be difficult to duplicate or photocopy.

According to the New York State Health Department, it is anticipated that the law will save $100 million in Medicaid and $75 million for private insurance companies in its first year. Sixty percent of New York doctors already use the forms, which have been required for several years in the prescription of Schedule II and benzodiazepine controlled substances (e.g., rohypnol). (Source: Newsday Web site, December 14, 2005.)

PUSH FOR ONLINE DRUG REGULATIONS IN WEST VIRGINIA

The TRIDENT Drug Task Force, operating in Raleigh and Fayette Counties in West Virginia, has determined that regulation is sorely needed for online drug and pharmacy sites. Approximately 60 percent of the cases investigated by TRIDENT involve pharmaceuticals, and the number is growing.

It is illegal to use different names other than one's own to order mass quantities of prescription medications. TRIDENT is lobbying to make the ordering of pills online illegal as well, in addition to having them shipped into the state. (Source: Drug Policy Central Web site, December 14, 2005.)

LAWSUIT IN DEATH OF PATIENT USING FENTANYL PATCH

The family of a Salt Lake City area woman who died in 2003 of multiple organ failure has filed a lawsuit against ALZA Corp. (and a partner company, Janssen Pharmaceutica Products), the manufacturer of the Duragesic fentanyl patch that the woman was using to control pain associated with Paget's disease. Marilyn Titus, aged 72 at the time of her death, was using a 50 mcg timed-release patch prescribed by a doctor.

The lawsuit states that after starting to use the patch, Titus began having difficulty breathing and lost consciousness while on the phone with a 911 dispatcher, dying three weeks later. These symptoms match those associated with fentanyl overdose, others of which include tiredness, extreme sleepiness or sedation, inability to think or talk normally, difficulty ambulating, and feeling dizzy or confused. The lawsuit also alleges that ALZA and Janssen sold leaking and defective patches to patients throughout Utah and elsewhere, that the companies engaged in negligent research and testing practices, and that the companies failed to disclose the full extent of the patch's risks to its users.

The US Food and Drug Administration (FDA) issued a public health advisory on its Web site in July 2005, stating, "Patients who are using the fentanyl skin patch and their caregivers should be told about the directions for safe use of the patch and should follow the directions exactly." They are currently investigating the Duragesic patch to further determine risks associated with its use.

The lawsuit comes in the wake of a *Los Angeles Times* article published in November 2005, which stated that the county coroner's office had investigated more than 230 deaths involving fentanyl in the past six years, more than 100 of which were classified as accidental.

Neither ALZA nor Janssen could be reached for comment. (Source: Drug Policy Central Web Site, December 14, 2005.)

SAMHSA GRANT RENEWED

The Joint Commission on Accreditation of Health Care

Organizations (JCAHO) has received $650,000 for the first year of a three-year grant from the Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (SAMHSA) to partially subsidize the cost of accreditation surveys for opioid treatment programs. The Joint Commission accredits more than 380 opioid treatment programs nationwide, which provide rehabilitation and medical support specifically for individuals addicted to opioid drugs.

The SAMHSA grant is also used to provide web-based, audio conference and face-to-face accreditation training programs for opioid treatment programs. For more information about these programs, call JCAHO Customer Service at 877-223-6866. For information about opioid treatment program accreditation, contact Megan Marx, associate director, at *mmarx@jcabo.org*. (Source: JCAHO Web site, December 16, 2005.)

SEROQUEL AND OPIATE WITHDRAWAL

The use of the antipsychotic drug Seroquel (quetiapine, AstraZeneca, Wilmington, DE) during opioid cessation appears to help relieve the symptoms of withdrawal, according to a study published in the October 2005 issue of the Journal of Clinical Psychiatry. Dr. Harold B. Pinkofsky and colleagues from the University of Pittsburgh School of Medicine, Pennsylvania, studied patients undergoing outpatient detoxification from opioids.

The patients were initially given eight 25-mg tablets of Seroquel. They were told to take one or two tablets every four hours, as needed, for symptoms of withdrawal or craving. Doses were increased if the drug was tolerated and the patient reported a benefit.

A total of 213 patients were treated with Seroquel in the clinic. Of these, 41 percent completed the program, with at least five days of abstinence. After some initial success with Seroquel, the patients were asked to complete a medication questionnaire for quality-assurance purposes.

Of the 107 patients who completed the survey, 79 (74 percent) reported that Seroquel helped reduce cravings for opioids and 52 (49 percent) said that it helped reduce withdrawal-associated anxiety. A reduction in pain was reported by 24 patients (22 percent), and 22 patients (21 percent) reported that Seroquel helped alleviate insomnia. Fourteen patients (13 percent) reported an improvement in appetite.

Four subjects said that Seroquel had no benefit. Seven patients were not able to tolerate the drug because of side effects. The patients received an average Seroquel dose of 206 mg per day. The authors therefore concluded that further research is needed into the mode of action of Seroquel when used for this purpose.

(Source: Medline Plus Web site, November 23, 2005.)

Iatrogenic addiction in patients treated for acute or subacute pain: A systematic review

Ajay D. Wasan, MD, MSc
Darin J. Correll, MD
Igor Kissin, MD, PhD
Sarah O'Shea, BA
Robert N. Jamison, PhD

ABSTRACT

We conducted a systematic review of the literature on the evidence for iatrogenic addiction in patients treated for acute and subacute pain. Literature searches yielded 1,943 articles, 53 of which were reviewed in detail, and 41 of which met criteria for inclusion in the review of iatrogenic addiction. Two authors independently reviewed and summarized the findings of each article. Discrepancies of ratings were resolved by discussion. We identified no randomized trials or comparative longitudinal studies. The results of nine studies of low methodological quality suggest conflicting findings. This manuscript discusses some possible mechanisms of iatrogenic addiction and concludes with suggestions for methodologically stronger studies to provide more definitive data regarding the evidence for or against iatrogenic addiction in patients treated for acute and subacute pain. The systematic review of the literature could not adequately answer the study questions; thus, it is not known whether the risk for iatrogenic addiction among patients treated with opioids for acute or subacute pain is relatively high (> 10 percent) or low (< 0.1 percent).

Key words: iatrogenic addiction, acute pain, opioids, substance abuse

INTRODUCTION

The addiction of a patient to a drug initially prescribed for a medical condition is referred to as an iatrogenic addiction. The postoperative or short-term use of prescription drugs with addictive potential, such as opioid analgesics, increases the risk of iatrogenic addiction. Although a number of studies have examined the rate of iatrogenic addiction in chronic pain patients receiving long-term opioid therapy, few investigations have documented its incidence among hospitalized patients who receive opioids for acute pain. Results from the Drug Abuse Warning Network (DAWN) indicate that the abuse of prescription opioids rose 71 percent from 1997 to 2002.[1] Given this trend, the issue of iatrogenic addiction among hospitalized patients is a particularly salient topic related to the prescription of opioids.

Epidemiologic data from the National Comorbidity Survey of Psychiatric Disorders in the United States indicate a lifetime prevalence of 7.5 percent for drug dependence (illicit or prescription) and of 14.1 percent for alcohol dependence.[2] In 2003, 2.7 percent of Americans (18 years or older) met criteria for illicit drug abuse or dependence as defined by the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[3] During this same year, almost 8 percent of the population of the United States met DSM-IV criteria for alcohol dependence or abuse.[4] Among a sample of 363 hospitalized patients, Brown and colleagues found that 21.8 percent had a current addiction disorder to alcohol or illicit drugs.[5]

Addiction is generally understood to be a chronic condition from which recovery is possible; however, the underlying neurobiologic dysfunction, once manifested, is believed to persist.[6] This condition represents a biological susceptibility to addiction to any substance with an addictive potential, even in the absence of any ongoing addictive behaviors or psychological cravings. Therefore, the prescription of opioid analgesics to a patient with a predisposition for, or history of, addiction can initiate an addictive disorder or its relapse. Many patients are discharged from the hospital with prescriptions for long- and short-acting opioid analgesics for postoperative pain without accurate data indicating the probability of their developing an addiction to these medications.

Investigations supported by the National Institute of Drug Abuse suggest that addiction is characterized by destructive motivations and behaviors reinforced and

perpetuated by underlying physiological abnormalities in the brain.[7,8] For certain individuals (6.1 to 16.7 percent of the population), substances of abuse create changes in the brain that "hijack" motivational priorities and lead to a pattern of loss of control, craving, and continued use despite adverse circumstances.[9-11] These individuals are described as having a "switch" in the brain that changes behavior from voluntary to compulsive. Functional changes are thought to occur in the dopamine-mediated reward system, primarily in the left prefrontal cortex and nucleus accumbens. These regions interact with multiple areas of the brain implicated in the pathophysiology of addiction.[12]

DEFINITIONS

For purposes of this study, we adopted the following definitions accepted by the American Academy of Pain Medicine, the American Pain Society, and American Society of Addiction Medicine.[13] Addiction is a primary, chronic, neurobiologic disease with genetic, psychological, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Physical dependence is defined as a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, or decreasing blood levels of the drug and/or by administration of an antagonist. Tolerance is defined as a state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time. Abuse is defined as the use of any drug in a manner other than how it is indicated or prescribed.[13] In one of the first reports of iatrogenic addiction, Rayport[14] described an individual with this syndrome as "One who states that he first received narcotics from a physician to the point of addiction in a disease treatment course." Finally, acute and subacute pain is defined as short-term pain or pain with an easily identifiable cause and is the body's warning of present damage to tissue or presense of disease.

STUDY AIM

The aim of this study was to systematically review the relevant literature on iatrogenic addiction. The following questions were addressed:

1. What is the incidence of iatrogenic addiction among persons treated for acute pain?

2. What are the predictive markers for addiction among patients treated with opioids for acute and subacute pain?

3. What steps are currently being taken to treat addiction from short-term opioid use?

METHODS

We searched PubMed, the National Library of Medicine's literature database, using the following words and phrases (MESH headings): "iatrogenic addiction," "acute pain and addiction," "acute pain and opioid abuse," "acute pain and opioid addiction," "acute pain and iatrogenic addiction," "headache pain and opioid abuse," "acute headache and opioid abuse," "acute headache and addiction," "sickle cell pain and opioids," "sickle cell pain and opioid addiction," "sickle cell pain and opioid abuse," and "postoperative pain and addiction." Articles were included if they addressed issues related to iatrogenic addiction. We excluded redundant studies (i.e., reported identical data), abstracts from conference proceedings, and studies whose design had nothing to do with assessment of iatrogenic addiction.

Two authors independently reviewed each citation to determine whether it might meet our criteria for inclusion in the review. If either author thought that the article might meet the inclusion criteria, two authors then independently reviewed the abstract. If either thought, based on the abstract, that the article might meet the inclusion criteria, two authors then independently read the entire article to make a final decision. Discrepancies in decisions were resolved by discussion, with input from the other authors as needed.

We classified the methodological strength of each study using a scheme previously used by other reviewers.[15,16] Articles were grouped into study design types: I) prospective, randomized controlled trials (RCTs); II) nonrandomized comparative studies with standardized measures, inclusion/exclusion criteria, and follow-up; III) uncontrolled case series with pre- and post-treatment and follow-up; and IV) descriptive studies, case reports, or expert opinion. For each article we attempted to include information on sample, study design, outcomes, and conclusions.

RESULTS

A search of PubMed with the previously mentioned MESH headings revealed a total of 1,946 articles. Many of these articles were duplicates; 53 were selected for detailed review, and 41 met inclusion criteria. The authors independently reviewed and judged nine articles to be most relevant to the study topic, although other related articles were included for discussion. No randomized or nonrandomized controlled studies were found. Results of the review are summarized in Table 1.

Studies suggesting high rates of iatrogenic addiction

Selected studies are described here in detail to address

Table 1. Summary of studies related to iatrogenic addiction				
Authors	**Title**	**Sample**	**Study design and type**	**Conclusion**
Elander et al. 2004	Understanding the causes of problematic pain management in sickle cell disease	51 adults with sickle cell disease	Class IV; semistructured interviews	Presents evidence that aberrant drug behaviors can begin in the hospital but may not necessarily represent an addiction, and that it may be most appropriate to interpret this behavior as evidence of poorly managed pain
Jamison, et al. 1994	Survey of opioid use in chronic nonmalignant pain patients	112 chronic pain patients from two pain centers who were taking opioids for chronic pain	Class IV; patient survey	63.7 percent of patients expressed some fear of addiction or dependence
Jamison, Kauffman, and Katz, 2000	Characteristics of methadone maintenance patients with chronic pain	248 subjects from three methadone maintenance centers	Class IV: subject interviews	61.3 percent of subjects reported chronic pain; 44 percent of those with pain believed prescribed opioids had led to addiction; most stated that they had always required some substance (alcohol or opioids) to feel normal
Lander, 1990	Fallacies and phobias about addiction and pain	63 staff nurses surveyed/ 42 staff nurses consulted for case assessment	Class IV; surveys and clinical case assessment	One-third of nurses think that > 5 percent of hospital patients become addicted; 63 percent of nurses rated 5 or higher the likelihood on a 7-point scale that patients could become addicted after 10 days of q4hr meperidine
Marks and Sachar, 1973	Undertreatment of medical inpatients with narcotic analgesics	Physicians of 37 medical inpatients who were taking narcotics for > 48 hr	Class IV; physician survey and case series	40 percent of physicians surveyed stated that the chances were close to 1 percent that a patient receiving 100 mg meperidine for 10 days would become addicted; 22 percent thought chances were > 6 percent; the authors concluded that the probability was < 1 percent that narcotic addicts in the US became addicted while hospitalized and that doctors greatly overestimate the actual chance of iatrogenic addiction
Miller and Jick, 1978	Clinical effects of meperidine in hospitalized medical patients	Record review of 3,634 hospital inpatients treated with meperidine	Class IV; case review estimates	Four of 3,634 subjects showed iatrogenic addiction; two were addicted before entering the hospital
Perry and Heidrich, 1982	Management of pain during debridement: a survey of US burn units	181 physicians and nurses representing 10,000 hospitalized burn patients	Class IV; case series	12 percent of those surveyed knew of a patient who had become a drug abuser upon discharge as a result of receiving narcotics for pain; most patients had a prior history of abuse; 22 were reported to abuse drugs after discharge, but all had a prior history of drug abuse
Porter and Jick, 1980	Addiction rare in patients treated with narcotics	11,882 inpatients who had received at least one narcotic preparation	Class IV; chart review	Four of 11,882 patients with no previous addiction showed addiction after treatment with narcotics while hospitalized
Rayport, 1954	Experience in the management of patients medically addicted to narcotics	277 patients from an addiction unit interviewed; many stated they had become addicted after treatment for their disease	Class IV; retrospective interviews	89 of 1,065 admissions to an addiction clinic suffered iatrogenic addiction; medically addicted patients accounted for 27 percent of inpatients

the study questions. Some studies showed support for a high prevalence of iatrogenic addiction. Pescor[17] in 1939 was one of the first to address the issue of addiction to opioids prescribed for acute pain, reporting that 3.8 percent of a group of 1,036 hospitalized patients "became addicted to morphine given legitimately for the alleviation of a painful or distressing disease" both during and after hospitalization. However, no operational definition of addiction was given in the paper. In a survey study of 1,020 opioid-addicted men consecutively admitted to a hospital, Rayport[14] in 1954 found that the incidence of medical addiction to narcotics was as high as 27 percent and that addiction had begun during treatment of an acute illness in a majority of these patients. These descriptive studies, published 66 and 51 years ago, respectively, leave unanswered how addiction was defined. While the incidence of iatrogenic addiction cannot be relied on in these studies, they do suggest that it can be a consequence of opioid treatment first administered during hospitalization.

More recently, in a study of 363 patients on general medical, surgical, and orthopedic wards of a university hospital, Brown et al.[5] used two standardized measures based on DSM-IIIR criteria for substance abuse to determine the rate of abuse among short-term inpatients. The authors reported a lifetime prevalence of 2.8, 10.2, and 25.3 percent for abuse of opioid analgesics, any drug excluding alcohol, and any drug including alcohol, respectively. Given this relatively high incidence of substance abuse, the authors concluded that the probability is high that doctors will administer opioid analgesics for acute pain to inpatients with a history of an addictive disorder.

In a survey study of 112 patients taking opioids for chronic pain, 63.6 percent reported being bothered by the fear of addiction or dependence.[18] In a recent survey study of 248 individuals at three methadone maintenance centers, 44 percent of those surveyed believed that opioids prescribed for pain had led to an addiction.[19] Moreover, many patients receiving methadone maintenance therapy said they had always required some substance (alcohol or opioids) to "feel normal." The authors suggested that, among persons prone to substance abuse, the treatment of pain with opioids could trigger an addiction disorder, regardless of the treatment setting.

A qualitative study by Elander and colleagues sheds light on how the process of iatrogenic addiction may begin.[20] They performed semistructured interviews with 51 adult inpatients hospitalized in the United Kingdom for a sickle cell crisis, examining issues of analgesic misuse and substance dependence. They found that disputes between patients and physicians or nurses about pain level or the amount of opioids prescribed fueled dissatisfaction over pain treatment, which in turn led some patients to inappropriately manipulate their patient-controlled analgesia pumps, acquire pain medications from other patients, or use analgesics apart from those prescribed. A portion of these patients continued similar aberrant behaviors after discharge: obtaining analgesic prescriptions from more than one doctor, using analgesics prescribed to another person, using illicit drugs, or injecting oral forms of analgesics.

Studies suggesting low rates of iatrogenic addiction

Other investigations have suggested low rates of iatrogenic addiction to opioids among patients treated for acute pain. Using data accumulated during the Boston Collaborative Drug Surveillance Program on drug safety in hospitalized patients, Porter and Jick[21] surveyed the files of 11,882 patients who had received at least one narcotic preparation. They found only four cases (0.03 percent) of iatrogenic opioid addiction in patients without a prior history of an addictive disorder. In a similar study, Miller and Jick[22] examined the files of 3,364 hospitalized medical patients who received meperidine. Only four (0.1 percent) patients, two of whom were addicted before entering the hospital, exhibited symptoms of dependence on meperidine. These brief reports support a belief that prescription opioids have minimal potential for addiction when used to treat either acute or chronic pain. Both of these studies, however, only reported on the period of hospitalization, when access to opioids is highly monitored and inappropriate use of opioids would be difficult.

In a study examining how pain is assessed and managed during wound debridement in US burn facilities, Perry and Heidrich[23] analyzed 181 responses to questionnaires sent to the medical staff (one-third of whom were physicians) of various burn units. They calculated that the responders to their survey represented the accumulated knowledge of at least 10,000 hospitalized burn patients. The survey included a question about the rate of iatrogenic addiction to opioid analgesics in burn patients. Twelve percent of the respondents indicated that they knew of a patient who had become a drug abuser on discharge from the hospital as a result of receiving narcotic analgesics for pain. All but one of these iatrogenically addicted patients had a history of drug abuse. The authors concluded that the risk of developing an addiction to opioid analgesics prescribed for pain is low. No information was given about the duration of patients' pain.

Studies examining physicians' fears of creating opioid addiction suggest that the incidence of iatrogenic addiction to opioid analgesics among patients treated for acute pain is less than 1 percent.[24-26] In a survey by Marks and Sachar,[26] physicians were asked about the probability of a hospitalized patient developing an addictive disorder after a 10-day treatment regimen with 100 mg of meperidine intramuscularly every four hours. The majority of

physicians (60 percent) stated that the chances of addiction were less than 1 percent, while only 22 percent stated that they were greater than 6 percent. Based on the physicians' responses, the authors of this survey concluded that the development of addiction to meperidine likely occurs in fewer than 1 percent of patients treated for acute pain.

A study by Zacny et al.[27] offered further support for this position. Under experimental conditions, human subjects with no history of drug abuse reported less opioid reward from a dose of fentanyl paired with a painful stimulus (cold water) than from the same opioid challenge without pain (warm water). The positive psychological effects of fentanyl (e.g., euphoria or elation) were found only when accompanied by warm water, suggesting that the painful stimulus (cold water) abolished this effect. At the same time, studies of the reinforcing effects of drugs in the presence versus the absence of pain in animals showed the opposite outcomes. These studies suggest that pain increases the reinforcing efficacy of opioid analgesia and blunts the psychoaffective effects.[28, 29]

DISCUSSION

A thorough review of the literature did not produce a single controlled trial devoted to the investigation of iatrogenic addiction to opioids. All articles were classed as Type IV (descriptive studies, case reports, expert opinion), and conclusions were often based on subjective impressions. There were no follow-up studies, and most articles could not answer the question of whether patients develop iatrogenic addiction after taking opioids. Given the recent rise in the prescribing and abuse of opioid analgesics,[30] accurate data on the rate of addiction among inpatients administered opioids for acute pain, although needed, do not seem to exist.

Vanyukov and colleagues[31] argue that some patients have a predisposition for an addiction disorder based on a multifactorial genetic liability. This liability concept is supported by research documenting cross-tolerance for different substances, the cotransmission of substance abuse disorders within families, and addiction to multiple drugs. They conclude that common physiological mechanisms underlie addiction disorders. Clinical studies have documented a high correlation among substance abuse, smoking, and other addictive disorders, such as gambling. It is likely that this relationship is at least partially modulated by characteristics of innate temperament.[32]

Some of the conflict between the results of studies reporting an extremely low risk of addiction for hospitalized patients and the high proportion of substance abuse in the general population can be explained by the unreliable methodology of existing surveys of iatrogenic addiction in hospitalized patients. The studies by Prescor[17] and Rayport[14] can be criticized for being descriptive studies lacking a rigorous study design. It is also important to note that the studies by Porter and Jick[21] and Miller and Jick[22] were designed to evaluate the clinical effects of opioid analgesics on patients with acute pain, and that findings related to addiction were peripheral to their focus. Furthermore, the authors excluded all individuals with a history of addiction when determining incidence of iatragenic addiction. As with these surveys, the study by Perry and Heidrich[23] was not specifically designed to assess iatrogenic addiction to opioids but rather to examine the pharmacologic management of burn patients in general. No specific diagnostic criteria, standardized addiction screens, or structured clinical interviews were used. Thus, the rates of iatrogenic addiction to opioid analgesics reported in these studies should be interpreted with caution.

Specific factors in the hospital drug-taking environment might also account for the reported differences. For example, patients in a controlled environment have few opportunities to demonstrate aberrant drug behavior. Once patients are discharged there may be limited coordination of care to identify and follow those patients who may develop iatrogenic addiction.

In sum, a careful review of the studies that assess risk of addiction to opioids in hospitalized patients treated for acute pain show that these studies have methodologic limitations. No well-controlled longitudinal studies on this issue have been reported in the literature. Thus, we do not know whether the risk is relatively high (> 10 percent) or low (< 0.1 percent). The absence of reliable data on the risk of addiction in hospitalized patients is a significant concern because iatrogenic addiction could pose a major public health concern. At present, we do not know whether the expectation of addiction after administration of opioids for acute or subacute pain is exaggerated, and there is no system for closely monitoring the signs of opioid addiction following treatment of acute pain.

Given the current confusion in the literature, we suggest that the following recommendations be considered. First, a simple screen for addiction risk potential based on a history of substance abuse in the family would help patients be aware that they may be at increased risk for medication abuse. Several screening tools currently exist to help identify risk for abuse, including the Screening Instrument for Substance Abuse Potential (SISAP),[33] the Prescription Abuse Checklist,[34] the Prescription Drug Use Questionnaire,[35] the Pain Assessment and Documentation Tool (PADT),[36] the Pain Medication Questionnaire (PMQ),[37] and the Screener and Opioid Assessment for Patients with Pain (SOAPP).[38] Limitations of these measures have been identified.[39,40]

Second, further exploration of different delivery systems that adequately treat pain, while also decreasing the risk for substance misuse, should be encouraged. This includes the development of short- and long-acting opioid

medications that are not easily compromised. Finally, priority should be given to the development of rigorous, controlled, longitudinal studies of patients prescribed opioids for acute pain. A unified call for designated support through federal agencies (e.g., the National Institutes of Health) to fund these studies and help clarify this issue is needed. Future studies in which patients are assessed preoperatively for family and personal history of substance abuse and are followed for more than six months after discharge would help to assess the incidence of iatrogenic addiction. This systematic review of the literature could not adequately answer the study questions.

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Problematic terminology for problematic drug use

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INTRODUCTION

The use of opioid therapy in chronic noncancer pain (CNCP) has been described as controversial.[1-9] While the use of opioids in CNCP is now accepted by many pain specialists,[10-17] a major concern is that CNCP patients will develop patterns of problematic drug use, including abuse and addiction.[18-24] Consequently, over the years there have been numerous calls for more research into the long-term use of opioids in CNCP.[7-9,18,24-26] However, it is also observed that prejudice and ignorance still impede optimum prescribing of these drugs.[9,14,27] This is partly attributable to problems arising from the incorrect use of terminology pertaining to problematic drug use,[2,6,28-34] and there is still a need for agreement on clear definitions for problematic behavior in CNCP patients.[35,36] This focused review of literature examines the perceived origins of the problem and discusses attempts at redress along with some examples of ongoing contributory factors. The paper then concludes with suggestions on future remedial action.

ORIGINS OF THE PROBLEM

The anti–opium movement

According to Schaler,[37] a little more than 200 years ago the concept of addiction was unknown. Schaler noted that the tremendous change of opinion that led to the disease model of addiction did not originate from scientific research, but instead emanated from the moralistic rhetoric of the 19th Century anti-opium and temperance movements. The anti-opium movement arose largely from opposition to British and American involvement in trafficking opium into China; namely, the British government of the day, along with successive 19th Century governments, argued in favor of the traffickers, that the long-term use of opium was relatively safe.[38] Indeed, before the establishment of the anti-opium movement, self-medication with opium was considered as quite normal and not to pose a problem. Most people purchased opium in the same way as we now buy aspirin or paracetamol (acetaminophen)—many households would have stocked a bottle of tincture of opium, or laudanum, for the treatment of aches, pains, and stomach upset. The apparent absence of an epidemic of problematic opioid drug use may be partly explained by the theory that self-medication was the most common reason for opioid use at this time.[38] However, there is no doubt that opioids were also used recreationally, although the boundaries between medical and recreational use were often blurred. Opium was often used as a tonic, a "pick-me-up," or a "calmer of nerves." Both Wilberforce and Gladstone are said to have taken opium before speaking in the British House of Commons.[38]

In 1895, a Royal Commission on opium use, initiated by the British Government, concluded that the "evil effects of opium consumption" had been greatly exaggerated, dismissing any connection between opium use and crime and likening its moderate use to that of alcohol; furthermore, they stated that the extensive use of opium for "non-medical and quasi-medical purposes" was, for the most part, without injurious consequences.[38] The Royal Commission also felt that nonmedical and medical uses of opium were perceived as so interwoven that it was deemed to be impractical to make a distinction between different types of usage with regard to the distribution and sale of the drug.

In contrast, the anti-opium movement, with the backing of the emerging medical profession, who desired greater control over the prescription of opioid substances, claimed that all regular use of opium would, without exception, lead to addiction.[38] In concurrence with Schaler,[37] Berridge[38] noted that, as a part of 19th Century progress, many medical conditions were newly classified or categorized as disease entities according to new "scientific" theories. However, the boundaries between studying chemistry, physics, biology, and sociology were not as fixed as they are today, and it was not uncommon to refer to phenomena in terms of the "moral sciences." It was in such a climate that medical professionals began to study the newly specialized area of addiction and, therefore, viewed opium consumption under the auspices of inebriety, which was classified as a disease.[38] Schaler claimed that by following the trend to "medicalize" social deviancy, it became easier for the

anti-opiumists to scare people away from drug use.[37] This hybrid theory suited the anti-opium movement well because it emphasized the moral aspect of disease causation and therefore disease symptoms could be viewed in terms of personal responsibility.[38]

Unresolved question

Any evidence of the existence of a class of regular yet moderate therapeutic user would undermine the claims of the anti-opium movement and be seriously damaging to the movement's case for ending the opium trade in China.[38] Consequently, during the 19th century opium debate, the central argument became the question of whether or not there was a class of moderate, long-term, "nonaddicted" opium users, which also encompassed the use of opium products for the treatment of long-term chronic illnesses.[38] This issue remains unresolved today and is central to the present controversy as to whether or not there exists such a class of CNCP patients.

ATTEMPTS TO REDRESS THE SITUATION

World Health Organization and Diagnostic and Statistical Manual definitions

Observing that the term "addiction" was originally used to describe a habit, Fishbain et al.[2] noted that in 1957, the World Health Organization (WHO) defined addiction as "a state or period of chronic intoxication characterized by: an overpowering desire or need (compulsion) to continue taking a drug and to obtain it by any means, a tendency to increase the dose, a psychological and generally a physical dependence on the effects of the drug, and a detrimental effect on the individual and/or society." However, because it was recognized that some individuals could be physically dependent on a drug without compulsive use and vice versa, the WHO decided to adopt the term "dependence."[2]

In 1964, the WHO defined drug dependence as "a state of psychic or physical dependence, or both, on a drug arising in a person following administration of that drug on a periodic or continuous basis."[2] Thus, the dichotomy between physical dependence and psychological dependence was made explicit, as was the possibility of experiencing one without the other (e.g., the possibility of being physically dependent without being addicted). Subsequently, however, in a working paper for the WHO, Glatt described the conditions of "psychological" or "emotional dependence," formerly known as "habituation."[39] Glatt then noted the condition of "physical dependence" followed by the bracketed word "addiction," suggestive of synonymity between the two.

The 1980 *Diagnostic and Statistical Manual*, 3rd edition (DSM-III),[40] used two terms: "abuse" and "dependence" (Table 1). Abuse included a pathological pattern of use, while dependence included the concepts of tolerance and withdrawal.[2,40] The DSM-III made no distinction, however, between dependency and legitimate long-term medical use of an opioid or sedative, which could result in tolerance and withdrawal symptoms on abrupt cessation of drug.[2] Furthermore, opioid and sedative dependence with no abuse were considered to be psychiatric disorders, whereas similar conditions related to prolonged administration of antihypertensive or antidepressant drugs were not.[2] Also, there was no provision for assessing the severity of dependence.[2] Subsequently, the WHO convened an international working party which defined "dependence" as "a syndrome manifested by a behavioral pattern in which the use of a given psychoactive drug or class of drugs is given a much higher priority than other behaviors that were once given a higher value."[2] Dependence syndrome was thus perceived as not absolute but existing in degrees, with compulsive drug-using behavior at the extreme end,[2] which in turn led to revised DSM-III criteria (DSM-III-R).[41]

CONTRIBUTORY FACTORS

Opiophobia

Despite these attempts to redress the situation, in 1985, Morgan[42] popularized the term "opiophobia," which was used to describe the undertreatment of severe pain owing to irrational and undocumented fears of opioid drug addiction. Morgan contended that opiophobia was associated with faulty knowledge, resulting in physician inability to distinguish between physical dependence and drug addiction.[42] While Halpern and Robinson[43] proposed that it may be difficult to distinguish between psychological dependence and physical dependence, they concurred that drug addiction is distinctly different from physical dependence on a drug, and that while physical dependence can be a part of addiction, physical dependence does not have to be present for addiction to occur.

Portenoy[29] observed that practitioners commonly failed to distinguish between physical dependence, addiction, drug abuse, drug dependence, and compulsive use, and felt that the term "drug dependence" could refer to psychological dependence, physical dependence, or both. He defined drug addiction in the chronic pain patient as an intense desire for the drug, compulsive drug use, continued use despite significant side effects, unapproved drug use during periods of no symptoms or to treat symptoms not prescribed for, manipulative behavior, acquiring drugs from other sources, drug hoarding, drug selling, and unapproved use of other drugs.[29] Drug abuse was defined as the use of an agent outside socially and medically approved patterns in a

given culture, or in a way that results in physical, psychological, or social harm to the individual or others.[29] Finally, Portenoy advocated that physical dependence could occur after minimal exposure to opioids and should be expected to be present in any patient who had taken opioids for more than a few days.[29]

Attempts at defining prevalence of problematic opioid use

One of the factors that has continued to perpetuate misuse of terminology has been an ongoing attempt by various authors to define the prevalence of problematic opioid use among pain patients, using incorrect definitions combined with generally unsound research methods.

In what was perceived by some as a landmark publication in 1954, Rayport[44] used the term "medical addiction," defining those addicted as having been initially given opioids by a physician. Rayport's survey purported to demonstrate a higher prevalence of patients (28.2 percent) who were medically addicted to narcotics (i.e., opioids) than had previously been recognized.[44] However, there were methodological problems with the survey; 43.5 percent of those undergoing treatment for addiction were convicted criminals referred by courts for treatment, who would be sent to prison if they did not complete treatment. If the patient stated that addiction to opioids owed to prescription by a physician, they were defined as medically addicted; no external checks were made as to the validity of the claim, such as by checking criminal records to verify whether the patient had been convicted of opioid possession before they claimed to have been medically addicted.[44]

In 1974, Glatt stated that users of narcotics (i.e., opioids) become both psychologically and physically dependent on relatively small therapeutic doses after a relatively short period of administration, thus, reinforcing the concept of the medical addict.[45] Further attempts were made to establish the prevalence of problematic drug use among CNCP patients. Fordyce[46] claimed from experience that addiction or habituation—these terms being used interchangeably, with no definitions given—was seen in over 50 percent of chronic pain patients. No evidence was offered in support of this claim.

As a warning of the dangers of drug dependency and drug abuse in patients with chronic pain, Medina[47] undertook a prospective survey of patients with headache. While acknowledging "great confusion" in the use of terminology, Medina provided definitions of psychological dependence, physical dependence, and drug abuse. Medina then added to the confusion, however, by classifying some problematic users as "physically addicted"—a term for which Medina offered no definition and also contradicted his earlier definitions.[47]

To support the claim that prescription drug abuse is a significant problem in CNCP patients, Maruta et al, using a sample of 144 patients, reported 41 percent as being drug abusers and 24 percent as being drug dependent.[18] While acknowledging the difficulties in defining operational criteria for abuse of prescription drugs, Maruta et al. arrived at their definitions of "drug abuse" and "drug dependency" by modifying existing criteria; however, they also acknowledged that their definitions were too broad to demonstrate meaningful differences between the groups of patients they studied.[18] The authors made no distinction between physical drug dependency and psychological drug dependency and conceded that refinement of their definitions were necessary.[18] However, two years later, Maruta and Swanson,[19] contrary to refining definitions, further broadened them, stating that abuse had occurred if a patient with no evidence of a nonprogressive disease had taken a narcotic (opioid) on a daily basis for more than a month, which yielded a 100 percent abuse rate for patients taking oxycodone.[19]

In comparing study populations, Bouckams et al.[48] stated that the prevalence of "addiction" in Maruta et al.'s population[18] was identical to their own. However, Bouckams et al. appear to have overlooked the fact that Maruta et al.'s very broad definition was of "dependence" and not "addiction." This does not correlate with the former's own definition of "addiction," described as a behavioral pattern of drug use and characterized by overwhelming involvement with the use of the drug, the securing of its supply, and a high tendency to relapse after withdrawal.[48]

Continued problems using World Health Organization and *Diagnostic and Statistical Manual* terms to define problematic use

In undertaking a survey of 110 patients to determine the prevalence of problematic drug use among CNCP patients, Kouyanou et al.[31] commented on the confusing terminology in the field of psychoactive substance abuse and/or dependence, noting that the DSM III-R criteria for the diagnosis of such conditions had limitations (Table 1). Interestingly, while six (4.8 percent) patients were classified as dependent on opioid analgesics, there were more patients (five, 4 percent) classified as abusing nonopioid analgesics than there were abusing opioid analgesics (four, 3.2 percent).[31]

Chabal et al.[49] concluded that applying DSM-III-R criteria, the WHO's International Classification of Disease diagnostic criteria (WHO-ICD-10),[50] or more recent DSM-IV criteria[51] presented difficulties in distinguishing between dependency and legitimate long-term use of opioids in CNCP patients. To address these problems, a 5-point checklist for prescription opioid abuse was proposed, including the following items: overwhelming

Table 1. Common diagnostic criteria	
Source	**Criteria**
DSM-III Diagnostic Criteria for Psychoactive Substance Dependence. (APA,1980)	"Substance Dependence" generally is a more severe form of substance use disorder than substance abuse and requires physiological dependence, evidenced by either tolerance or withdrawal.
	Invariably there is also a pattern of pathological use that causes impairment in social or occupational functioning, although in rare cases the manifestations of the disorder are limited to physiological dependence. An example would be an individual's inadvertently becoming physiologically dependent on an analgesic opioid given to him by a physician for the relief of physical pain.
	The diagnosis of all Substance Dependence categories requires only evidence of tolerance or withdrawal, except for alcohol and cannabis dependence, which in addition requires evidence of social or occupational impairment from use of the substance or a pattern of pathological substance use.
DSM-III-Revised Diagnostic Criteria for Psychoactive Substance Dependence. At least three of the following nine conditions must be present. (APA, 1987)	1) Substance is often taken in larger amounts or over a longer period than the person intended.
	2) Persistent desire or one or more unsuccessful efforts to cut down or control substance use.
	3) Great deal of time spent in activities necessary to get the substance (e.g. theft), take the substance (e.g. chain-smoking), or recover from its effects.
	4) Continued use substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance (e.g., keeps using heroin despite family arguments about it, has cocaine-induced depression, or has an ulcer made worse by drinking).
	5) Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (e.g. does not work because hung over, goes to work "high," is intoxicated while taking care of children), or when substance use is physically hazardous (e.g., drives when intoxicated), important social, occupational, or recreational activities are given up or reduced because of substance use.
	6) Marked tolerance: a need for markedly increased amounts of the substance (i.e. at least 50 percent increase) to achieve intoxication or the desired effect, or markedly diminished effect with continued use of the same amount of substance.
	7) Characteristic withdrawal symptoms.
	8) Substance is often taken to relieve or avoid withdrawal symptoms.
	9) Some symptoms of the disturbance must have persisted for at least one month, or have occurred repeatedly over a longer period.
DSM-IV Diagnostic Criteria for Substance Dependence. A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period. (APA, 1994)	1) Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or (b) markedly diminished effect with continued use of the same amount of substance.
	2) Withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for the substance, or (b) the same or a closely related substance is taken to relieve or avoid withdrawal symptoms.
	3) The substance is often taken in larger amounts or over a longer period than the person intended.
	4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.
	5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects.
	6) Important social occupational or recreational activities are given up or reduced because of substance use.
	7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).
ICD-10 Diagnostic Guidelines for Dependence Syndrome. A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year. (WHO, 1992)	1) A strong desire or sense of compulsion to take the substance.
	2) Difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use.
	3) A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance or use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
	4) Evidence of tolerance, such as increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users).
	5) Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance, or to recover from its effects.
	6) Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning, or could be expected to be aware of the nature and extent of the harm.

patient focus on drug issues during clinic visits; asking for early prescription replenishments on three or more occasions; multiple visits or telephone calls to request more opioids; a pattern of lost, spilled, or stolen medications; and supplemental sources of opioids obtained from multiple providers or illegal sources.[49]

Wesson et al.[52] noted that the seemingly more precise term "dependence" did not encompass all of the attributes of addiction, defined as being present when a person's life is dominated by drug use and which continues in spite of repeated adverse consequences. They suggested that the DSM III-R criteria had actually lost the criteria with most appeal to psychiatrists, namely, the thought process of the patient. According to DSM III-R, physical dependence and tolerance (criteria 7 and 8) combined with any of criteria numbers 2, 3, 5, 6, or 9, will qualify a patient for diagnosis of drug dependence (Table 1).[41] Given this broad latitude, Wesson et al. suggested additional considerations when using the DSM III-R criteria for the assessment of addiction in CNCP patients, such as drug-taking reliability, loss of control over drug uses, drug-seeking behaviors, the abuse of alcohol or street drugs, and general communication style.[52] Similarly, Sees and Clark[30] observed that no precise or satisfactory definition of addiction among chronic pain patients existed, and only three of nine DSM III-R criteria persisting for one month or more or repeating over a longer period was required (Table 1). Accordingly, five of the nine diagnostic criteria related to physical dependence or tolerance may easily be met in CNCP patients on long-term opioid therapy.[30] If the term "addiction" is to be used in relation to CNCP patients, it must be defined in terms of compulsive drug use, drug-seeking behavior, loss of control over drug use (dose and frequency), and continued drug use in spite of adverse consequences and medical advice to discontinue opioids.[30] Sees and Clark also suggested the addition of questions on adverse life consequences not owing to pain, contact with street drug culture, and cooperation with treatment plan, including alternative pain management techniques, because although tolerance and physical dependence should be expected in CNCP patients on long-term opioid therapy, the maladaptive behavioral changes associated with addiction should not.[30]

Subsequent to their review of literature, Fishbain et al.[2] concluded that terminology to describe problematic drug use was not being used in a universally acceptable fashion. However, they noted that the DSM had no plans to adopt the term "addiction" or develop operational criteria for this syndrome.[2] Observing that the undertreatment of pain could lead to behaviors that might be mistaken for addiction, Fishbain et al. predicted that the situation was unlikely to improve and would continue to cause research difficulties.[2] Despite the introduction of newer DSM-IV criteria,[51] Compton et al.[33] acknowledged the challenging task of determining whether or not a CNCP patient who is physically dependent on opioids is in fact addicted. Because the DSM-IV criteria for substance dependence were still heavily weighted toward the presence of physical dependence and tolerance, some CNCP patients could meet these criteria without actually being addicted, and conversely, some who were addicted may not (Table 1). To overcome these problems, Compton et al. introduced a multiple-item screening questionnaire.[33] Responses of known addicted patients differed significantly from those of nonaddicted patients as demonstrated by total questionnaire scores in a sample of 52 patients.[33]

American Society of Addiction Medicine

The American Society of Addiction Medicine (ASAM) public policy statement on definitions related to the use of opioids in pain treatment highlights the unreliability of the now commonly used DSM-IV criteria for diagnosing opioid use disorder in pain patients.[36] These same shortcomings can also be noted in the WHO-ICD-10. As noted, both DSM-IV[51] and WHO-ICD-10[50] lack a definition for "addiction," and both quote the potential for drug tolerance and physical dependence in their equivalent diagnoses for addiction, "Opioid Dependence" and "Dependence Syndrome," respectively.[36] The ASAM defines addiction as a primary, chronic, neurobiological disease, characterized by one or more of the following types of behavior: impaired control over drug use, compulsive use, and continued use despite harm and drug craving.[36]

REGULATORY AND INVESTIGATIVE POLICIES

"Dangerous gap"

The United States federal government is currently focusing on problematic drug use associated with the prescription of opioids for CNCP, although it has been noted that there remains a "dangerous gap" in the medical literature.[53] Resulting in confusion and anxiety, this gap is now exacerbated by the US Drug Enforcement Administration's (DEA) regulatory and investigative policies.[9] The debate and media stories regarding ongoing prosecutions of physicians who prescribe opioids are highlighted by the Pain Relief Network (PRN), an organization which focuses on US law enforcement agencies' increasing role in contributing to the undertreatment of pain due to irrational fears of problematic drug use.[54] The PRN claims that it is becoming increasingly clear that patients in pain who are dependent on opioid medications to function are being targeted by law enforcement agencies to increase their conviction statistics, and that pain clinics are being targeted by state and federal agencies and summarily shut down.[54] Patient records are

being removed from doctors' offices, and the patients themselves essentially abandoned by society, unable to find replacement care.[54]

Drug Enforcement Administration's action on OxyContin

Illustrating the aforementioned regulatory difficulty, several interesting points were raised by Ronald T. Libby in a piece titled, "The DEA's OxyContin Action Plan: An Unproven Drug Epidemic."[54] Libby cites the US Government Accountability Office's highly critical report in 1999, stating the DEA had no measurable proof that it had reduced the illegal drug supply in the United States.[55] The US Department of Justice also gave the DEA a negative evaluation, concluding that its goals were not consistent with the federal National Drug Control Strategy and questioning why the DEA was not doing more to combat prescription drug abuse.[56] In 2001, the DEA responded to this criticism by announcing a major new campaign, the "OxyContin Action Plan,"[57] claiming that OxyContin was responsible for a deadly drug epidemic spreading throughout rural America.[58]

However, Libby cited the use of questionable methodology by the DEA in the collection of their data on so-called "OxyContin-verified" deaths, noting that most of the decedents had multiple drugs in their bodies.[54] More than 40 percent of the autopsy reports contained benzodiazepines, approximately 40 percent contained an opioid in addition to oxycodone, 30 percent contained an anti-depressant, 15 percent contained cocaine, and 14 percent contained over-the-counter antihistamines or cold medications—therefore, death could have been attributed to any number of drugs or combination of drugs or diseases.[54] In addition, Libby suggested there are problems with the DEA's estimate of death risk.[54] With Libby's calculations of eight deaths (0.00008 percent) for every 100,000 OxyContin prescriptions, and with an average of 2.5 of these as verified deaths and 5.5 likely related deaths, it is somewhat ambitious to claim that these low numbers constitute a deadly prescription drug epidemic.[54]

Despite this, ongoing DEA drug diversion investigations focus on physicians who prescribe high levels of OxyContin and other opioids to alleged "addicts."[54] The DEA defines addicts as individuals who habitually use any narcotic drug that endangers the public morals, health, safety, or welfare; this, according to Libby, leads to the mistaken belief that CNCP patients who are prescribed large amounts of opioids are addicts, and that physicians who treat them are conspirators in the illegal drug trade.[54] Similar to the 19th Century, we still see a hybrid mixture of moral and health concerns. The DEA takes the position that narcotics such as OxyContin should be the drug of "last resort for chronic pain."[59] However, Libby advocated that determining whether a pain patient is an "addict" and whether OxyContin is "medically necessary" in treating chronic pain is clearly beyond the expertise and mission of the DEA.[54]

However, if medical specialists still cannot agree among themselves what is meant by addiction and drug dependence and sometimes fail to acknowledge the differences between therapeutic dependence, physical dependence, and psychological dependence, then it can hardly be expected that law enforcement agencies and lay juries will be able to make this distinction. In the meantime, opioid-maintained CNCP patients continue to be labeled as junkies, addicts, or abusers, sometimes based merely on their time-scale of opioid use.[34,54,60-62]

"TERMINOLOGICAL MINEFIELD"

Bearing out Fishbain et al.'s prediction made more than 10 years ago,[2] the continuation of the problematic use of terminology is highlighted in a recently published book.[63] *Living with Drugs*, by Professor Gossop of the National Addiction Centre in London, gives a historical perspective on drug use and discusses the use, effects, social context, and control of some common contemporary drugs such as alcohol, tobacco, cannabis, LSD, and heroin. While Gossop indicates that in this particular book he prefers to examine the issues of drugs and drug taking themselves rather than the language used to talk about them, by way of an "Author's Apologia," Gossop indicates that the words used to describe drug taking confront us with a "terminological minefield."[63] Gossop notes that the word "addiction" is strongly disliked by many because of its implied "excess meaning" but sees a place for the term as it captures something of the element of compulsion to use drugs, which has underlying physiological foundations—although he sees it as describing a learned psychological process.[63] Gossop notes further that there is a lobby that objects to the term "syndrome" being used in relation to dependence because it has medical connotations.[63] There should be no objection to such medical connotations, however, if we are talking about a diseased state.

DISEASE OR NOT?

Once again, this takes us back to the 19th century root of the problem. In disputing that addiction really is a disease, Schaler suggests that the disease model has previously been mistakenly applied in judging the moral conduct of those who society conveniently sought to control or marginalize through "treatment."[37] For example, it was not until 1973 that the American Psychiatric Association—which defines the disease of "substance dependence" in DSM-IV[51]—declassified homosexuality as a disease.[37] Clearly, to avoid confusion and contradiction, the decision to classify something as a disease must be underpinned by robust evidence and in some cases

regularly reviewed. Such a review is now required regarding the concepts of addiction and dependence. While ASAM defines addiction as a primary, chronic, neurobiological disease,[36] according to the WHO classification of diseases,[50] the disease of addiction apparently does not exist, yet there is a classification for "dependence syndrome."[50] This lack of clarity gives rises to the question, which is really the disease: addiction, dependence, both, or neither?

TIME FOR NEW DIAGNOSTIC CRITERIA

The ASAM acknowledges that its definitions do not constitute formal diagnostic criteria but hopes that they may serve as a basis for future development of more specific, universally accepted diagnostic guidelines.[36] Indeed, the ASAM advocates that universal agreement on definitions of addiction, physical dependence, and tolerance is critical to the optimal treatment of pain and management of disorders arising from addiction and continues to work toward this end with the American Academy of Pain Medicine and the American Pain Society.[36]

In current practice, the term "addiction" is commonly used to impose a category, resulting in people being labeled as "addicted" or "not addicted." This type of categorization prevents any possibility of viewing people as being anywhere in between. Clearly, this is a problem that the WHO had sought to overcome in defining "dependence syndrome" as existing in degrees, with compulsion to use drugs at the extreme end of a spectrum.[50] However, it is still unusual for professionals to refer to people as being "slightly" or "severely" addicted.

It is time to start advancing through the aforementioned "terminological minefield" to try and formulate new diagnostic criteria. For example, a new classification of psychological opioid dependence syndrome (PODS) may be useful. This could be characterized by one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and drug craving. This could be further qualified by items such as those suggested by Portenoy,[29] Sees and Clark,[30] Compton et al.,[33] Chabel et al.,[49] and Wesson et al.[52] in the form of a checklist, and thus graded in degrees of severity. Also, it could be noted whether other phenomena such as physical dependence and tolerance are present or not. Although physical dependence and tolerance are separate entities, they can nonetheless be problematic. However, before this can happen, further clarification and agreement is also needed as to whether we are describing a diseased state, this being all of the time or perhaps just some of the time.

CONCLUSION

Clearly, the use of correct terminology pertaining to problematic opioid drug use is fraught with difficulties. This is particularly so with regard to CNCP patients but also applies to wider recreational drug use. The unstable foundation of the 19th century hybrid moral-scientific theory that underlies the concept of addiction has resulted in failure to reach a consensus on the application of correct terminology. This has been exacerbated over the years by the continued application of inappropriate, inadequate, and unreliable criteria, which have been used by many as "gold standard" definitions. Furthermore, to compound the problem, inappropriate methodology has been applied in seeking to determine the prevalence of problematic opioid drug use, including death rates.

These issues have clear implications for the discipline of pain medicine and contribute to the difficulties of assessing for problematic drug use among CNCP patients. The question as to whether or not there exists a class of long-term, unproblematic, opioid-maintained CNCP patient remains unresolved and is central to the present controversy. Before conclusive research into the long-term effects of opioids in CNCP patients can be undertaken on a large scale, however, universal agreement is required on the application of terminology with regard to precisely what terms are to be used, how such terms are defined, and if they are to be graded according to severity. Such agreement will in turn need to be underpinned by additional research, for example, further studies that build on the earlier cited work by Fishbain et al.,[2] Portenoy,[29] Sees and Clark,[30] Kouyanou et al.,[31] Compton et al.,[33] Chabel et al.,[49] and Wesson et al.[52]

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ORIGINAL ARTICLE

Opioids in the parturient with chronic nonmalignant pain: A retrospective review

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ABSTRACT

The purpose of this research was to determine the neonatal outcomes of women who had been taking medically prescribed opioids throughout their pregnancy. A retrospective case study was done of 15 pregnancies associated with maternal opiate use between January 1, 1999, and September 30, 2002. Two cases were excluded due to coaddiction. Neonatal data were collected including gestational age, head circumference, length, birth weight, Apgar score at one and five minutes, details of resuscitation required, and Neonatal Abstinence Score. There were 13 pregnancies, which resulted in 13 live births; opioids prescribed included oxycodone, codeine, meperidine, fentanyl, dilaudid, morphine, and methadone. There were four babies with one-minute Apgar score = 5, and two babies with five-minute Apgar score = 5. It was concluded that neonatal growth markers in this population were within normal limits as plotted on the standard growth and development record of Gairdner-Pearson. Five out of 13 (38.5 percent) neonates were diagnosed with opioid discontinuation syndrome.

Key words: opioids, prescription, pain, pregnancy, neonatal development

INTRODUCTION

The use of opioids for chronic nonmalignant pain is becoming more widely accepted, spurred by evidence from clinical trials and an evolving consensus among pain physicians.[1,2] The appropriate use of these drugs requires skill in prescribing, knowledge of addiction medicine principles, and commitment to perform and document repeated assessments.

Most of the literature on maternal and neonatal effects of opioids has dealt with an addicted population.[3] Commonly abused substances during pregnancy include alcohol, nicotine, opioids, cocaine, heroin, and benzodiazepines. The use of these drugs has been associated with an increased incidence of spontaneous abortion, abruption placenta, congenital malformation, fetal growth retardation, low birth weight, and infections such as human immunodeficiency virus.[4] Problems associated specifically with heroin use during pregnancy include first trimester spontaneous abortion, premature delivery, meconium stained liquor, maternal/neonatal infection, and opioid discontinuation syndrome.[5,6]

The purpose of this study was to review neonatal outcomes of women who had been taking medically prescribed opioids throughout their pregnancy. We are not aware of any previously published study focusing on the use and effects of opioids for chronic nonmalignant pain management in pregnancy.

MATERIALS AND METHODS

The perinatal and neonatal databases from St. Joseph's Health Care, the tertiary perinatal referral center in southwestern Ontario, Canada, were searched from January 1, 1999, to September 30, 2002. Fifteen pregnancies associated with a chronic pain diagnosis and taking of prescription opioids were identified in that time period. On reviewing the chart, opioid use was ascertained by the referral letter from the patient's general practitioner or by the attending physician's notes at the first antenatal visit. Pregnant women with documented coaddiction disorder (e.g., cocaine) were excluded from the study.

The following maternal data were collected: age, height, weight, parity, obstetric and medical antenatal risk factors, smoking/alcohol history, pain syndrome diagnosis, all medication doses including opioids, methods of labor analgesia, and mode of delivery.

Neonatal variables collected were gestational age, birth weight, length, head circumference, Apgar score at

Table 1. Maternal and neonatal characteristics

Patient	Diagnosis	Medication	Mode of delivery	Neonatal gestational age (wk)	Neonatal weight (g)	Apgar 1 min	Apgar 5 min
1	Fibromyalgia	Oxycodone/acetaminophen	C/S	39 + 1	2,910	8	8
2	Crohn's disease	Meperidine	C/S	39 + 6	3,180	6	9
3	Crohn's disease	Fentanyl patch/meperidine	C/S	36	2,460	9	9
4	Severe rheumatoid arthritis	Tylenol #3 (acetaminophen 325 mg/codeine 30 mg)	C/S	28 + 1	920	1	5
5	Chronic back pain	Oxycodone/acetaminophen	Vaginal	28 + 4	1,130	7	8
6	Bone pain	Morphine	Vaginal	35 + 6	2,180	9	6
7	Degenerative disc disease	Tylenol #3	Vaginal	38	3,115	5	9
8	Chronic back pain	Oxycodone/acetaminophen	Vaginal	39 + 4	2,665	5	7
9	Chronic pelvic pain	Oxycodone/acetaminophen/ meperidine	Vaginal	38 + 2	4,630	0	5
10	Degenerative disc disease/scoliosis	Oxycodone/acetaminophen/ meperidine	Vaginal	36 + 6	2,475	8	9
11	Chronic hip pain	Codeine oxycodone/ acetaminophen	Vaginal	40 + 3	2,305	8	9
12	Chronic abdominal pain	Fentanyl patch/oxycodone/ acetaminophen	Vaginal	41 + 2	3,965	9	9
13	Chronic osteomy elitis	Meperidine/MS contin	Vaginal	38 + 3	3,675	6	8

C/S, Caesarean section.

one and five minutes, umbilical venous/arterial gases, Neonatal Abstinence Score (NAS), urine/meconium drug screen, administration of naloxone, need for mechanical ventilation, and duration of ventilatory support.

After delivery, NAS was performed using a scale from 1 to 5 (adapted from Finnegan LP, 1986). The NAS score is used to determine when to initiate therapy as well as monitoring therapeutic effects. A NAS of greater than 8 is deemed to be significant, and treatment is usually commenced with oral morphine according to a standardized regime. The scoring system, consisting of 21 signs and symptoms commonly seen in the neonate born to pregnant women who were on opioid treatment, is a comprehensive and precise way of permitting an objective estimate of the withdrawal syndrome. Each symptom is assigned a score based on severity observed over a period of time. Decision to admit to the Neonatal Intensive Care Unit (NICU) was at the discretion of the neonatal team. The duration of admission was recorded.

RESULTS

Two cases were excluded due to coaddiction, leaving 13 for analysis. Table 1 provides demographic information based on maternal data. Opioids prescribed included a range or a combination of the following: morphine, fentanyl patch, meperidine, codeine, and oxycodone.

All opioids were taken throughout the pregnancy; however, the exact doses were difficult to determine because the study is retrospective and doses were missing

Table 2. Mean neonatal growth markers, Apgar, and NAS in study subjects (N = 13)						
Mean gestational age (wk)	**Mean weight (g)**	**Mean head circumference (cm)**	**Mean length (cm)**	**Number of patients with one-min Apgar = 5**	**Number of patients with five-min Apgar = 5**	**Abstinence score > 8 on day one**
37 ± 1	2,739 (920 to 4,630); SD = 1,035	32.8 (26.0 to 35.5); SD = 3.0	46 (31 to 55) SD = 5.7	4	2	5*

* Two patients were intubated and unable to be scored. Numbers in parentheses indicate ranges. NAS, Neonatal Abstinence Score; SD, standard deviation.

from the patient data. The antenatal care was supplemented by psychiatric or psychological counseling and social worker input where necessary. A consult to a pain specialist was often made.

Table 2 summarizes the neonatal data of the 13 live births. Mean gestational age was 37 ± 1 weeks, mean birth weight was 2,739 ± 1,035 g, mean head circumference was 32.8 ± 3.0 cm, and mean length was 46 ± 5.7 cm. After obtaining the mean for neonatal growth markers (length, head circumference and weight), we plotted the results on the standard growth and development record (Gairdner-Pearson 1988). All were within normal limits. Four out of 13 neonates had an Apgar score equal or less than 5 at one minute, two of which required active resuscitation and subsequent NICU admission. Opioid reversal (using Naloxone) was never given during resuscitation because it was not felt to be indicated.

There were a total of five neonates who had a NAS equal to or more than 8, which required NICU admission with subsequent initiation of assessment and oral morphine treatment protocol.

DISCUSSION

The results of this small retrospective study of neonatal outcomes in women taking medically prescribed opioids are reassuring in that neonatal growth markers were within normal limits; this is in contradistinction to previous retrospective reviews, which indicated low birth weights and prematurity in heroin-addicted mothers. The exact Canada-wide prevalence of opioid exposure in pregnancy is unknown. However, estimates range between 1 and 3 percent.[7,8] In utero exposure to opioids is associated with abstinence symptoms in 55 to 94 percent of exposed infants.[9]

All infants born to known opioid-dependent women should be initially observed in the high-risk nursery for observation of neonatal abstinence symptoms. Affected infants can require treatment for many days, leading to a prolonged stay in the NICU. This has a major impact not only on maternal and infant bonding but also on bed occupancy. In one institution in Dublin, Ireland, three neonatal beds were always occupied by infants with NAS.[10]

Studies examining growth are frequently difficult to interpret because of high attrition rates and the compounding social factors that contribute to intrauterine growth retardation. In one series, some catch-up growth was demonstrated, but persistent poor weight gain at age one year correlated with methadone usage during pregnancy.[11]

The literature suggests there may be potential risks of maternal exposure to opioids other than intrauterine growth retardation. Infants of pregnant patients taking opioids, particularly methadone, have a two to three times increased risk of unexplained sudden death in infancy,[12] possibly owing to abnormal respiratory control. Sorensen et al. studied the relationship between prenatal exposure to analgesics, both opioid and nonopioid, and the risk of schizophrenia, using data from perinatal cohort and from the Danish Psychiatric Central Register. They concluded that there was a four-fold greater risk of schizophrenia in those children who were exposed to an analgesic in the second trimester.[13]

Developmental outcome may be impaired in infants of women who abuse drugs, as indicated by the wide variety of mild cognitive effects in preschool children reported by researchers using the Bayley scales of mental development.[14] Children born to pregnant patients maintained on methadone have been suggested to be more likely to show poor development, further compounded by factors associated with drug misuse such as smoking; alcohol misuse; and poor nutrition, housing, and education. Examination of children aged 36 months, however, highlighted that some children appear to be resistant to the effects of maternal drug use, as they had developed appropriately.[15]

Lester et al. studied the effects of prenatal cocaine and/or opiate exposure on auditory brain response in infants at one month.[16] Infants with prenatal opiate exposure (n = 477) showed a longer absolute and interpeak latency than control infants matched for race, gender, and gestational age (n = 554). However, the authors concluded that determination of the clinical significance of these effects required a larger sample with control for gestational age, other drugs, and level of cocaine use.

In conclusion, this small study suggests that maternal

use of opioids may be safe for the neonate if medically prescribed. However, opioid discontinuation syndrome is common and usually requires specialized treatment in a NICU. Long-term implications of in utero opioid exposure remain a concern. Further research incorporating a multicenter database with follow-up over five to seven years is necessary to ensure that this modality of treatment is safe for the pregnant woman.

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ORIGINAL ARTICLE

Barriers and facilitators to methadone maintenance therapy use among illicit opiate injection drug users in Vancouver

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ABSTRACT

Methadone maintenance therapy (MMT) has been increasingly implemented as the treatment of choice for opiate-addicted individuals and has been associated with reduced harm related to opiate addiction. Barriers to MMT uptake still exist, however, and many opiate-addicted individuals do not access this form of treatment.

We examined barriers to and facilitators of MMT access among opiate users enrolled in a prospective cohort study of injection drug users (IDUs). We identified individuals who had initiated MMT during follow-up interviews and used generalized estimating equations to identify sociodemographic and drug-related variables associated with MMT access.

Of the 1,587 participants recruited into the Vancouver Injection Drug User Study, 1,463 individuals were eligible for the present analysis. Factors negatively associated with MMT use included male gender (odds ratio [OR] = 0.41; 95 percent confidence interval [CI], 0.32 to 0.52), Aboriginal ethnicity (OR = 0.37; 95 percent CI, 0.29 to 0.48), recent incarceration (OR = 0.82; 95 percent CI, 0.72 to 0.93), Downtown Eastside residence (OR = 0.86; 95 percent CI, 0.75 to 0.97), sex-trade involvement (OR = 0.80; 95 percent CI, 0.67 to 0.95), syringe lending (OR = 0.76; 95 percent CI, 0.66 to 0.89), denied addiction treatment (OR = 0.81; 95 percent CI, 0.68 to 0.96), heroin injection (OR = 0.51; 95 percent CI, 0.44 to 0.59), nonfatal overdose (OR = 0.59; 95 percent CI, 0.51 to 0.68), and injecting in public (OR = 0.75; 95 percent CI, 0.63 to 0.89). Older age (OR = 1.03; 95 percent CI, 1.01 to 1.04), human immunodeficiency virus (HIV) positivity (OR = 1.89; 95 percent CI, 1.52 to 2.23), and crack cocaine smoking (OR = 1.41; 95 percent CI, 1.22 to 1.62) were positively associated with MMT use.

Our study identified a large number of barriers to and facilitators of MMT use among IDUs. While some populations such as HIV-positive individuals are frequently accessing MMT, identified barriers among men and Aboriginal IDUs are of great concern. These findings indicate the need for additional interventions aimed at maximizing coverage of MMT and other treatments for opiate-addicted individuals.

Key words: methadone maintenance therapy, injection drug use, opiate addiction, treatment

INTRODUCTION

The high rates of opiate addiction in Vancouver, British Columbia, is of particular concern due to the array of health and social harms associated with illicit injection drug use, including high rates of human immunodeficiency virus (HIV), hepatitis C, and overdose deaths.[1-3] One treatment option for opiate-addicted individuals is methadone maintenance therapy (MMT). Methadone is a synthetic opiate with a half-life of approximately 24 to 36 hours, which allows for once-daily administration. MMT has been widely recognized and implemented as the treatment of choice for reducing the harms associated with opiate addiction.[4-9]

MMT has been shown to be successful in blocking the effects of opiate withdrawal symptoms and the euphoria produced by opioids, such as heroin, and may correct and stabilize a lesion or defect in the endogenous opioid system.[10-12] Consequently, MMT is the most cost-effective strategy for reducing major risks, harms, and costs associated with untreated opiate addiction among patients attracted to and successfully retained in MMT.[9,13,14] Retention in MMT has been associated with reductions in, and even the elimination of, use of opiates,[15-20] as well as reductions in criminal activity, unemployment, and mortality rates.[15,16,21-26] MMT has also been shown to reduce

HIV and viral hepatitis transmission rates.[23,27-30] Reductions in risk behaviors, including needle sharing, number of sexual partners, engaging in sex without condom use, and exchange of sex for drugs or money have also been demonstrated.[18,31-34]

Despite considerable evidence to support the efficacy of MMT,[5,15] problems with uptake of MMT, as well as its limited success in retaining patients in treatment, remain major concerns. Studies of community-treated opiate addicts indicate that MMT programs may lose one-third of their original treatment population within the first 12 months and another one-third within the following 24 months.[35,36] Barriers to MMT uptake were examined in a cohort of opiate users in Toronto, Ontario, and the findings indicated that homelessness, illegal income generation, illicit opiate and other drug use, illicit drug market activities, and increased use of emergency care were more common among those who did not access treatment.[12]

While there are numerous studies examining patient retention in and treatment outcomes from MMT, data examining barriers to MMT are lacking.[37] Additionally, the majority of evaluations of MMT efficacy that have been presented have a number of key limitations. In particular, these studies have generally been restricted to clinic-based populations that are willing to initiate MMT[38] and who are retained in treatment long enough for outcomes to be evaluated.[39] We therefore undertook the present study to evaluate the barriers to MMT use among opiate users within a community-recruited cohort of injection drug users (IDUs) in Vancouver.

METHODS

The Vancouver Injection Drug User Study (VIDUS) is a prospective study of injection drug using individuals who have been recruited through self-referral and street outreach from Vancouver's Downtown Eastside since May 1996. The cohort has been described in detail previously.[3,40] Briefly, persons were eligible if they had injected illicit drugs at least once in the previous month and resided in the greater Vancouver region. At baseline and semiannually, subjects provided blood samples and completed an interviewer-administered questionnaire. The questionnaire elicited demographic data, as well as information about drug use, HIV risk behavior, and enrollment into addiction treatment. All participants provided informed consent and were given a stipend ($20 Canadian) at each study visit. The study was approved by the University of British Columbia's Research Ethics Board.

The present analyses included participants who were enrolled in the VIDUS cohort between May 1, 1996, and May 30, 2004. Current guidelines specify that MMT provision should be restricted to individuals addicted to opiates, and therefore the sample was restricted to individuals who reported opiate use of some kind in the six months before their interview. In total, 1,463 individuals in the VIDUS cohort were identified as eligible for MMT during follow-up.

The primary endpoint in this analysis was access to MMT during the previous six months. Explanatory variables of interest in this analysis included sociodemographic information: gender, age, Aboriginal ethnicity (yes/no), and unstable housing. As in previous analyses,[3] unstable housing was defined as living in hotels, hostels, or recovery houses, or being homeless. The drug use variables considered refer to behaviors in the past six months, and included heroin and cocaine injection, crack cocaine smoking, nonfatal overdose, injecting in public, and borrowing and lending used syringes. Also, as in our previous analyses,[3] the variables for cocaine and heroin injection and crack smoking were defined as "daily" versus "nondaily" use. Other risk characteristics considered included sex-trade involvement and incarceration in the past six months, being denied addiction treatment, residing in the Downtown Eastside (i.e., Vancouver's illicit drug use and HIV epicenter), having a history of sexual abuse, and HIV sero status (positive/negative).

Our analyses of factors potentially associated with MMT use during follow-up included serial measures for each subject; we used generalized estimating equations (GEE) for binary outcomes with logit link for the analysis of correlated data to determine which factors were independently associated with reporting MMT use throughout the follow-up period. These methods provided standard errors adjusted by multiple observations per person using an exchangeable correlation structure. This approach has been used successfully in previous studies examining correlates of addiction treatment access in prospective cohort studies of IDUs.[41] Variables potentially associated with MMT use were examined in bivariate GEE analyses. To adjust for potential confounding, we also fit a multivariate GEE model using an a priori defined model-building protocol of adjusting for all variables that were statistically significant at the $p < 0.05$ level in bivariate analyses. All statistical analyses were performed using SAS software version 8.0 (SAS Inc., Cary, NC). All p values are two sided.

RESULTS

In total, 1,587 participants were recruited into the VIDUS cohort between May 1, 1996, and May 30, 2004. This sample for this analysis was, however, restricted to 1,463 individuals who reported using opiates at baseline or during follow-up. Among these participants were 538 (36.8 percent) women and 389 (26.6 percent) individuals of Aboriginal ethnicity. The median age of the sample was 33.2 years (interquartile range, 25.6 to 39.9). Overall, these participants contributed to 7,006 observations during the follow-up period, and the median number of follow-up

Table 1. Bivariate and multivariate generalized estimating equation of factors associated with methadone maintenance therapy use during follow-up (n = 1,463)

Characteristic	Unadjusted OR (95 percent CI)	p value	Adjusted OR (95 percent CI)	p value
Older age (per year older)	1.04 (1.03 – 1.05)	< 0.001	1.03 (1.01 – 1.04)	< 0.001
Gender (male vs. female)	0.60 (0.50 – 0.73)	< 0.001	0.41 (0.32 – 0.53)	< 0.001
Aboriginal ethnicity (yes vs. no)	0.54 (0.43 – 0.68)	< 0.001	0.37 (0.29 – 0.48)	< 0.001
HIV positivity (yes vs. no)	2.23 (1.86 – 2.69)	< 0.001	1.89 (1.52 – 2.23)	< 0.001
Homelessness (yes vs. no)	0.74 (0.62 – 0.89)	0.001	0.86 (0.71 – 1.05)	0.141
Incarceration* (yes vs. no)	0.67 (0.59 – 0.76)	< 0.001	0.82 (0.72 – 0.93)	0.002
DTES residency** (yes vs. no)	0.79 (0.70 – 0.90)	0.004	0.86 (0.75 – 0.97)	0.018
Sex-trade involvement* (yes vs. no)	0.73 (0.61 – 0.87)	0.003	0.80 (0.67 – 0.95)	0.011
Borrowed syringes* (yes vs. no)	0.62 (0.54 – 0.72)	< 0.001	0.88 (0.76 – 1.02)	0.086
Lent syringes* (yes vs. no)	0.58 (0.50 – 0.68)	< 0.001	0.76 (0.66 – 0.89)	0.003
Denied addiction treatment* (yes vs. no)	0.66 (0.56 – 0.78)	< 0.001	0.81 (0.68 – 0.96)	0.016
Daily heroin injection* (yes vs. no)	0.47 (0.41 – 0.54)	< 0.001	0.51 (0.44 – 0.59)	< 0.001
Daily cocaine injection* (yes vs. no)	0.73 (0.65 – 0.83)	< 0.001	0.95 (0.84 – 1.08)	0.473
Daily crack smoking (yes vs. no)	1.35 (1.19 – 1.54)	< 0.001	1.41 (1.22 – 1.62)	< 0.001
Nonfatal overdose* (yes vs. no)	0.51 (0.44 – 0.58)	< 0.001)	0.59 (0.51 – 0.68)	< 0.001
Sexual abuse (yes vs. no)	1.43 (1.19 – 1.72)	0.002	1.18 (0.94 – 1.49)	0.155
Injecting in public* (yes vs. no)	0.66 (0.56 – 0.77)	< 0.001	0.75 (0.63 – 0.89)	0.008

CI, confidence interval; OD, odds ratio. *Denotes activities/events in the previous six months; ** DTES, Downtown Eastside.

visits was 5.6. Use of MMT was reported for 2,362 (33.7 percent) of all observations, and by 623 (42.6 percent) individuals.

The bivariate GEE analyses shown in Table 1 indicate that all sociodemographic and drug use factors considered were significantly associated with MMT. Factors positively associated with MMT use included: older age (odds ratio [OR] = 1.04; 95 percent confidence interval [CI], 1.03 to 1.05), HIV positivity (OR = 2.23; 95 percent CI, 1.86 to 2.69), crack cocaine smoking (OR = 1.35; 95 percent CI, 1.19 to 1.54), and a history of sexual abuse (OR = 1.43; 95 percent CI, 1.19 to 1.72). Factors negatively associated with MMT use included male gender (OR = 0.60; 95 percent CI, 0.50 to 0.73), Aboriginal ethnicity (OR = 0.54; 95 percent CI, 0.43 to 0.68), homelessness (OR = 0.74; 95 percent CI, 0.62 to 0.89), recent incarceration (OR = 0.67; 95 percent CI, 0.59 to 0.76), Downtown Eastside residence (OR = 0.79; 95 percent CI, 0.70 to 0.90), sex-trade involvement (OR = 0.73; 95 percent CI, 0.61 to 0.87), syringe borrowing (OR = 0.62; 95 percent CI, 0.54 to 0.72), syringe lending (OR = 0.58; 95 percent CI, 0.50 to 0.68), having been denied addiction treatment (OR = 0.66; 95 percent CI, 0.56 to 0.78), daily heroin injection (OR = 0.47; 95 percent CI, 0.41 to 0.54), daily cocaine injection (OR = 0.73; 95 percent CI, 0.65 to 0.83), nonfatal overdose (OR = 0.51; 95 percent CI, 0.44 to 0.58), and injecting in public (OR = 0.66; 95 percent CI, 0.56 to 0.77).

In the multivariate GEE analysis shown in Table 1,

factors that were positively associated with MMT use included older age (OR = 1.03; 95 percent CI, 1.01 to 1.04), HIV positivity (OR = 1.89; 95 percent CI, 1.52 to 2.23), and crack cocaine smoking (OR = 1.41; 95 percent CI, 1.22 to 1.62). Factors negatively associated with MMT use included male gender (OR = 0.41; 95 percent CI, 0.32 to 0.53), Aboriginal ethnicity (OR = 0.37; 95 percent CI, 0.29 to 0.48), recent incarceration (OR = 0.82; 95 percent CI, 0.72 to 0.93), Downtown Eastside residence (OR = 0.86; 95 percent CI, 0.75 to 0.97), sex-trade involvement (OR = 0.80; 95 percent CI, 0.67 to 0.95), syringe lending (OR = 0.76; 95 percent CI, 0.66 to 0.89), having been denied addiction treatment (OR = 0.81; 95 percent CI, 0.68 to 0.96), daily heroin injection (OR = 0.51; 95 percent CI, 0.44 to 0.59), nonfatal overdose (OR = 0.59; 95 percent CI, 0.51 to 0.68), and injecting in public (OR = 0.75; 95 percent CI, 0.63 to 0.89). We also conducted a subanalysis in which we restricted the sample to those individuals who were not receiving MMT at baseline. The results of the final model were unchanged in this analysis.

DISCUSSION

In the present study, 42.6 percent of all eligible individuals had accessed MMT, and a number of barriers to and facilitators of MMT use were identified. Factors negatively associated with MMT use included male gender, Aboriginal ethnicity, recent incarceration, Downtown Eastside residency, sex-trade involvement, being denied addiction treatment, syringe lending, heroin injection, nonfatal overdoes, and injecting in public, while HIV-positive status, frequent crack cocaine use, and older age were independently and positively associated with MMT use. Despite the high uptake of MMT among local IDUs, a high proportion of opiate users in this study have never accessed MMT. This finding is of concern given the substantial health-related harms associated with untreated opiate addiction that have been identified previously.[12]

Male gender was the characteristic most strongly associated with failure to access MMT in this analysis, with our results suggesting that men are approximately 60 percent less likely than women to have accessed MMT. This result is consistent with findings from a previous study of MMT use in a cohort of IDUs in Baltimore[38] and findings from Vancouver,[42] which indicate men are less likely to initiate addiction treatment than women. However, further investigation of the association between gender and MMT use is needed in our setting to explain this result and inform efforts aimed at attracting and retaining male IDUs in treatment.

The finding that Aboriginal IDUs in this cohort were considerably less likely than non-Aboriginal IDUs to use MMT is of particular concern due to the well-noted protective effects of MMT against HIV infection and evidence indicating that Aboriginal IDUs in Vancouver are at heightened risk for HIV infection.[43] It is possible that low uptake of MMT among Aboriginal IDUs reflects a lack of culturally appropriate addiction treatment programs.[44] Low uptake of MMT among Aboriginal IDUs may be further explained by the emphasis on abstinence-based addiction treatment models in Aboriginal communities in Canada.[45] These explanations have not, to our knowledge, been thoroughly examined, and therefore there is a need to more closely examine barriers to MMT uptake among Aboriginal IDUs in Vancouver and elsewhere.

The finding of a negative association between recent incarceration and MMT use may be interpreted in several ways. Participants in this study were asked to indicate whether they had been incarcerated in the previous six months, and therefore the observed association of lower MMT use among those recently incarcerated could be explained by the well-noted impact of MMT in reducing criminal behavior (and, hence, lower rates of incarceration),[15,22] or could alternatively be interpreted as incarceration acting as a barrier to the initiation of MMT.[46] It is important to note that policies are now in place that allow individuals to begin or continue MMT within Canadian correctional settings[47]; however, previous research has demonstrated that difficulties exist in accessing and continuing MMT within prisons.[46] Because of the aforementioned issues, the association between incarceration and MMT use needs to be investigated further.

Similar concerns regarding possible reverse causality apply to the observed association between MMT use and sex-trade involvement. Previous studies have associated MMT use with reduced participation in sex-trade work[33,48]; however, barriers to addiction treatment have also been identified among this population.[49] Given previously observed associations between sex-trade work and increased engagement in various risk behaviors, the observation of lower uptake of MMT among this population is of particular concern.[50,51] As such, further study of the association between sex-trade involvement and potential barriers to MMT use is needed in Vancouver and elsewhere. Despite this limitation, the observed negative associations between heroin use, syringe lending, occurrence of nonfatal overdose, injecting in public, and MMT is more likely representative of the benefits rather than barriers to access of MMT. This is likely given that the most consistently noted benefits of MMT are the reductions in heroin use and injection-related risk behaviors (e.g., syringe sharing).[18,52,53] The negative association between being denied addiction treatment and MMT use is also of particular concern. This relationship may be explained by individuals simply being denied MMT on seeking it; however, this association requires further investigation given evidence indicating that individuals who are unable to access addiction treatment are at a heightened risk for HIV infection.[54]

HIV positivity was most strongly associated with MMT use in this analysis, a finding consistent with a recent analysis involving Vancouver IDUs that showed an elevated rate of initiation of HIV treatment among IDUs receiving methadone.[55] These findings may also reflect an increased motivation on the part of healthcare providers to pair MMT with the provision of HIV medications, as this has been shown to improve patient adherence to the HIV medications.[56,57] Similarly, a positive association between MMT use and crack cocaine smoking was also observed and is somewhat surprising, given that cocaine use has typically been associated with a greater likelihood of discharge from MMT.[58,59] MMT has been shown to reduce use of stimulants in some studies[60,61]; however, this reduction in stimulant use has only been observed in studies of individuals who were retained in treatment.[62] One potential explanation is that on accessing MMT and discontinuing opiate injection, some individuals may substitute crack smoking for cocaine injection to further reduce or eliminate injection-related risks. Additionally, it is possible that some individuals use crack cocaine simply to "get high," which is an effect that they were getting with heroin but are lacking with methadone. Further examination of these issues is necessary to validate these interpretations.

The findings observed here are highly consistent with a previous report from our setting that examined MMT use among polysubstance users.[63] This, coupled with the fact that numerous opiate-addicted individuals are eligible for MMT, but fail to uptake treatment, suggests further work focused on identifying the distinct barriers to MMT use among opiate users is needed. Additionally, further consideration should be given to other opiate-dependence treatment modalities. One possible approach is heroin prescription treatment, which has been implemented with some success in Europe and is currently being evaluated in three major Canadian cities.[64,65] Furthermore, evidence of poor retention in opiate replacement therapies also indicates a need for increased coverage and uptake of nonsubstitution-based inpatient and outpatient opiate addiction treatments.

This study has several limitations. First, there are the aforementioned concerns related to the timing of measurement. While the statistical method used proved to be effective for accommodating individual data in which MMT use was initiated on multiple occasions, it is not known whether some of the observed associations reflect a consequence of MMT use, as behaviors could have occurred after MMT was initiated. However, it is important to emphasize that this limitation does not apply to the strongest associations in this study (e.g., male gender, Aboriginal ethnicity, and HIV positivity). Second, the VIDUS study is not comprised of a random sample, and therefore it is not known if these findings will generalize to other IDU populations. Furthermore, studies relying on self-report and reporting of stigmatized behaviors are always subject to the possibility of reporting biases; as such, behaviors such as syringe borrowing or lending may have been underestimated.[66] Third, our measure of MMT use is limited, as self-report was used to determine MMT uptake, and therefore the exact timing of initiation of MMT and treatment duration cannot be confirmed. Nonetheless, this measure of MMT use produced a number of strong statistical associations, including many consistent with previous studies that used more precise measures of MMT use.[15]

In summary, our study identifies a large number of barriers to and facilitators of MMT among IDUs in a Canadian setting. Male and Aboriginal IDUs in this study were much less likely to access MMT, while HIV positive individuals were much more likely to access MMT. Given the positive outcomes associated with prolonged MMT use, this study points to the need for further study of MMT access in this setting as a means of informing efforts aimed at maximizing uptake of MMT among the target population.

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CASE STUDY

Poor pain relief and possible toxicity from high-dose intrathecal opioid treatment: Report of two cases

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INTRODUCTION

Chronic intrathecal (IT) opioid treatment has proved helpful for the treatment of advanced terminal cancer pain when systemic opioid treatment fails through loss of efficacy or intolerable side effects. The IT opioid dosage is only a small fraction of the oral dose (1/300 for morphine), and side effects such as sedation, constipation, and urinary retention tend to occur less frequently than with systemic administration. This treatment is particularly useful for multifocal, refractory pain. The success of IT opioid therapy in cancer patients and the technological advances that have improved the availability, feasibility, and safety of implanted pumps have prompted the extension of IT opioid therapy into the realm of chronic nonmalignant or nonterminal pain. Patients are now treated this way not only for the last few months of their lives but possibly for many years.

We were briefly involved in the pain care of two IT opioid-treated chronic pain patients during their hospital admission for nonpain-related medical emergencies. In both cases, unusually high IT doses were used and failed to provide analgesia; also in both cases, concomitant endocrine disease complicated the clinical picture. Possible mechanisms for failed analgesia and for toxicity from high-dose opioid therapy are discussed.

CASE 1

A 51-year-old woman was admitted to the hospital complaining of severe occipital headache and neck stiffness, four days after uneventful recovery from nasal endoscopic fat graft obliteration for a persistent cerebrospinal fluid leak secondary to empty sella syndrome. Right parietal intracranial hemorrhage was confirmed by magnetic resonance imaging; she was treated conservatively with steroids and antibiotics and discharged after 15 days with full resolution of headache.

During hospitalization, she had a persistent complaint of severe bilateral lower extremity pain. Pain was shooting in quality, with a stocking distribution, and rated 10 out of 10 on a verbal scale. Pain history was notable for persistent severe peripheral neuropathy (earliest notation in patient history was 1995), initially treated with oral opioids and adjuncts. In 1997, an IT pump was placed and opioid therapy was started. The IT opioid dose was gradually increased to the admission dose: hydromorphone 33 mg per day (66 g oral morphine equivalent) plus fentanyl 2,560 mcg per day (76.8 g oral morphine equivalent). Other pain medications at admission included OxyContin (Purdue Pharma LP, Stamford, CT; 40 mg t.i.d.), Percocet (Endo Pharmaceuticals, Chadds Ford, PA; one to two tablets every four to six hours), oral hydromorphone (2 to 4 mg every 4 hours), gabapentin (800 mg t.i.d.), and baclofen (20 mg t.i.d.). During hospitalization, the preadmission pain regime was continued, and analgesia was supplemented with hydromorphone via patient-controlled analgesia as well as intermittent nurse-administered intravenous morphine. The hospital Pain Service was then consulted because of the failed analgesia and the unusually high opioid doses.

Medical history was complex. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) and empty sella syndrome were diagnosed in 1995. Painful lower extremities were assumed to owe to POEMS. Other significant past medical history included carcinoid tumor of the appendix, polycystic ovary (Stein-Leventhal syndrome), hypertension, hypothyroidism, gout, and hyperlipidemia. Past surgical history included total abdominal hysterectomy and bilateral salpingo-oophorectomy. Medications in addition to those taken for pain were labetalol (200 mg p.o. b.i.d.), captopril (12.5 mg t.i.d.), oral phenytoin (200 mg t.i.d.), allopurinol (300 mg q.d.), oral furosemide (40 mg b.i.d.), oral atorvastatin (10 mg q.d.), levothyroxine (200 mcg q.d.), paroxitine (50 mg q.d.), estradiol (0.05 mcg every 72 hours), triamterene (37.5 mg q.d.)/hydrochlorothiazide (25 mg q.d.), and oral sustained-release potassium

chloride. Significant endocrinological screen on post-admission day nine revealed the following laboratory values: thyroid stimulating hormone 0.33 μU per mL (low), prolactin 18.3 ng per mL (high), adrenocorticotropic hormone 128.0 pg per ml (high), a.m. cortisol 26.2 ug per dL (high), luteinizing hormone < 0.2 U per L (low at postmenopausal range), follicular stimulating hormone 0.6 U per L (low at postmenopausal range). Serum electrolytes were normal.

The Pain Service reduced the patient's IT hydromorphone dose by 10 percent per day, from 33 mg per day to a discharge dose of 8 mg per day. The IT fentanyl dose was unchanged. She was discharged on her preadmission oral pain regime for follow-up with her local pain clinic. Further weaning of the IT opioid was recommended. Intrathecal hydromorphine wean did not cause withdrawal or a change in pain intensity.

CASE 2

A 56-year-old woman was admitted to the hospital after three episodes of loss of consciousness lasting 10 to 15 seconds, associated with stiffening of all extremities. One episode was witnessed in the emergency room, where she had a 10- to 12-second sinus pause followed by spontaneous regaining of consciousness. The patient gave a two-year history of unexplained falls without loss of consciousness. She also reported frequent spontaneous myclonic jerks for the past several years, mostly during sleep. There was no temporal relationship between the falls and the myoclonic episodes. Myoclonus without neural deficit was obvious at the time of admission. The patient was emaciated and frail, with ecchymoses over all extremities. She was lethargic but arousable, and oriented but with poor attention and concentration and flight of ideas. Holter monitoring revealed sinus node dysfunction, and a permanent pacemaker was placed. Hospital course was complicated by development of hemopericardium and pericardial tamponade requiring pericardiocentesis. She was discharged after three weeks with normalized paced cardiac rhythm, improvement in myoclonus, and normalized mental status.

Throughout the hospitalization the patient complained of widespread pain, mostly below the waist, associated with tactile allodynia. Pain was described as continuous, unrelenting, and gripping in character. Pain was rated as an 8 or 9 out of 10 on a verbal scale throughout admission. She had experienced chronic pain since childhood. Scoliosis had been treated with Harrington rod placement when she was a teenager. The pain and scoliosis were disabling, and she was wheelchair bound. She had been treated with oral opioids for the past 28 years. Two weeks before her hospital admission for sinus arrest, an IT pump had been placed. The oral morphine dose before pump placement was 320 mg per day. At the time of admission, IT opioid dose was 15 mg morphine per day (4.5 g oral morphine equivalent), and oral morphine had been continued in controlled-release form, 60 mg before bed. The only adjustment made in her pain regime in the hospital was to discontinue the regular oral morphine.

The patient's medical history was complex. In addition to chronic pain syndrome, she carried diagnoses of bipolar disease, fibromyalgia, hypertension, chronic obstructive pulmonary disease, and Addison's disease. Addison's disease had been diagnosed one year before admission. Cardiac workup one year before admission revealed normal myocardial and valvular function and absence of ischemia. Medications at admission included oral cortisone acetate (25 mg b.i.d.), modafinil (200 mg per day), clonidine (0.1 mg twice a day), hydrochlorothiazide (25 mg per day), atenolol (50 mg per day), bupropion (150 mg b.i.d.), venlafaxine (37.5 mg per day), and Premarin (Wyeth Pharmaceuticals, Madison, NJ).

The patient's pain neither improved nor deteriorated during hospitalization. Myoclonus gradually improved and mental status cleared. The pain remained severe, rated an 8 or 9 out of 10, despite IT opioid therapy.

DISCUSSION

Intrathecal opioid therapy for intractable chronic nonterminal pain is still under considerable scrutiny in terms of its efficacy and safety. Early reports suggest that the therapy improves pain relief and function for a proportion of treated patients, and that the complication rate is low, although complications can be serious. Retrospective case series published between 1985 and 2001 suggest high rates of patient satisfaction (up to 92 percent[1]), good analgesic efficacy (pain reduction up to 60 percent[1-3]), and improvements in mood and function for up to four years.[1-9] More recent prospective studies[10-13] conducted for up to nine years report good analgesic efficacy (25 to 50 percent pain reduction) and improvements in mood and function, but in only a proportion of patients (up to 50 percent of patients fail the treatment for various reasons[11]). Thus, prospective studies report good results, but they are less impressive than the retrospective study results. For ethical reasons, it has not been possible to conduct randomized controlled studies, or even nonrandomized studies with truly comparable controls, although one carefully conducted recent study[13] did use controls (patients failing IT trials and newly presenting patients). System-related problems, including catheter and pump malfunction, dislodgement, and infection occur in up to 30 percent of implants but are usually reversible without removal.[11] Granulomatous catheter mass formation, a potentially disastrous complication of continued IT therapy, may occur in 5 percent of cases and can result in permanent neurological injury.[14,15]

Common side effects include sedation, nausea, edema, and, in male patients, hypogonadism. The side effects are usually controllable and rarely a reason for abandoning the treatment.[13]

Intrathecal opioid therapy has a record of success in literature reports but did not provide good analgesia in the two cases reported here, in which unusually high doses had been reached. In both cases, treatment did not provide the expected improvement in pain relief, systemic opioids were still being used, and the systemic and/or IT opioid treatment complicated the clinical presentation of an endocrine disorder. These case reports add to a growing literature that is helping us understand the limitations of chronic IT opioid therapy, especially in terms of sensible, validated dosing limitations, and precautions associated with concomitant disease.[15,16]

In the first case, the IT opioid dose was exceptionally high (475 mg per day IT morphine equivalent or 142.5 g per day oral morphine equivalent). In the second, dose escalation to 15 mg per day (4.5 g per day oral morphine equivalent) within two weeks was rapid, starting doses usually being lower (2 to 6 mg per day[17]). Could the phenomenon of opioid induced hyperalgesia have interfered with treatment success at these high doses? The propensity of opioids to produce hyperalgesia (as well as analgesia) has been recognized for some time; in fact, as early as 1954, it was noted in animals that high-dose IT opioids had strychnine-like effects.[18] The clinical phenomenon of opioid-induced hyperalgesia, often manifested as generalized allodynia, is increasingly recognized, especially in the context of high-dose intravenous opioid infusions used in intensive care, and after remifentanil anesthesia.[19-22] In the treatment of pain with IT opioids, a hyperalgesia syndrome—painful dose-limiting toxicity characterized by onset of pain and hypersentivitity (allodynia, particularly below the waist, sometimes with myoclonus)—has been reported and is considered a rationale for cautious dose escalation, especially above 20 mg per day.[17] It has been postulated that morphine metabolites, notably morphine-3-glucuronide, acting on glycine receptors, may have strychnine-like effects.[1,23]

Recently, a great deal of experimental work has focused on the phenomenon of opioid-induced hyperalgesia in the hope of elucidating mechanisms of failed analgesia and tolerance during opioid treatment. The role of the N-methyl-D-aspartate receptor in the development of opioid-induced hyperalgesia, opioid tolerance, and neuropathic pain has been recognized.[24-26] The exact mechanism of opioid-induced hyperalgesia—whether dose related, drug related, or somehow related to mode of administration (e.g., worse during IT administration)—remains elusive. Nevertheless, caution should be used when escalating opioid doses, whether IT or systemic, and failed analgesia with worsening physical and psychological status should warn of the possibility that dose escalation is making matters worse.[16] Measures aimed at reducing opioid tolerance (e.g., opioid "holiday," opioid rotation, rotation to methadone, epidural or intrathecal nonopioid therapies such as clonidine or local anesthetic) may be a better choice than persistent dose escalation.[15,16]

Both patients reported on here had underlying endocrine disorders. Although it would be inappropriate to implicate IT opioid therapy in their endocrine disease, one must certainly question the contribution of IT opioid therapy, especially knowing the irrefutable evidence that IT opioids have significant endocrine effects. Opioids suppress the hypothalamopituitary adrenal and gonadal axes and may also have direct adrenal and gonadal effects.[27-30,31] These effects have been described in animals and in humans. In humans, the effects are seen in heroin addicts,[31-36] former addicts in stable methadone programs,[32,33,37] chronic pain patients treated with opioids in the long term,[38-40] and patients treated with IT opioids. Probably because of relatively high cerebrospinal fluid opioid levels directly impacting the hypothalamus and pituitary, clinically important hormonal effects arise most commonly, although not exclusively, during IT opioid therapy.[3,8,13,41-44] Male patients may display loss of libido and energy, impotence, infertility, and depression. Testosterone replacement has been found to be restorative in male patients treated with IT opioids.[34,38,41,42,45] Female patients may display loss of libido, galactorrhea, ammenorrhea, and infertility.[46,47] In addition to gonadal effects, opioids may suppress adrenocorticosteroids,[48-52] and onset of Addison's disease has been reported in one IT opioid-treated patient.[41] The clinical significance of opioid cortisol effects is unclear.

For carefully selected patients—particularly those in whom opioid therapy has been effective but becomes impaired by intolerable side effects—IT opioid therapy can dramatically improve quality of life, function, and pain relief. This does not mean that IT opioid therapy should be considered a panacea for failed analgesia. It will be successful only when patients are carefully selected, doses are carefully titrated (possibly incorporating nonopioids into the IT drug mix), and adverse effects such as neuroendocrine effects are recognized and appropriately avoided or treated. There is still much to be learned about IT opioid therapy, and the cases discussed here raise the question of whether high-dose IT opioid therapy is therapeutic or merely toxic.

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CASE STUDY

High-dose methadone and QTc prolongation: Strategies to optimize safety

John Schmittner, MD
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INTRODUCTION

Methadone is an effective treatment for opioid dependence and chronic pain and, until recently, was viewed as a medication without cardiac properties. However, high-dose methadone has been linked to prolongation of the rate-corrected QT interval (QTc) and torsade de pointes (TdP). TdP is a form of polymorphic ventricular tachycardia that requires the presence of underlying QTc prolongation. QTc changes in the electrocardiogram (ECG) are often subtle and may be difficult to discern when U-waves are present. The risk of arrhythmia is related to the magnitude of the QTc change from baseline. Clinicians should be cognizant of methadone's potential cardiovascular effects and weigh the benefit-to-risk ratio for each patient, given the individual predisposition for arrhythmia. This manuscript describes a case of presyncope in a patient receiving methadone and highlights cardiac considerations surrounding methadone therapy.

Educational objectives:

1. Describe the QTc-prolonging effects of methadone.

2. Recognize how medications affecting hepatic cytochrome P-450 3A4 enzymes can alter methadone effects.

3. Weigh the benefits of high-dose methadone against the risks of possible TdP.

Key questions:

1. Does high-dose methadone confer additional risk of arrhythmia?

2. Is routine ECG warranted in methadone-treated patients?

3. What degree of QTc prolongation implies definitive risk of arrhythmia?

4. What concomitant medications should raise concern in methadone-maintained patients?

CASE PRESENTATION

Mrs. Y is a 42-year-old African-American woman with hypertension, Type II diabetes mellitus, and human immunodeficiency virus (HIV), who receives 300 mg of methadone daily for chronic pain and opioid maintenance. She presents with complaints of palpitations and presyncope escalating over the past few weeks. Within the last two days, she has felt her heart racing with "skipped beats" and has experienced marked dizziness on three occasions. However, she denies overt syncope, seizure activity, or postictal confusion.

The etiology of the patient's chronic pain is a crush injury to her hip from a motor vehicle accident four years ago. She has no history of prior drug abuse. After three years of using various physician-prescribed narcotics and nonsteroidal anti-inflammatory agents, she became opiate dependent. One year ago, she was referred to your pain clinic and started on oral methadone to address chronic pain and subsequent opiate addiction. For the past six months her pain has been well controlled, but she has needed progressively higher doses of methadone. She started a regimen of oral lamivudine 150 mg b.i.d., stavudine 40 mg b.i.d., and efavirenz 600 mg per day for HIV suppression several months ago. Other medications include hydrochlorothiazide 25 mg per day and metformin 500 mg b.i.d. Her podiatrist also started her five days ago on itraconazole 200 mg per day for onychomycosis.

On physical examination, blood pressure is 132/80 mm Hg without orthostatic changes, heart rate is 70 beats per min, respiratory rate is 15, and pulse oximetry saturation is 96 percent while breathing room air. Cardiovascular and neurologic examinations are entirely normal.

Table 1. Selected medications associated with QTc interval prolongation
Antiarrhythmic drugs
Amidarone
Disopyramide
Dofetilide
Procainamide
Quinidine
Antihistamines
Terfenadine
Astemizole
Antibiotics
Azithromycin
Clarithromycin
Erythromycin
Pentamidine
Sparfloxacin
Moxifloxacin
Antifungals
Itraconazole
Ketoconazole
Psychotropic drugs
Chlorpromazine
Haloperidol
Thioridazine
Fluoxetine
Other
Ephedra
Chloroquine
Cisapride
Levomethadyl
Organophospates
Cocaine

You perform a 12-lead ECG, which reveals normal sinus rhythm, heart rate of 75 beats per min, and no atrioventricular block or conduction abnormalities. However, the QT interval is 455 msec, and the QTc is 510 msec. You retrieve an electronic copy of her ECG from an emergency room visit for chest pain last year and discover that her baseline QTc at that time was 440 msec. You now suspect that her current symptoms may have been caused by QTc prolongation with transient TdP.

Serum electrolytes reveal normal concentrations of potassium, magnesium, and calcium. You discontinue itraconazole immediately and arrange to see the patient in one week, with instructions that she proceed immediately to the emergency department if symptoms recur. She returns with no further symptoms, and repeat ECG demonstrates that the QTc has decreased to 475 msec.

CLINICAL QUESTIONS

What causes QTc prolongation, and what represents an unacceptable increase?

QTc prolongation is most commonly associated with drugs and electrolyte disorders, primarily hypokalemia and hypomagnesemia.[1-3] Additional etiologies include congenital long-QT syndrome, subendocardial ischemia, and central nervous system insult.[4,5]

It is generally accepted that women have a slightly longer QTc interval than men, with a prolonged QTc interval defined as > 470 msec and > 450 msec, respectively.[3,6] Although there is disagreement over the exact risk QTc prolongation confers,[3,5-8] it is generally accepted that measurements over 500 msec indicate a significant risk for the development of TdP and increases of 40 msec over baseline merit clinical concern.[3,5-9]

How might methadone cause QTc prolongation?

Methadone and its derivative, levomethadyl acetate (LAAM),[10,11] have been demonstrated to prolong the QTc interval and may predispose susceptible patients to ventricular arrhythmias such as TdP.[12-23] A potential mechanism of arrhythmia may be blockade of the cardiac ether-a-go-go-related gene (HERG) potassium current.[5,26] Blockade of this cardiac ion channel leads to delayed repolarization, which manifests as QTc interval prolongation on the surface 12-lead ECG.[25,26]

Is methadone–associated QTc prolongation dose dependent?

For some medications (e.g., sotalol), there is a clear relationship between dose and plasma levels and the magnitude of QTc interval prolongation.[1,5] For methadone, the relationship is less clear; however, one

prospective study[18] demonstrated a modest impact of oral methadone therapy on the QTc interval. In this study, patients were initiated on oral methadone, 30 mg daily, and increased in 10-mg increments according to self-reported opiate use, presence of opiate withdrawal symptoms, and urine toxicology results. At six months, the median daily methadone dose was 80 mg (interquartile range, 60 to 100 mg; range, 20 to 180 mg). At 12 months, the median daily methadone dose was 90 mg (interquartile range, 60 to 120 mg; range, 20 to 200 mg). This study demonstrated mean QTc increases of 12.4 ± 23 msec at six months, 10.7 ± 30 msec at 12 months, and that mean QTc change from baseline to 12 months correlated with trough ($r = +0.37$, $p = 0.008$) and peak ($r = +0.32$, $p = 0.03$) serum methadone concentrations.[18]

Also, a retrospective linear regression analysis of 17 methadone-treated patients who developed TdP demonstrated a dose-dependent relationship between methadone and the absolute QTc interval ($r = +0.51$, $p = 0.03$).[23] Daily methadone dose ranged from 65 mg to 1,000 mg, with a mean daily methadone dose of 397 ± 283 mg per day. These data suggest that escalating doses of methadone are likely to modestly increase the risk of QTc interval prolongation. No predefined cutpoint for a dose-QTc relationship can be readily identified to predict arrhythmia risk due to the modest effects of methadone on QTc and the wide individual variation.

How might other medications interact with methadone to increase the likelihood of QTc prolongation?

Methadone is metabolized by the hepatic cytochrome P-450 3A4 enzyme and does not possess active metabolites.[27,28] Medications that inhibit or induce CYP3A4 may alter plasma methadone levels dramatically,[14,16,27,29] increasing a patient's propensity for arrhythmia.[1,7,14,16] Such medication interactions are especially important for HIV patients, as many HIV treatments have P-450 effects.[12,27,29-31]

Also, there are a multitude of US Food and Drug Administration (FDA)-approved medications and herbal preparations that cause QTc prolongation on their own.[3,14,32] Medications associated with a prolonged QTc interval far outnumber those that have been proven to cause TdP.[32] Selected medications associated with QTc prolongation are shown in Table 1. However, it is notable that the majority of patients receiving QTc-prolonging drugs manifest no adverse cardiac sequelae.[3,5,8,32]

What medications may have caused this patient's prolonged QTc interval?

Efavirenz, a non-nucleoside reverse transcriptase inhibitor, may have induced P-450 metabolism of her methadone,[30] which therefore required escalation of

Table 2. P450-methadone interactions

Decreases plasma methadone concentration via hepatic P450 induction
Phenobarbital
Carbamazapine
Phenytoin
Ethanol
Rifampin
Dexamethasone
Efavirenz
Griseofulvin
Nevirapine
Rifabutin
Increases plasma methadone concentration via hepatic P450 inhibition
Cimetidine
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Amitriptyline
Fluvoxamine
Fluoxetine
Grapefruit juice
Itraconazole
Ketoconazole
Nifedipine
Omeprazole
Protease inhibitors
Verapamil

Adapted with permission from Krantz MJ, Mehler S: Treating opioid dependence. Growing implications for primary care (Table 2). *Arch Intern Med.* 2004; 164: 277-288.

Table 3. Clinical indications for electrocardiogram in patients receiving methadone
Prior history of long-QT syndrome or torsade de pointes
Family history of long-QT syndrome or early sudden cardiac death
Structural heart disease
Cardiac arrhythmia and heart block (second- or third-degree AV block)
Anorexia nervosa
Frequent electrolyte depletion (potassium, calcium, magnesium)
Human immunodeficiency virus-infected patients on multiple-antiretroviral therapy
Active cocaine abuse
Methadone dosages greater than 150 mg per day
Initiation of a P-450 inhibitor
Initiation of medications associated with QTc prolongation
Presyncopal or syncope symptoms
Unexplained tonic-clonic seizures with anormal electroencephalogram

methadone dosage. The dose increase, in turn, may have increased the QTc interval from baseline 440 msec to 475 msec.

Once itraconazole was started, there could have been a dual effect: first, itraconazole can increase QTc on its own[32]; second, it inhibits P-450, thereby increasing methadone plasma levels.[27] Either of the two, or a combination, may have caused an increase in QTc to 510 msec and induced self-terminating TdP. A list of medications that may induce or inhibit the metabolism of methadone are depicted in Table 2.

Given the patient's persistently abnormal QTc interval, should her methadone dose be decreased?

The patient's symptoms have resolved, but the physician is faced with an abnormal QTc interval of 475 msec. Treatment options include the following: one, her methadone could be decreased until her QTc returns to baseline; two, her HIV medications could be changed to a regimen that does not include P-450 inhibitors, such as abacavir/didanosine/lamvudine[32]; three, she could be taken off methadone, placed on long-acting morphine or other narcotics, and eventually switched to buprenorphine (a synthetic opioid FDA approved for addiction, which appears to have minimal to no impact on QTc interval in vivo[19]);. four, she could be kept on her present medications, as her symptoms have resolved, but to avoid any QTc prolonging agents or P-450 interactions.

Should methadone initiation be preceded by a screening electrocardiogram?

For most heroin addicts presenting in acute opioid withdrawal, screening ECG is probably unwarranted and extremely impractical. However, a screening ECG is indicated if there are other pertinent risk factors for QTc prolongation, such as drug-drug interactions or long-standing cocaine abuse, which may lead to significant left ventricular systolic dysfunction or accelerated coronary artery disease. ECG screening should be considered when methadone dosages exceed 150 mg. Screening may also be considered in patients with multiple risk factors for QTc prolongation—a family history of long-QT syndrome or early sudden cardiac death, a history of electrolyte depletion, and on initiation of a P450 inhibitor (Table 3).

Are other tests of clinical value?

Echocardiography is not indicated unless a patient presents with a history consistent with structural heart disease such as congestive heart failure or myocardial infarction. A 24-hour Holter monitor could provide useful information but only if the symptoms are frequent enough to be captured with brief monitoring. In cases in which syncope owing to TdP is suspected, immediate hospitalization with ECG monitoring is warranted. If asymptomatic QTc prolongation is detected by a 12-lead ECG, then a Holter monitor would not likely change treatment decisions.

Plasma levels of methadone may be of academic interest but probably will not change treatment decisions. Genetic testing for congenital long-QT syndrome is expensive and not widely available. At present, it should be performed only if a congenital disorder is suggested by the family history or as part of a research initiative.

What are some limitations and challenges in identifying risk for arrhythmia?

QTc prolongation remains a specialized area of cardiology in which there is significant disagreement over the validity of ECG machine measurements, formulas for the "corrected" QT interval, the role of QT dispersion, the influence of genetic markers, and what actual risk for arrhythmia a prolonged QTc represents.[1,3,4,6-7,33-37]

Due to automated ECG inaccuracy in measuring the QTc intervals, manual confirmation with calipers is often required. QTc is calculated by the following formula: QTc = QT interval (in msec) divided by the square root of the preceding RR interval (in sec).[8,38] It is often preferable to measure the QTc interval in limb leads; however, precordial interpretation is acceptable if the termination of the T-wave is better discerned.[7] Readers should recognize the effects of bradycardia, position, time of day, and food intake on QTc interval variability.[8,39,40] If there is uncertainty regarding the presence of significant QTc prolongation, it may be prudent to repeat the ECG and/or have the tracing interpreted by a cardiologist.

What is the rationale for continuing to administer methadone in cases in which QTc prolongation could occur?

Methadone is an opioid agonist with a longer duration of action than morphine, making it effective for opioid dependence and chronic pain management.[28,41-43]

In opioid-dependent patients, the benefits of methadone (particularly when combined with psychosocial services) include reducing illicit drug use, crime, HIV/hepatitis risk, and death, and improving employment and social adjustment.[44-50] Higher doses of methadone are associated with decreased opioid use and improved treatment retention, as shown in randomized clinical trials[51-53] and in retrospective analyses of outcome in clinical populations.[54-57] Even temporary dose increases can lead to decreases in illicit drug use and improvement in social functioning.[58]

In patients with chronic pain, methadone presents a therapeutic alternative to other narcotics, as it is well-absorbed orally, has a long half-life, and provides analgesia similar to that of morphine (via affinity to μ-receptors) without detrimental euphoria.[59,60] Methadone appears to possess other ancillary properties that enhance analgesic efficacy. In particular, it has been demonstrated to have antagonist activity at the N-methyl-D-aspartate receptor in animal studies.[27,61] This antagonist activity may decrease both pain and development of tolerance to the analgesic effects of methadone.[62-64] Thus, the higher doses of methadone that may increase risk of arrhythmia may also be more effective for opioid maintenance and alleviation of chronic pain.

DISCUSSION

This case review illustrates that methadone prolongs the QTc interval in some, but not all, patients. QTc prolongation is associated with an increased risk of ventricular arrhythmias such as TdP. QTc changes may occur over a wide range of doses but are more likely to occur at higher dose. Because the metabolism of methadone can be altered by other drugs via multiple hepatic P-450 pathways, complex medication interactions may occur. Sorting out the etiology of a medication-induced QTc change or arrhythmia may present a significant clinical challenge.

Routine ECG screening for methadone induction is not indicated unless risk factors for QTc prolongation/arrhythmia are present. However, as methadone's cardiac properties are not always predictable, and can even occur in individuals without predisposing risk factors, patients should be monitored for symptomatic manifestations of arrhythmia (i.e., syncope, presyncope). ECG is indicated for patients with structural heart disease and among patients receiving QTc prolonging drugs, and when methadone doses exceed 150 mg per day. Any QTc interval over 500 msec confers a significant risk for the development of TdP. Increases of 40 msec also merit clinical concern. Decreasing methadone dosages or drug discontinuation has been shown to result in normalization of QTc prolongation.[19,20,22] This may, however, lead to other unfavorable results: for patients with opioid dependence, undertreatment may lead to relapse to intravenous heroin use and its associated morbidity. For patients with chronic pain, undertreatment may cause unacceptable pain and loss of function. On the other hand, knowingly keeping a patient on medications or dosages of medication that pose potential cardiovascular risk is unacceptable from a safety perspective.

Treatment decisions to optimize safety must weigh the patient's benefits (e.g., alleviation of pain, abstinence from illicit opioids, decreased risk of HIV/hepatitis C) against their risk profile for arrhythmia. Clearly, a patient with structural heart disease or concurrent cocaine abuse presents a higher risk compared to a patient without such risk factors. Just as many QTc-prolonging drugs are given safely, methadone can be dispensed effectively in high dosages, as long as the potential for QTc prolongation is recognized.

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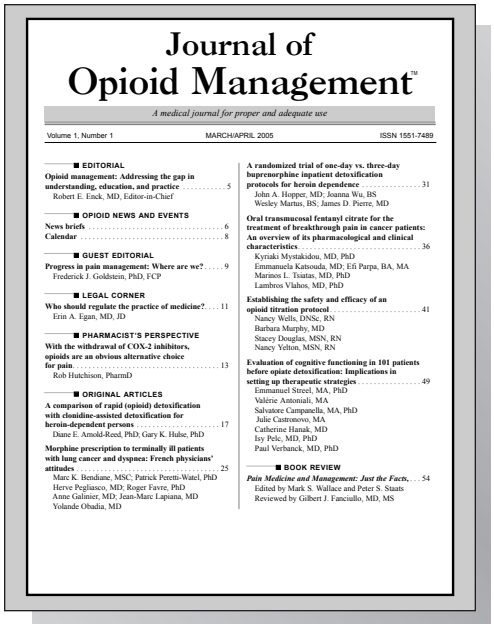
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