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A medical journal for proper and adequate use

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GUEST EDITORIAL

Can we continue to do business as usual?

B. Eliot Cole, MD, MPA

In a 2006 issue of the *Journal of Medical Licensure and Discipline*, David C. Greenberg, MD, MPH, writes about "the distressed chronic pain practitioner (DCPP)" (92[2]: 5-7). He states that DCPPs are "physicians willing to sell prescriptions for controlled substances without bothering to obtain a history and work up the patient's complaint, perform a physical exam, arrive at a proper diagnosis, utilize testing or consultation, choose a rational treatment plan or properly monitor their patients . . . ." DCPPs are, in Dr. Greenberg's view, "self-declared experts in chronic pain medicine . . . with no formal training in chronic pain medicine or any history of studying under a qualified mentor in a prolonged clinical fashion . . . [and] lacking any sort of comprehensive CME participation in recognized chronic pain educational programs . . . . [They do] not [belong] to professional pain treatment organizations and . . . [do] not [read] recognized current textbooks or journals regarding chronic pain." For most DCPPs, "it appears that . . . their main source of chronic pain diagnostic and treatment information is limited to what is supplied by pharmaceutical industry representatives and their patients . . . ."

Dr. Greenberg also notes that not being properly trained in pain management, relying solely upon proprietary pharmaceutical information, and not maintaining basic currency in pain therapeutics are practices that endanger the health, safety, and welfare of people in pain. Dr. Greenberg concludes his editorial by saying that "physicians and other stakeholders need to seriously deal with prescription abuse and diversion or the government will do it. The medical profession must better train and police itself . . . to avoid being forced to take many giant steps backward into a setting where chronic pain patients were undertreated, ignored, shamed or labeled as hypochondriacs and malingerers . . . ." I refer to this past as the "bad old days."

A clear-cut example of a DCPP is Dr. X, a physician who completed only an internship after medical school and who is now operating a "pain clinic" that receives 160 or more walk-in patients daily. With the help of two "extenders," Dr. X's patients could receive prescriptions for opioids and other controlled substances with only the most cursory history taking, virtually no physical examination, no review of prior medical records, and no laboratory or imaging studies ordered, for the cash-only fee of $250 per prescription if they are willing to wait in the one- or two-city-block line—or $350 per prescription if they want "express service." No one should confuse this behavior with the practice of medicine; this is criminal activity being performed under the guise of medical care.

What about the busy primary care practitioner (PCP) trying to see 30, 40, 60, or more patients daily in a typical office setting while caring for a few hospitalized patients, responding to telephone calls, reviewing previously ordered labs and imaging studies, and refilling medication requests? Is that setting appropriate for the management of complex patients with chronic medical problems such as chronic noncancer pain? How much time is necessary to take an adequate pain-related history, perform an appropriate medical examination, determine which studies or imaging methods might clarify the underlying diagnosis, develop a plan of care, and then monitor the patient through time? Is it 10, 15, 30, 60 minutes per patient? More? Who pays for such care? How much must be done to satisfy the standards promulgated by the US Federation of State Medical Boards and adopted by the majority of state medical boards in our country?

After two decades of belt-tightening on the part of the US government and managed care organizations, most physicians are now forced to see more patients and devote less time to each patient just to stay alive in practice. "Problem-oriented medicine" means that only the presenting problem is going to be evaluated. There is no real attempt to get to the bottom of anything; all the physician can do is address the issue at hand and move on to the next patient. Can these busy practitioners adequately manage complex patients requiring years or decades of treatment? If PCPs can not care for these patients, who, exactly, will? Do these busy providers really have any understanding of the issues associated with long-term opioid therapy at anything beyond a brainstem level? Do they know about the concepts of opioid-induced hyperalgesia, immune suppression, and endocrine changes associated with opioid use? To whom will they refer patients, when the number of multidisciplinary pain programs has been steadily decreasing over the

last 10 to 15 years and interventionists now dominate the field of pain medicine? What will PCPs do with patients who are sent back to them for longitudinal care (continuing long-term opioid therapy) after referral to pain interventionists, when the interventions have all been conducted but the patients still need ongoing medication management?

These are not simple questions, but they represent the state of pain management in America, and they are exactly the type of concerns that are expressed by PCPs. These are ultimately complex societal issues, for which there are currently no good answers. Some pain specialists and many PCPs argue that only those pain sufferers with tissue-proven terminal illnesses should receive opioid therapy, or that they should only have opioids provided when interventional methods are not helpful. Others support what they feel is a more humane position: if opioids relieve pain, why not provide opioids regardless of potential long-term consequences? Today there are many published strategies for controlled-substance prescribers that will supposedly keep them out of trouble with regulators; however, none has actually been tested by the US judicial system. There are numerous screening methods and techniques that aid practitioners in making better treatment decisions about opioid therapy. Little is said about the fact that all of these strategies and techniques demand additional time, paperwork, and expense on the part of PCPs, and they hardly fit into the delivery of healthcare within our existing medical models.

Dr. Greenberg suggests that physicians themselves must monitor and police their profession. How many of us have ever taken the time to voice our concerns about colleagues to any regulatory body? How many of us have actually reported a colleague to anyone for anything at all? Weren't we trained to believe that it is improper to speak ill of another member of our profession? Those who have found themselves in trouble for their prescribing practices have usually been turned in by pharmacists, nurses, or disgruntled patients and their family members; rarely, if ever, are these doctors reported by their colleagues. In our complaint-driven system, only the most outrageous behavior or consequence (i.e., death) is ever questioned, not the day-to-day "small stuff" that involves open-ended opioid therapy that carries on for years without evidence that pain is being relieved, activity has increased, a return to work has been made possible, or even that quality of life has improved. Prescriptions are expected to be renewed, and in group practices these renewals are almost never questioned. What may have started out as an acute pain problem managed with opioid therapy soon becomes a chronic pain problem controlled with ever increasing amounts of more potent opioids.

What do good pain practitioners do that many PCPs fail to do? They take more time—enough time to understand the pain problem and the patient at a journalistic level, asking who, what, when, where, and why. They disrobe the patient, inspect the painful area, and lay their hands on it. They do their own reconnaissance, rather than assume that someone else has already done it. They question the current treatment and propose new directions for treatment based upon the presumed underlying mechanisms creating the pain, while utilizing information about the mechanisms of action for each of the therapies considered. Ultimately, they may (rightly) refuse to continue whatever is not working.

Pain management may be the only area of medicine where lack of efficacy is confused with patient rights. Many patients in pain incorrectly assume that they have a right to opioid therapy, when no such right exists. When a neurologist is faced with a patient who is continuing to experience seizures despite the current therapy, further modifications are made until the seizures abate. Uncorrected hypertension is continuously addressed until the patient's blood pressure is reduced to the desired goal. Antibiotics are modified until cultures are negative. There is no disagreement about the goal of therapy in most of routine medical care; the exception is the management of pain. For less than obvious reasons, goals of treatment are not always clear, expectations about therapy are not necessarily agreed upon from the outset, and sometimes years go by before anyone begins to consider the possibility that whatever is being done may not be working.

The remedy for the doctor who may be a DCPP but who actually wants to be a responsible pain practitioner is appropriate pain-related education. After 30 years as an area of professional interest, pain management/medicine has developed pain-related core curricula for healthcare practitioners to master. Learning opportunities are available for practitioners of all levels and backgrounds, as are several excellent professional publications and textbooks. The International Association for the Study of Pain has continued to evolve its standardized pain curriculum for healthcare professionals. The American Pain Society, American Academy of Pain Medicine, American Academy of Pain Management, and other groups offer annual conferences providing up-to-date information about pain research, pain practice, and the importance of multidisciplinary pain management. The Society for Pain Practice Management, American Society of Interventional Pain Physicians, and American Society of Regional Anesthesia and Pain Medicine provide hands-on training for physicians who want to learn specific procedures and techniques. This journal and the Opioid Management Society advance the knowledge and science of opioid therapeutics while providing necessary training for those who intend to use opioid therapy as a cornerstone in their management of people with pain. The American Society of Pain Educators offers healthcare professionals methods, techniques, and tips necessary for their successful

service as professional pain educators. Numerous publications in the form of newsletters, magazines, scientific journals, and Web sites disseminate information about pain-related diagnostics, common pain syndromes, therapeutic options, evolving regulatory challenges, risk management techniques, and more. Annually in the United States alone, there are more than a dozen major national pain conferences, dozens of smaller regional meetings, hundreds of articles published, and thousands of "one off" programs—ultimately leaving no excuse for anyone to be a DCPP.

Collectively, those who consider themselves to be frontline professional pain practitioners must challenge those who "casually" provide similar services to become more knowledgeable, to view pain practice as a serious endeavor, and to not just prescribe more medication. Pain practitioners must be willing to serve as mentors and pain educators for PCPs, other specialists, insurers, regulators, and members of the media. Pain practitioners must actively establish national standards, work with regulators, be active in the political process, and refuse to tolerate the behavior of those who intend to degrade pain management into "pill pushing." Being part of the solution requires that those who are in pain medicine for the long haul put words into action, lead by example, and, rather than just see more patients, see more patients *well*.

Developing new branches of medicine takes time, the presence of charismatic leaders, and subsequent adoption of the new ideas by others. As members of a 30-year-old profession which is recognized by the American Board of Medical Specialties as a distinct area of subspecialization, those of us who are pain practitioners must now do our part to reach out to our colleagues in other areas of medicine and help them learn more about what we do. It is our obligation to uphold the same standards of care (especially when prescribing controlled substances for the treatment of pain) and to continue the professional development of pain management/medicine. The profession on the whole is not mature enough today that we can afford to sit back and enjoy the spoils of our efforts.

The remedy for issues related to the practice of pain medicine will not be more governmental interference, the crafting of additional regulations and rules, or punitive action against the occasional "bad apple." The remedy lies in the deans of curriculum at our medical schools, the program directors for all residency programs, the directors of education for pain and primary care organizations, and a commitment to serve as pain educators made by the thousands of dedicated pain physicians and other pain practitioners who deliver care to those who suffer. Those providing appropriate pain-related therapeutics will become the best pain educators, and this will be much more than self-promotion; this will be effective self-preservation.

As most current healthcare providers were not formally trained to be healthcare educators beyond the "see one, do one, teach one" stage, those planning to serve as pain educators must now seek special training to become effective teachers. PAINWeek 2007 (September 6–9, 2007, at the Red Rock Casino, Resort and Spa in Las Vegas, Nevada) will be a "first of its kind" meeting, designed to blend teaching skills and techniques (the Pain Educators Forum) with primary care–tailored knowledge about pain and its management (the Fundamentals of Pain Medicine), along with other significant symposia to create one-stop learning for those interested in being part of the educational solution. It is expected that by the end of PAINWeek 2007, those who might be potentially "distressed" will be enlightened, and those already knowledgeable will be enthused about teaching what they know to others.

Collectively, pain professionals can seriously deal with prescription misuse, abuse, and diversion without the need for draconian governmental measures. We already know what is legal and what is illegal. The medical profession must better train its members and never allow itself to be forced into taking many giant steps backward to the bad old days, when chronic pain patients were undertreated, ignored, shamed, or labeled as hypochondriacs and malingerers. This is the promise of pain education: to improve patient care across the board and prepare a generation of leaders for the profession of pain management.

B. Eliot Cole, MD, MPA, Executive Director, American Society of Pain Educators, Montclair, New Jersey.

CALENDAR

The Cleveland Clinic Foundation Center for Continuing Education
Palliative Medicine 2007
March 15–17, 2007
Hyatt Regency Coconut Point Resort & Spa, Bonita Springs
Fort Myers, Florida

For registration information, contact:
UNITECH Communications
Tel.: 800-238-6750
Web site: *www.clevelandclinicmeded.com/pm2007*

American Society for Pain Management Nursing
2007 National Conference
March 24–27, 2007
InterContinental Dallas Hotel
Addison, Texas

For registration information, contact:
ASPMN National Office
Tel.: 888-342-7766
Fax: 913-895-4652
E-mail: *aspmn@goamp.com*
Web site: *www.aspmn.org/Conference/index.htm*

The Australian Pain Society
27th Annual Scientific Meeting of the Australian Pain Society: The Torture of Pain
April 1–4, 2007
Adelaide Convention Centre
Adelaide, Australia

For registration information, contact:
Conference Secretariat
Tel.: 61-2-9954-4400
Fax: 61-2-9954-0666
E-mail: *APS2007@dcconferences.com.au*
Web site: *www.dcconferences.com.au/aps2007*

American Society of Regional Anesthesia and Pain Medicine
32nd Annual Regional Anesthesia Meeting and Workshops
April 19–22, 2007
Westin Bayshore
Vancouver, BC, Canada

For registration information, contact:
ASRA
Tel.: 847-825-7246 / Fax: 401-765-6677
E-mail: *asra@expotrac.com*
Web site: *www.asra.com/education/32nd-Annual/*

The British Pain Society
Annual Scientific Meeting 2007
April 24–27, 2007
Scottish Exhibition + Conference Centre
Glasgow, Scotland

For registration information, contact:
British Pain Society Secretariat
Tel.: 020-7269-7840 / Fax: 020-7831-0859
E-mail: *info@britishpainsociety.org*
Web site: *www.britishpainsociety.org/meet_glasgow2007asm.htm*

Department of Pain Medicine and Palliative Care, Beth Israel Medical Center
The International Association for Pain and Chemical Dependency
The 7th International Conference on Pain & Chemical Dependency
June 21–24, 2007
Sheraton New York Hotel & Towers
New York, New York

For registration information, contact:
ICPCD Registration
Tel.: 866-908-8398 / Fax: 732-274-2423
E-mail: *Registration@IAPCD.com*
Web site: *www.iapcd.com*

FDA ACCEPTS LABOPHARM'S RESPONSE TO APPROVABLE LETTER FOR ONCE-DAILY TRAMADOL AS COMPLETE

Labopharm Inc. has announced that its response to matters raised by the US Food and Drug Administration (FDA) in the approvable letter for Labopharm's once-daily formulation of tramadol has been accepted for review by the FDA as complete. The action date assigned by the FDA under the Prescription Drug User Fee Act is June 19, 2007. Labopharm received the approvable letter for its once-daily formulation of tramadol on September 28, 2006, following submission of its New Drug Application, sent November 28, 2005. Following discussions with the FDA, Labopharm submitted its response to the matters raised in the approvable letter for once-daily tramadol on December 19, 2006.

Labopharm Inc. is an international specialty pharmaceutical company focused on the development of drugs that incorporate the company's proprietary controlled-release technologies. The once-daily tramadol formulation has already been approved in Europe. Last week, the company said tramadol is available, under differing brand names, in Italy, Germany, Spain, and the United Kingdom, and it will soon be available in France and Belgium. For more information, please visit *www.labopharm.com.*

This press release contains forward-looking statements that involve a number of risks and uncertainties relating to the company's once-daily tramadol product in the United States that could cause actual results to differ materially from those indicated here. These statements reflect the company's current expectations regarding future events. Specifically, the risks and uncertainties the company faces include but are not limited to the company's ability to resolve the issues identified by the FDA to the FDA's satisfaction in a timely manner; the uncertainties related to the regulatory process, including regulatory approval; and the commercialization of the drug thereafter. There can be no assurance that Labopharm will be able to resolve the issues identified by the FDA using existing data, or at all. If the company is unable to resolve the issues identified by the FDA using existing data, it will need to generate additional data in order to obtain FDA approval. (Source: LAVAL, QC, January 16, 2006.)

STUDY FINDS 90 PERCENT OF ACTIQ "LOLLIPOP" PRESCRIPTIONS ARE OFF-LABEL

A recent Prime Therapeutics (Prime) study found significant patterns of "off-label" prescribing for Actiq among patients using the powerful painkilling "lollipop." Prescribing Actiq according to FDA guidelines is important for patient safety reasons because of the drug's serious side effects, including the risk of addiction. The results of the Prime study confirm concerns about the drug which have been highlighted recently by the national news media. Prime, a thought leader in pharmacy benefit management, provides programs that manage the use of Actiq and other dangerous drugs in an effort to promote health and safety while ensuring that patients get the treatment they need.

"The FDA has only approved Actiq for use by cancer patients who are already taking a long-acting, chronic painkiller but suffer from severe spikes in pain," stated Pat Gleason, PharmD, Director of Medical and Pharmacy Integration Services for Prime. "The Prime study, however, found that only slightly more than 10 percent of the patients receiving the drug over a three-month period in 2005 met those guidelines. Nearly 90 percent of Actiq prescriptions in our study were off-label, or not prescribed according to the guidelines set forth by the FDA."

Actiq contains fentanyl, a potent synthetic opioid with a high potential for abuse and overdose. In addition, fentanyl has been linked to fatal respiratory complications. As a result, while physicians are allowed to prescribe medications for unapproved or "off-label" use, the FDA recommends strict adherence to Actiq's prescribing guidelines.

Last year, in response to the safety concerns highlighted in the study, Prime began offering programs to promote Actiq's safe use. These programs include a monthly limit of 120 doses of Actiq or a newer, related drug, Fentora. Patients are also required to have prior authorization from their doctor, and prescriptions are limited to a 12-month period. Prime's program also encourages members to take a long-acting opioid for chronic pain. The program guidelines follow FDA recommendations.

"There are serious safety issues regarding Actiq, so doctors need to be careful how it is prescribed," said Gleason. "Prime integrates pharmacy and medical data to identify misuse of drugs such as Actiq and then develops programs to ensure patient safety. Our drug-utilization programs not only keep members safe but save health plans thousands of dollars a month."

The study analyzed Actiq patient claims from a Midwestern commercial health plan between April and June 2005. Of the 95 patients who received prescriptions for the lollipop during that time, only 21 had a diagnosis of cancer or AIDS. In addition, only 10 of those 21

patients were taking a long-acting opioid painkiller. Overall, 84 of the 95 Actiq prescriptions—nearly 90 percent—were for off-label purposes. The study also found that more than 15 percent of Actiq prescriptions were for more than the FDA's recommended 120 lollipops per month, suggesting that some patients may be overusing the drug. (Source: Prime Therapeutics, LLC/PRNewswire, January 16, 2007.)

A QUICK-RELIEF OPIOID: CEPHALON REPORTS POSITIVE RESULTS FROM PHASE III TRIALS WITH FENTORA

Fentora, approved by the FDA in September 2006, is the first pain reliever in seven years to be approved for the management of breakthrough pain in cancer patients who are already taking opioids for underlying, persistent cancer pain. In the earlier clinical trials submitted as part of the Fentora New Drug Application, the company reported pain relief at 15 minutes. It usually takes 30 to 45 minutes for other pain medications to take effect.

The trial, which assessed the efficacy of Fentora in a variety of chronic conditions associated with neuropathic pain, was a double-blind, placebo-controlled study involving 75 opioid-tolerant patients. In patients treated with Fentora, the onset of pain relief began in 10 minutes; the results seen in patients receiving placebo were consistent with a previously announced study of opioid-tolerant patients with chronic low back pain. In a different placebo-controlled study that evaluated Fentora in 78 opioid-tolerant patients with cancer, the result was much the same, with the patients beginning to experience pain relief in 10 minutes. (Source: The Connors Group, Inc., January 13, 2007.)

DOCTOR FREES INMATE IN ORDER TO ADMINISTER DRUG

A Madison County Jail policy that forbids anyone from bringing prescription medicine to inmates, even doctors, prompted a doctor to post $1,000 to bail out a patient who suffers from cerebral palsy and was apparently denied painkillers by jail staff. Madison County's sheriff said the man was not treated differently from other inmates.

Jim Stewart, who lives outside Granite City, takes multiple medications every day, including one to six tablets of hydrocodone to control severe muscle pain and help him sleep. He was arrested December 27, 2006, after fighting with his brother and was charged with a felony count of aggravated battery.

Stewart's mother was worried that he wasn't getting his hydrocodone while in custody. Hours after the arrest, she called his doctor, Alexander Kalk, who has a general medicine practice in Creve Coeur. Kalk said he drove to Edwardsville that night and dropped off a new bottle of hydrocodone for Stewart, along with a written prescription. Stewart has been taking the drug for about 15 years, and Kalk said he was concerned about withdrawal effects that would result if he were suddenly taken off it.

The next day, a nurse called Kalk and said she had concerns about giving such a strong pain medication to a person in jail. Kalk said the nurse told him that Stewart had been given just one dose of hydrocodone since he had been in jail. Stewart also said he only received one tablet, despite complaining of severe muscle pain and asking a dozen times to be taken to the hospital.

Kalk said he faxed details of Stewart's medical history to the jail, but he wasn't satisfied it would do any good. "I could tell he wasn't going to get his medicine," Kalk said. So on December 28 he made a second trip to Edwardsville and posted Stewart's $1,000 bond.

Kalk, 36, said Stewart looked haggard and in pain when he was released and didn't feel better until he took his hydrocodone. Kalk said it's unbelievable that a jail would not allow a physician to bring medicine to a sick inmate. "That's a medical mistake to have that policy," Kalk said.

Madison County Sheriff Bob Hertz would not comment on Stewart's case because of confidentiality concerns, but he said the jail simply followed its policy. "We don't allow medication to come into the jail from the outside," Hertz said. The sheriff said it would be too risky to accept someone's word that the medicine in a bottle was indeed the prescribed medicine and that it's up to the jail's medical staff to determine what prescriptions inmates receive.

Each Illinois jail can choose its own policy about how inmates get prescription drugs, said Derek Schnapp, a spokesman for the state's Department of Corrections, which oversees county jails. No information was available about how many jails ban bringing in such medications. The St. Clair County Jail allows family members and doctors to drop off medicine with a written prescription, said Capt. Thomas Knapp, the acting jail superintendent. Jail staff then call the doctor who wrote out the prescription to make sure it's valid, and they also check the medicine itself to confirm it's the prescribed medication. (Source: Leah Thorsen, St. Louis *Post-Dispatch*, January 17, 2007.)

Opioid administration for acute abdominal pain in the pediatric emergency department

Adi Klein-Kremer, MD
Ran D. Goldman, MD

ABSTRACT

The use of opioid analgesia for acute abdominal pain of unclear etiology has traditionally been thought to mask symptoms, alter physical exam findings, delay diagnosis, and increase morbidity and mortality. However, studies in children and adults have demonstrated that administering intravenous opioids to patients with acute abdominal pain induces analgesia but does not delay diagnosis or adversely affect diagnostic accuracy. This review discusses the effects of opioid administration on pain relief and diagnostic accuracy in children with moderate to severe acute abdominal pain who have been evaluated in the emergency department. We hold that current evidence supports the administration of opioids to children with acute abdominal pain, and future trials will help determine safe and effective timing and dosing related to opioid administration.

Key words: opioids, children, abdominal pain, emergency department

INTRODUCTION

Acute appendicitis is the most common serious pediatric abdominal emergency[1] and the most common indication for an urgent operation, with a lifetime incidence in the population of 7 percent.[2] Fifteen percent of school-aged children are brought to a physician with a chief complaint of abdominal pain,[1,2] making it one of the most common pediatric complaints in the emergency department (ED). The incidence increases with age, from an annual rate of one to two in 10,000 in children between birth and four years to one of 19 to 28 in 10,000 in children younger than 14 years.[3] Abdominal pain most frequently presents in the second decade of life.[2]

The recommendations for pain management in children with suspected appendicitis include withholding analgesia in order to avoid masking physical signs prior to a surgical evaluation.[4] It has been suggested that analgesia—especially when induced by opioids—might mask symptoms and physical findings, delay formulation of an accurate diagnosis, and possibly lead to increased morbidity.[5]

MANAGING PEDIATRIC ABDOMINAL PAIN

Accuracy of diagnosis

Clinical studies conducted in the past several years have challenged the traditional belief that analgesia should be withheld by providing evidence that analgesia significantly reduces pain without interfering with diagnostic accuracy (Table 1). Despite the mounting evidence, however, a recent survey of adult and pediatric emergency physicians in the United States and Canada reported that the majority of physicians choose to withhold analgesia at least until an evaluation by a surgical specialist has been provided. This is true regardless of whether or not they believe that analgesia will change important physical findings.[6]

A study involving 100 adult patients with abdominal pain found that localization of pain was not affected by giving papaverine as compared to placebo, and the number of appendectomies for noninflamed appendicitis was lower when analgesia was given. The number of incorrect decisions to operate was higher in the placebo group.[5]

A number of studies have examined the use of analgesia in young patients.[1,7-9] Tramadol 1 mg/kg versus placebo did not change an abdominal examination utilizing a seven-component score in a randomized, double-blind, controlled trial involving almost 70 patients older than 11 years old. The abdominal examination score included assessment of tenderness in four quadrants by light and deep palpation, localization of palpation to any area where tenderness was elicited, tenderness on rebound, cough tenderness, and tenderness on percussion of the abdomen.[7] Kim et al.[8] demonstrated effective pain relief with intravenous morphine in children with acute abdominal pain, without causing adverse events or delay

Table 1. Clinical studies providing evidence that analgesia significantly reduces pain without interfering with diagnostic accuracy				
Reference number	**Location**	**Year**	**Population**	**Findings**
2	Canada (Toronto)	2006	Patients 0 to 16 years old	Children with abdominal pain receive more analgesia when the physician suspects appendicitis
1	Canada (Halifax)	2005	108 children, ages five to 16 years	Morphine did not increase the rate of missed appendicitis
8	Finland	2005	63 children, ages four to 15 years	Effective pain relief with buccal oxycodone
7	Milwaukee	2002	60 children, ages five to 18 years	Morphine did not alter areas of tenderness
6	Singapore	2000	70 patients, ages 11 years and older	Tramadol didn't change abdominal examination as compared to placebo

in diagnosis. Among 60 children five to 18 years old, administration of morphine did not alter the localization of tenderness or the diagnostic accuracy. Similarly, Green et al.[1] demonstrated that morphine administration did not increase the rate of missed appendicitis. While the diagnostic accuracy was not affected by giving opioids, morphine was found to decrease pain scores significantly, both statistically and clinically, among 108 children aged five to 16 years old presenting to the pediatric ED with acute abdominal pain. The rate of perforated appendicitis was unchanged after treatment with morphine.

Kokki et al.[9] demonstrated effective pain relief with buccal oxycodone in 63 children between the ages of four and 15 years with acute abdominal pain, without adversely influencing the clinical examination or the appropriateness of the decision to operate; on the contrary, the researchers noted a small, nonsignificant improvement in diagnostic accuracy in children treated with oxycodone.

These results challenge some pediatric surgeons' long-held assumptions that analgesia will significantly mask crucial symptoms associated with acute abdominal pain[1,5] and that providing early treatment with narcotics affects the ability of the surgeons—faculty and senior residents alike—to make accurate diagnoses.[1,10]

We recently documented the use of analgesia in accordance with probability assessment of appendicitis by physicians in a pediatric ED.[2] Only half of the children with a high suspicion of appendicitis received analgesia in the tertiary ED in Toronto, Canada. Thirty percent of them received acetaminophen and ibuprofen from triage nurses even before being seen by a pediatrician, probably for antipyretic rather than analgesic purposes.[2] We showed that even when opioids were administered by the treating physician, almost a quarter of the children were underdosed, limiting the analgesic effectiveness of the drugs. We suggested that the misconception of the risk of a higher rate of adverse events while using morphine compared with other medication was responsible for physicians' underdosing.[2]

Our findings served as another testimony to the well-known phenomenon of "oligoanalgesia" in acute care.[11] These findings are disappointing in light of the significant effort in the last decade to increase awareness surrounding pediatric pain. While there is a better understanding of the mechanisms of pain in children and the need to treat the pain to avoid long-term consequences, abdominal pain still seems to be a challenging area, and there is still tremendous hesitancy to administer analgesia in general and opioids in particular.

The current literature on analgesia for acute abdominal pain in children suffers from several limitations. First, the small sample size in many studies[1,8,9] limits researchers' power to detect true differences between groups. Another drawback of small sample size is the resultant difficulty of detecting rare adverse events associated with opioid administration, prohibiting the thorough evaluation of the drugs' relative safety in children. Furthermore, previous studies were conducted with children of diverse age groups and with abdominal pain that was defined in different ways, limiting researchers' ability to provide definite conclusions as to the beneficial effects of opioids.

Analgesic effect of opioids

We previously showed that acetaminophen and morphine were given more commonly to children with a

high probability of appendicitis[2]; this could be explained by the fact that these drugs can be administered via routes other than oral—acetaminophen can be given rectally, and morphine can be given parenterally, eliminating the need for fluid intake in children who might require general anesthesia and should not be given anything by mouth. However, one of the limitations of that study is the fact that the analgesic drug acetaminophen was given by nurses as an antipyretic, and it was impossible to determine whether analgesia would have been prescribed by the physician had this not been the case. In Kokki et al.'s[9] 2005 study, the placebo effect was significant as measured by the mean summed pain intensity difference (SPID), but buccal oxycodone provided significantly better analgesia than buccal saline. Pain was assessed using a visual analogue scale.[12] Analgesia was measured by SPID, which reflects the cumulative response to the intervention. The mean SPID was more significant in the oxycodone group than in the placebo group (mean difference 13 cm, with a 95 percent CI of 2 to 24 cm; $p = 0.04$).[9]

Green and colleagues[1] examined whether treatment with narcotic analgesia would affect pain perception in children. A statistically and clinically significant difference in pain perception was detected in children receiving early narcotic analgesia. However, pain was not eliminated completely; the 2.2 cm change (out of 10) in the self-reported pain measure for the early-analgesia group was just beyond the threshold established for clinical significance. This change represents reduction of pain, not elimination of pain. Reducing but not fully eliminating pain through the use of early analgesia may provide a twofold benefit by decreasing the level of distress without altering diagnostic accuracy.[1,10]

Safety of opioids for acute abdominal pain

Previous studies using various opioid analgesics for acute abdominal pain did not report any significant adverse events.[1-5,7-10,13,14] However, given their small sample sizes it is still difficult to determine the absolute safety of the practice. A multicenter trial with a very large sample size is required to truly evaluate the adverse outcomes in patients who receive opioid analgesia for abdominal pain. A significant body of evidence does exist on the unlikelihood of addiction following short-term treatment with morphine. In a study of more than 11,000 patients in Boston given narcotics during a hospital stay, only four developed an opioid dependence.[15]

Kim et al.[8] confirmed that morphine provides significant reduction of abdominal pain in children. The group reported a significant reduction in pain score, as well as in the number of areas of tenderness found on palpation and percussion. They used morphine because no other analgesic agent has proven to be clinically superior in relieving pain. Morphine has also been the analgesic agent of choice for many clinical situations due to its well-published reliability, safety predictability, duration of action, and reasonable cost.[16,17]

FUTURE DIRECTIONS

Other opioids should be considered in future studies. Fentanyl may be superior to morphine due to its shorter half-life, making it appropriate for short-term evaluation in the ED. However, beyond ED evaluation, fentanyl may not be ideal because of the need for frequent administration and its higher cost.[18]

Tramadol hydrochloride, a synthetic, centrally active analgesic that selectively activates μ receptors, is another potential drug for the treatment of acute abdominal pain. Its effectiveness in controlling pain is similar to that of morphine, with a lower risk of adverse events.[7]

Oxycodone, a semisynthetic μ receptor agonist derived from thebaine, has an analgesic effect similar to that of morphine in patients undergoing surgical procedures, and due to its ability to reduce the release of histamine it might generate less nausea and vomiting than morphine. It induces less sedation and may cause fewer neurological adverse events compared to morphine. Buccal administration of oxycodone has recently been shown to be effective in the treatment of persistent postoperative pain in children.[9]

CONCLUSION

Opioid administration in children with acute abdominal pain induces analgesia without altering diagnostic accuracy. Current literature supports the need for a large-scale trial to further evaluate the safety of this approach and whether early analgesic treatment affects physicians' ability to diagnose acute abdominal pain. Guidelines for such trials should include assessing pain with valid pain scores, creating an effective response to the pain assessment, and administering appropriate analgesia for the pain scored.[19]

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Medicolegal rounds: Medicolegal issues and alleged breaches of standards of medical care in a patient motor vehicle accident allegedly related to chronic opioid analgesic therapy

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ABSTRACT

The objective of this medicolegal case report is to present the details of the case of a chronic pain patient (CPP) who was placed on chronic opioid analgesic therapy (COAT) and was involved in a motor vehicle accident, alleged in litigation to be related to COAT. COAT standards are in a process of evolution, and this process is influenced by recent literature developments. We aim to present both the plaintiff's and defendant's expert witnesses' opinions on whether the defendant physician fell below the "standard" in allowing the CPP to drive. Both the methadone and the driving literature are utilized to explain the defendant's and plaintiff's experts' opinions and the differences between them. Based on these opinions, we have attempted to develop some recommendations on how pain physicians should approach the problem of deciding whether patients should be allowed to drive when on COAT.

Key words: chronic pain, intractable pain, opioids, chronic opioid analgesic therapy, driving, motor vehicle accidents, standards of medical care, informed consent, breaches of standards, methadone

INTRODUCTION

Chronic opioid analgesic therapy (COAT) for chronic, benign, nonmalignant pain, although still controversial,[1] has become part of the pain physician's armamentarium and has recently been adopted as a treatment by other specialties, such as family medicine. The acceptance of COAT as a potential treatment option for chronic, benign, nonmalignant pain is the result of a number of pain medicine developments that began to surface in the early 1980s. The first and most important of these was the appearance of published studies claiming success in treating intractable chronic pain patients (CPPs) with COAT without the development of significant addiction.[2,3] Second, COAT treatment for pain was demonstrated to be efficacious. Recently, this literature has been compiled and analyzed in two meta-analyses and in one evidence-based, structured review.[4-6] Both meta-analyses (of over 40 double-blind, placebo-controlled studies) showed opioids to be more effective than placebo, and one demonstrated improvement in functional outcomes.[5] A significant body of literature developed which spoke to the chronic undertreatment of pain by healthcare professionals, and research studies reported that some physicians were prejudiced against the use of opioids ("opiophobia") because of fears of iatrogenic addiction.[7,8] In the late 1990s, the chronic undertreatment of pain led state licensing boards to begin to develop policies that supported appropriate opioid prescribing, rather than policies that hindered opioid prescribing. Early in this century, the Joint Commission on Accreditation of Healthcare Organizations incorporated the adequate treatment of pain as a patient right. Finally, in the 1980s drug technology developed a number of controlled-release opioids, which were believed to control pain in a more effective manner than the immediate-acting opioids.

In response to the widening use of COAT and publicity over the abuse of medically prescribed opioids, state medical boards developed state-specific physician practice guidelines for the appropriate utilization of COAT; these plans were based on some of the model guidelines developed by the American Academy of Pain Medicine and the American Pain Society.[1,9] The widening literature on how to "do COAT" and the development of the aforementioned guidelines then led to their application as "standards" in malpractice cases related to COAT.[1] Some

of these cases have been reported and explored in reference to pseudoaddiction, suicide related to unmanaged chronic pain, and methadone use.[10,11] An issue that has not yet been explored in the COAT/medicolegal/opioid-prescribing literature is that of the medicolegal standard for COAT in relation to driving rights. The medicolegal case discussed in this article addresses this issue.

CASE REPORT

Mr. X was a 45-year-old white male who presented to a pain physician's office with a chief complaint of chronic low back pain. His pain had started after a lifting injury at work when he was 40 years old. Subsequent surgery for an L5-S1 disc rupture had not relieved his pain. As a result, he was not working, had settled his workers' compensation case, and was on Social Security. Since the surgery, Mr. X's pain had worsened. He was prescribed hydrocodone (four 5 mg tablets per day), but the medication was yielding unsatisfactory pain control (pain levels over a 24-hour period ranged from 7 to 9 out of 10). No further surgery was indicated, and the current working diagnosis was degenerative disc disease and myofascial pain syndrome. Mr. X had also failed physical therapy but had not undergone any interventional procedures. He was referred by his family doctor for evaluation for the possibility of an epidural.

Mr. X denied any previous psychiatric treatment or any current psychiatric symptoms such as depression or anxiety. In addition, Mr. X denied ever having been a smoker, having a previous history of alcohol abuse/addiction, and any illicit drug use or treatment. There were no other medical problems, and he was not taking any medications other than the hydrocodone. Mr. X had a standard physical examination, and his recent imaging studies were reviewed. It was concluded that Mr. X was unlikely to benefit from epidurals and was offered COAT as an alternative. Mr. X consented and signed the standard COAT agreement. He was then placed on methadone 2.5 mg BID and was advised to discontinue hydrocodone use. In addition, he was started on tizanidine 4 mg HS for spasms. A follow-up appointment was scheduled for two weeks in the future, and Mr. X was provided with a call number. On the second day after the initiation of methadone treatment, Mr. X advised the prescribing office that he had been involved in a motor vehicle accident (MVA) (he had hit a tree) and that he thought this had happened because of the medication. He claimed that his low back pain was now worse. Two years later, the office received a letter from Mr. X's lawyers initiating a malpractice suit.

In the litigation discovery process for medical malpractice cases, the plaintiff's lawyer is allowed to name an expert who can determine whether the defendant (in this case the pain physician) fell below the standard of care in the plaintiff's treatment (that which a reasonably prudent and competent physician with the same or similar training would do in the same or similar circumstances).[10] If that expert finds that the plaintiff's care was below the standard, then in all likelihood the malpractice case will proceed. Similarly, upon receipt of the complaint the defendant's lawyer is able to name an expert who will then respond to all the allegations of falling below the standard as opined by the plaintiff's expert. Table 1 presents the opinions of the plaintiff's and the defendant's medical experts on the alleged breaches of the standard of medical care in Mr. X's case. As can be seen, the plaintiff's expert found eight alleged breaches of standards. The defendant's medical expert disagreed and absolutely refuted allegations 1, 3, 4, 7, and 8. He also partially refuted allegation 2. According to the record provided, he could not refute allegations 5 and 6. The eventual legal outcome of this case was that it was settled for much less than the requested amount.

DISCUSSION

The defendant's expert's responses to the allegations of the plaintiff's expert (Table 1) will be discussed below.

Allegation 1

In administering COAT and selecting CPPs for COAT, it is important to remember that most state practice guidelines indicate that CPPs selected for COAT should have intractable chronic pain and should have failed to find relief through other methods of pain treatment. This information should be documented to allow prescribers to avoid or refute this allegation.

Allegation 2

In a recent evidence-based, structured review, Fishbain et al.[12] examined the epidemiological evidence regarding whether opioids are associated with intoxicated driving, MVAs, or MVA fatalities. The evidence they found indicates that opioids are probably not associated with intoxicated driving, are not associated with MVAs, and are probably not associated with MVA fatalities. In another evidence-based review, Fishbain et al.[13] examined the evidence for opioid-related driving-skill impairment in opioid-dependent/tolerant patients. They found moderate, generally consistent evidence that there is no impairment of psychomotor abilities in patients on chronic opioid therapy. Their study reports strong, consistent evidence that there is no greater incidence in motor vehicle violations/MVAs in such patients versus comparable controls, and they present consistent evidence that no impairment has been measured in driving simulators for off- or on-road driving. It is to be noted that Mr. X had

Table 1. Allegations made by the plaintiff's expert witness as to breach of standards in Mr. X's medical care and the responses to those allegations made by the defendant's expert witness

Allegation	Response
1. There was no indication or reason to place Mr. X on COAT. Thus, this action is below the standard.	1. Mr. X's history indicated that he suffered from chronic pain that was not responsive to other forms of treatment, making him an "intractable" CPP. According to the state practice guidelines for COAT, this made Mr. X a candidate for COAT. Thus, no standard was breached here.
2. Mr. X's accident was related to his taking methadone.	2. Based on the literature, there is a reasonable degree of medical certainty that Mr. X's accident may not have been related to the opioid (methadone).[12] In contrast, the accident could have been related to other issues, e.g., patient characteristics, inattention, etc.
3. The defendant negligently prescribed methadone.	3. The defendant prescribed a very low starting dose of methadone that, according to equivalency tables, was approximately equivalent to or less than the dose of hydrocodone that the patient had been taking. Thus, no standard was breached here.
4. The defendant was negligent in that he failed to advise the plaintiff not to drive while on opioids.	4. There is a reasonable degree of medical certainty, as demonstrated in the literature, that patients taking opioids on a routine basis can drive safely.[12,13]
5. The defendant was negligent in that he failed to obtain informed consent from the plaintiff regarding the possibility that methadone could, under certain circumstances, be sedating, and could thus interfere with the plaintiff's ability to drive.	5. There is no evidence of this type of informed consent being obtained or requested in the defendant's notes or in the COAT agreement.
6. The defendant was negligent in that he failed to advise the plaintiff or seek informed consent regarding the possibility that methadone could, under certain circumstances, interact with other drugs (such as tizanidine) and thereby cause increased sedation.	6. There is no evidence of this type of informed consent being obtained or requested in the defendant's notes or in the COAT agreement.
7. The defendant was negligent in that he did not monitor the plaintiff closely enough after methadone treatment was initiated.	7. The defendant placed the plaintiff on methadone and tizanidine and scheduled a two-week follow-up appointment. The defendant was also available to the plaintiff by phone for advice regarding changes in medication dosages. If the plaintiff was feeling sedated on the new medication, a call should have been placed to the defendant.
8. The defendant was negligent in that he chose to place the plaintiff on methadone rather than another long-acting opioid with fewer side effects.	8. There is currently no absolute contraindication noted in the literature to utilizing methadone in COAT as a first-line drug. Although this literature may be developing, the defendant did not fall below the standard here.

previously been exposed to hydrocodone and was presumably tolerant to that opioid. Thus, he should have been partially tolerant to the effects of methadone. Based on the information in the two above-mentioned reviews, the defendant's expert concluded that Mr. X's accident may not have been related to methadone.

Allegation 3

When changing from one opioid to another, equivalency tables should be utilized, and the calculated dose of the new opioid should be documented in the patient's chart. This was done by the defendant, and the very low dose of methadone utilized in a non-opioid-naïve subject essentially negates the possibility that this standard was breached in this case.

Allegation 4

It is clinical lore that patients on psychotropic medications should be advised not to drive or should be warned about driving. However, according to the studies described above regarding allegation 2, this clinical lore may be incorrect in reference to opioids.[12,13] The

reviewed literature indicates that patients on opioids can drive safely, especially when they have developed a tolerance to the sedating effects of the medication.[12,13] Thus, the defendant's expert concluded that there was no breach here.

Allegation 5

Although the evidence in the two cited evidence-based reviews indicates that patients stabilized on COAT and tolerant to opioids can be advised that they can drive,[12,13] Fishbain et al.[13] present some caveats to this possibility.

First, patients placed on long-term opioid treatment should be advised of the current status of this driving research. They should then be advised that whether they do or do not drive should be based on this information, but that it is their own personal decision. Third, they should be advised that if they choose to drive, they should obey the following rules:

- After beginning opioid treatment or after a dose increase, the patient should not drive for four to five days.
- Patients should not drive if they feel sedated.
- Patients should report sedation/unsteadiness/cognitive decline immediately to their physicians so that a reduction in dosage can be initiated.
- Under no circumstances should patients use alcohol or other illicit drugs such as cannabinoids and then drive.
- Patients on opioids should avoid taking any over-the-counter antihistamines.
- Patients should not make any changes in their medication regimens without consulting with their physician.

A final issue pointed out by Fishbain et al.[13] relates to what the physician should do if he or she is requested to complete paperwork where questions are asked about a patient's driving ability. For this problem, the same type of approach was recommended. The physician should explain the current status of the relevant research in the paperwork. In addition, the physician should also report whether he or she has noted any opioid side effects that might interfere with driving (or the absence of such effects). However, if a specific question relating to whether the patient can or can not drive is encountered, that status should be marked as unknown. More specifically, the physician should state that he or she does not have knowledge of the patient's ability to drive, as that can only be determined via a driving simulator and/or on-road/off-road driving tests.

According to the above recommendation, some form of informed consent in reference to the risks of driving concurrent with opioid use should have been obtained from Mr. X. Ideally, COAT agreements could be utilized for this issue.

Allegation 6

Unfortunately, there are large variations in the pharmacokinetics of methadone from one individual patient to the next, and this makes it a difficult drug to use.[11] Methadone is characterized by a slow elimination phase, which can vary from 4.2 to 130 hours.[11] Thus, variations in the elimination phase could lead to accumulation toxicity in some patients. In addition, methadone may interact with other drugs, as it particularly inhibits the CYP2D6 isoenzyme systems. This inhibition can affect the levels of drugs metabolized by CYP2D6.[14] Tizanidine is 95 percent metabolized in the liver, and therefore any inhibition of liver metabolism could cause decreased tizanidine metabolism, resulting in increased sedation. Thus, there is a possibility that methadone, in spite of the low dose used, accumulated in the plaintiff and/or interacted with tizanidine, causing sedation. As noted in the allegations, no informed consent for these possibilities was furnished. It has been recommended that when mixing drugs, the patient should be educated about all potential problems.[15]

Allegations 7 and 8

It is recommended that the physician remain available for patient monitoring when a patient is placed on a new medication.[15] The defendant, by the nature of his situation, did not fall below the standard here. In reference to allegation 8, physicians can utilize whichever drug they wish over any other drug. This applies as long as the side-effect profile of the chosen drug is not so burdensome that there is a specific contraindication for use in the patient in question.

CONCLUSIONS

This case is interesting and instructive for a number of reasons. First, it outlines the process by which allegations are generated by the "experts." Second, it outlines how experts utilize the current literature in arriving at their opinions. Third, this presentation outlines the importance of the agreed-upon standards of care and how they are applied utilizing current literature. It is to be noted that there is an intimate relationship between the current literature and the development of the standards.

However, when a standard of care is in the process of being developed, such as with recent research reports, most jurisdictions recognize the "respectable minority" defense.[16] This defense applies when a standard of care is in a transitional phase, as are those being developed for COAT, and it may apply here to allegations 5 and 6. A "respectable minority" of physicians may not have provided informed consent for methadone in circumstances such as Mr. X's because this information was not widely disseminated. In that case, this alleged breach would not necessarily be deemed negligence by the courts. Finally, this case brings to light a potential area of malpractice liability for physicians administering COAT: patient driving risk.

Physicians utilizing COAT should remain abreast of the developing COAT literature. This can be an effective method for improving COAT patient care and decreasing liability risk.

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ORIGINAL ARTICLE

Morphine prescription in end-of-life care and euthanasia: French home nurses' opinions

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ABSTRACT

Objective: *This study aimed to investigate factors that might lead French homecare nurses to consider the prescription of high-dose morphine to terminally ill patients to be euthanasia.*

Methods: *The researchers conducted an anonymous telephone survey among a random sample of 602 French homecare nurses (response rate = 75 percent) in 2005.*

Results: *Overall, 27 percent of responding home nurses considered prescribing high-dose morphine to terminally ill patients to be euthanasia. Such an opinion was more frequently held by older nurses, those who had not followed terminally ill patients during the previous three years, and those with less knowledge about pain management involving opioid analgesics.*

Conclusion: *There is an urgent need to strengthen pain management education among French homecare nurses—especially regarding the use of morphine—in order to both improve their technical skills and correct some misconceptions about opioid analgesics.*

Key words: morphine, euthanasia, end of life, France

INTRODUCTION

Pain management is a key issue in increasing the quality of life of dying patients, and it is one of the most important goals of palliative care. Opioids, especially morphine, remain the treatment of choice for relieving severe pain, and high-dose morphine could be required in end-of-life care. In France, despite the priority given by international guidelines and public health authorities to the improvement of pain management in end-of-life care, many physicians are still reluctant to prescribe morphine to terminal patients with severe pain, and a minority consider such prescription to amount to euthanasia.[1,2] Nurses are also involved in pain management, and they have a vital role in pain assessment and titration of opioid doses. A French law passed in 2002 states that nurses have to assess patients' pain and must also adapt their treatment if necessary. Surveys conducted in other countries suggest that negative attitudes toward morphine use in pain management are not uncommon among nurses and that they may contribute to undertreatment of pain.[3-6] French health authorities are currently encouraging the development of end-of-life home care. This form of care is common in many developed countries, where most people state a preference for dying at home.[7-9] As a consequence, over the next decade home nurses will be increasingly confronted with end-of-life situations that may require the use of high morphine doses to relieve patients' pain. Such use of morphine at home is considered safe and is not thought to adversely affect the patient's life expectancy.[10] This article aims to study French home nurses' propensity to consider high-dose morphine prescription in terminal care to be euthanasia, using data from a nationwide survey conducted in 2005 by France's Southeastern Health Regional Observatory and the Health and Medical Research National Institute.

METHODS

Sampling and data collection

Between May and September 2005, a computer-assisted telephone-interview survey was carried out among a random sample of French home nurses. Eligible subjects were nurses currently delivering home care who had at least one year of professional experience. In France, most nurses are females, but we assumed that gender may

shape beliefs, attitudes, and practices regarding end-of-life and palliative care. For this reason, we stratified the sample to ensure an adequate representation of males. First, we randomly selected 2,400 nurses from the complete file of French nurses kept by the private society CEGEDIM.™ From this sample, 233 males and 722 females were contacted to participate in the survey.

Questionnaire

The questionnaire was developed by the South Eastern France Palliative Care Group, which comprises doctors, nurses, and sociologists. It included five modules dealing with the following topics, respectively: 1) patient-nurse communication, 2) description of the last terminally ill patient the home nurse had followed up until death, 3) knowledge of pain management, 4) opinions and attitudes toward palliative care and euthanasia issues, and 5) the nurse's personal and professional background (including gender, age, religiosity, specialized training in palliative care and pain management, and number of dying patients followed during the previous three years). In the fourth module, respondents were asked whether or not prescribing high-dose morphine to a dying patient should be considered euthanasia, and responses were based on a 5-point Likert scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree).

Nurses' knowledge of pain management was assessed using 27 items picked up from several questionnaires developed by McCaffery and Ferrell.[11,12] These deal with common misconceptions about pain assessment and analgesics. Two separate scores have been computed: a score of general knowledge about pain management (with no item related to opioid analgesics; score ranging from 0 to 15) and a score of knowledge about pain management involving opioid analgesics (with specific items; score ranging from 0 to 12) (see Appendix for details of the items).

Statistical analyses

The 5-point scale used in the question about considering the prescription of high-dose morphine to an end-of-life patient to be euthanasia was collapsed into a binary outcome ("strongly agree" or "agree" versus "neither agree nor disagree," "disagree," and "strongly disagree"). First, we used Pearson's χ^2 test (with Yates' correction) to test the relationships between respondents' characteristics and this binary outcome (we used Yates' correction to prevent overestimation of statistical significance for small data).[13] Secondly, to investigate factors associated with opinions toward morphine use in end-of-life care while controlling for potential confounding factors, we computed a multivariate logistic model with a stepwise method (entry threshold $p = 0.1$).

RESULTS

Data collected

Among the 955 home care nurses contacted, 152 ultimately did not participate in the survey because of incorrect phone numbers or ineligibility (insufficient professional experience, not delivering home care, retired). Among the remaining 803 nurses, 602 agreed to participate (451 females and 151 males) and 201 (161 women and 40 men) refused to participate. The response rate was 74 percent among female nurses and 79 percent among male nurses. Nonrespondents were asked to fill in a brief refusal questionnaire. The nonrespondents were found to be slightly older than respondents, and they most frequently explained their refusal to be interviewed as the result of a lack of time.

Two-thirds of respondents (68 percent) were under 50 years of age, and 74 percent reported that they did not believe in the existence of a god who controls their destiny (Table 1). Overall, 57 percent of participating home nurses had completed a specialized training program in pain management during the previous five years, but only 26 percent did so for specialized training in palliative care. Only 3 percent had not followed any terminally ill patients during the previous three years.

Factors associated with opinions regarding morphine prescription

Roughly one-fourth of responding home nurses stated that prescribing high-dose morphine to terminally ill patients should be considered euthanasia. In bivariate analysis, gender, religiosity, specialized training in palliative care, and general knowledge about pain management were not significantly correlated with such an opinion. Nurses trained in pain management were less likely to consider high-dose morphine prescription to be euthanasia (23 percent versus 30 percent, $p = 0.074$), but this difference was no more significant in the multivariate analysis. In contrast, several results were statistically significant in both bivariate and multivariate analyses. Prescribing high-dose morphine to a terminally ill patient was more frequently considered to be euthanasia by older nurses (35 percent among those 50 and older, versus 24 percent among those 49 and under, $p = 0.001$; adjusted odds ratio = 1.7). This opinion was also more prevalent among nurses who had not followed any terminally ill patients during the previous three years (44 percent, versus 26 percent among those who had followed at least one patient). Finally, greater knowledge about pain management involving opioid analgesics was significantly associated with a lower propensity to label high-dose morphine prescription for terminally ill patients as euthanasia.

Table 1. Home nurses' personal and professional characteristics and opinions toward the prescription of high-dose morphine to terminally ill patients (n = 602; France, 2005)				
Prescribing high-dose morphine to a terminally ill patient should be considered euthanasia.				
	No (1) 442 (73 percent)	**Yes (2) 160 (27 percent)**	**(2) vs. (1) bivariate p value**	**(2) vs. (1) adjusted OR [CI: 90 percent]**
	n (row percent)			
Gender				
Male (ref.) (n = 151) (ref.)	106 (70)	45 (30)	0.353	–
Female (n = 451)	336 (74)	115 (26)		
Age				
≤ 49 years (n = 410) (ref.)	318 (76)	92 (24)	0.001	1
≥ 50 years (n = 192)	124 (65)	68 (35)		1.7 [1.2 – 2.6]
Do you believe in the existence of a god who controls your destiny?				
No (n = 443) (ref.)	323 (73)	120 (27)	0.713	–
Yes (n = 159)	119 (75)	40 (25)		
Specialized training in palliative care (during the last five years)				
No (n = 406) (ref.)	292 (72)	114 (28)	0.230	–
Yes (n = 196)	150 (77)	46 (23)		
Specialized training in pain management (during the last five years)				
No (n = 342) (ref.)	241 (70)	101 (30)	0.074	–
Yes (n = 260)	201 (77)	59 (23)		
Number of terminally ill patients followed during the last three years				
0 (n = 43) (ref.)	24 (56)	19 (44)	0.022	1
1 – 10 (n = 363)	274 (75)	89 (25)		0.4 [0.2 – 0.9]
> 10 (n = 196)	144 (73)	52 (27)		0.5 [0.3 – 1.0]
General knowledge about pain management				
Mean score [SD] (score range: 0 – 15)	8.3 [2.1]	8.0 [2.3]	0.188	–
Knowledge about pain management with opioid analgesics				
Mean score [SD] (score range: 0 – 12)	5.2 [1.9]	4.9 [1.6]	0.015	0.9 [0.8 – 1.0]
SD: standard deviation; p value: computed for Pearson's χ^2 with Yates' correction; OR: odds ratio; –: not selected by the stepwise procedure.				

DISCUSSION

In the present study, 27 percent of responding home nurses (26 percent among females, 30 percent among males) considered prescribing high-dose morphine to terminally ill patients to amount to euthanasia. Such an opinion was more frequently held by older nurses, those who had not followed any terminally ill patients during the previous three years, and those with less knowledge about pain management involving opioid analgesics. Before discussing our results, however, we must acknowledge several limitations of the present study.

Answering questions on a sensitive topic such as euthanasia can be delicate when done over the phone. Moreover, a closed-ended questionnaire prevents respondents from qualifying or justifying their responses, and we investigated attitudes, not actual practice (legal constraints prevented us from asking any questions dealing with respondents' personal experience with euthanasia). For example, nurses may endorse positive attitudes toward morphine use but administer the lowest effective amount or encourage patients to take nonopioids rather than opioids for pain relief.[4] As our data were cross-sectional, we can not draw conclusions as to whether the relationship between age and opinion toward high-dose morphine prescription is due to either "age effect" (nurses' opinions change as they grow older) or "generation effect" (newer cohorts of nurses may have different opinions due to a shift in moral values or in nursing education). In either case, this effect is probably context dependent, as results opposite ours have been found in Korea.[6] However, both the Korean study and the present one found a relationship between practical experience caring for terminally ill patients and more positive attitudes toward morphine use (if one regards labeling high-dose morphine prescription to terminally ill patients as euthanasia as a "negative" attitude). A number of previous surveys dealing with nurses' knowledge and attitudes toward pain management have found serious knowledge deficits regarding opioid analgesics which could adversely affect the care of terminally ill patients with severe pain, especially because these deficits fuel irrational fears of creating opioid addiction.[14-17] Our results suggest that specific knowledge deficits about pain management utilizing opioid analgesics could also fuel another misconception that may be a cause for undertreatment of pain: considering the prescription of high-dose morphine to terminally ill patients to qualify as euthanasia. Finally, our results suggest an urgent need to strengthen pain management education among French home care nurses, especially regarding the use of morphine, in order to both improve their technical skills and correct some misconceptions about opioid analgesics. Indeed, previous studies have shown that training programs in palliative care and pain management can significantly improve nurses' knowledge and attitudes regarding this issue, for home care nurses as well as for hospital staff.[11,18]

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APPENDIX. QUESTIONS USED TO ASSESS NURSES' KNOWLEDGE OF PAIN MANAGEMENT[12,13] (CORRECT ANSWERS IN PARENTHESES)

Questions related to opioid analgesics

True or false

After the initial recommended dose of opioid/narcotic analgesic, subsequent doses are adjusted in accordance with the individual patient's response. (true)

Elderly patients can not tolerate strong medications such as opioids for pain. (false)

Opioid analgesics are best ordered on a PRN basis to encourage minimal dosing and reduce the risk of addiction. (false) (PRN: practicing registered nurse)

Patients with a history of substance abuse who require intravenous opioids should not be given patient-controlled analgesia. (false)

Beyond a certain dose of opioid (morphine, Dilaudid), increases in dose will not increase pain relief. (false)

Respiratory depression rarely occurs in patients who have been receiving opioids over several months. (true)

If opioids are used during the pain evaluation period, they will adversely affect your ability to correctly diagnose the cause of pain. (false)

Adjuvant analgesics such as tricyclic antidepressants and anticonvulsants should not be used in combination with opioid analgesics or NSAIDS. (false)

The usual duration of action of meperidine (Demerol) is four hours. (false)

Research shows that hydroxyzine (Vistaril) is a reliable potentiator of opioid analgesia. (false)

Multiple choice

What is the recommended route of administration of opioid analgesics for patients with prolonged cancer-related pain? intravenous, intramuscular, subcutaneous, oral, rectal (oral)

Which of the following analgesic medications is considered the drug of choice for the treatment of prolonged moderate to severe pain for cancer patients? Brompton's cocktail, codeine, morphine, meperidine, methadone (morphine)

Other questions about pain management

True or false

If the patient can be distracted from his pain, this usually means that he does not have as high an intensity of pain as he indicates. (false)

A patient may sleep in spite of severe pain. (true)

Because of an underdeveloped nervous system, children under the age of two have little sensitivity to painful stimuli and limited memory of painful experiences. (false)

Giving patients sterile-water injection (placebo) is a useful test to determine if the pain is real. (false)

Beyond a certain dose of nonopioid analgesics, increases in dose will not increase pain relief. (true)

Basically, pain is best managed with single analgesics rather than with a combination of drugs. (false)

Anticonvulsant drugs (e.g., carbamazepine) produce optimal pain relief after a single dose. (false)

Corticosteroids (e.g., dexamethasone) are a standard emergency treatment for suspected malignant spinal cord compression. (true)

Neuropathic pain may be particularly responsive to anticonvulsant drugs. (true)

Although benzodiazepines provide relief from painful muscle spasms, they are not effective analgesics. (true)

Lancinating pain may be particularly responsive to therapy with anticonvulsant drugs. (true)

Children can reliably report the intensity of their pain. (true)

Nondrug interventions (such as distraction and imagery) used alone can often relieve pain. (false)

Multiple choice

Why would a terminal cancer patient with chronic pain request increased doses of pain medication? The patient is experiencing increased pain, The patient is experiencing increased anxiety or depression, The patient is seeking more staff attention, The patient's requests are related to addiction (The patient is experiencing increased pain)

Who is the most accurate judge of the intensity of the cancer patient's pain? the treating physician, the patient's primary nurse, the patient, the pharmacist, the patient's spouse or family (the patient)

ORIGINAL ARTICLE

Patterns of illicit drug use and retention in a methadone program: A longitudinal study

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ABSTRACT

Objective: *This study aimed to analyze illicit drug use of participants in a methadone treatment program in relation to methadone dose, counseling, and retention.*

Methods: *This was a longitudinal study of a cohort of 204 heroin-dependent subjects admitted for the first time to a methadone program in Stockholm. The patients were admitted between 1995 and mid-2000 and were followed until December 2000 or discharge. Up to June 11, 1998, individual psychosocial counseling was provided; after this date individual counseling was replaced with group counseling. Clinical data were collected from patient records and from a laboratory database. Rates of drug-positive urine analyses during different time periods were measured.*

Results: *The mean observation time was 2.5 years for all patients. The one-year retention rate was 84 percent, and the two-year rate was 65 percent, with no major differences between the two counseling groups. Almost all patients relapsed to illicit drug use. Discharged patients had a significantly higher rate of positive urine samples (21 percent versus 9 percent) than patients who remained in treatment. Also, low methadone dose and younger age predicted discharge from treatment.*

Conclusion: *The frequent urine monitoring showed that illicit drug use was rather common, even in a program with structured psychosocial interventions, although it was lower than in other studies. This testing policy can be used for early identification of patients at risk for drop-out or discharge who should be offered complementary interventions.*

Key words: methadone maintenance treatment, urine samples, drug abuse patterns, discharge, drug abuse, methadone dose

INTRODUCTION

Methadone maintenance treatment (MMT), generally used in combination with psychosocial services, is a well-documented treatment for opiate addicts. It offers a number of reported positive effects, such as reduced opiate and other illicit drug use,[1,2] decreased risk for needle sharing and HIV transmission,[1,3-5] reduced risk of premature death,[6] reduced criminal behavior,[7] improved quality of life,[8] social rehabilitation, and reduced costs for society.[1,2,5,9,10] Illicit drug use is one of the most common reasons for clients' leaving MMT prematurely[11] and is related to the methadone dose[12] and level of psychosocial services[1,13] provided. Moolchan and Hoffmann[14] proposed a four-phase model with successively decreasing treatment interventions in relation to increased performance. The question of whether the impact of group-based counseling differs from that of individual counseling warrants study.

Information about illicit drug use during MMT can be obtained through interviews alone[1,15] or in combination with urine drug screening.[16,17] However, the validity of interview data is uncertain, as patient reports may be influenced by recall difficulties and perceived risk of negative sanctions if illicit drug use is exposed.[18,19] Magura and Lipton[20] concluded that urinalysis is the most objective measure for evaluating patients' illicit drug use, as well as for making clinical decisions during treatment. Studies employing data from both interviews and urine testing have focused on changes in illicit drug use during treatment periods shorter than one year.[16,17]

The Methadone Maintenance Treatment Programmes (MMTP) in Sweden were regulated by the National Board of Health and Welfare,[21] in accordance with Dole and Nyswander's initial model, until January 2005. The national goal of a drug-free society led to close scrutiny of MMTP,

and the maximum number of patients allowed in the treatment programs at the same time was limited (500 patients 1994 through 1996,[22] 600 patients 1997 through 1998,[23] 800 patients 1999 through 2003,[24] and 1200 in 2004[25]). The inclusion criteria were a minimum of four years of addiction involving compulsive intravenous opiate use, an age of at least 20 years, failed individual rehabilitation by drug-free treatment, absence of advanced polydrug use, and the patient's free choice to enter the program.[21] The two-year retention rate was 80 percent for all 655 patients in MMTP in Sweden until 1993, which is markedly higher than in most other reported studies.[26]

The Stockholm MMTP expanded from 100 patients in 1988 to 271 patients in 1994, to 310 patients in 2000. After detoxification, MMT was initiated in ward or at the outpatient clinic and, at least during the following three months, supervised daily intake of methadone and routine urine sampling were obligatory. Approximately every second urine specimen was selected for laboratory analysis. The methadone dose was increased for all patients—up to 50 to 60 mg—during the first three months; after this point doses were individually adjusted (usually increased) if a patient reported withdrawal symptoms and/or if the plasma methadone concentration was lower than 200 to 400 ng/ml.[27] If the patient used illicit drugs, a drug-free period of four weeks was demanded before dose adjustment. A positive urine sample resulted in daily testing until a negative sample was produced. If the rehabilitation progressed positively, urine sampling became more infrequent (usually two to four times a month), take-home doses were allowed, and psychosocial services were gradually decreased. Decisions regarding involuntary discharge were made after discussion and evaluation of the patients' treatment performance and potential to benefit from further treatment. The criteria for inevitable involuntary discharge were threat of violence, criminal acts leading to a prison sentence, drug dealing, providing or smuggling narcotic substances and/or methadone, tampering with a urine specimen, and, from 1997 on, not taking methadone according to prescription.

MMTP thus made use of frequent monitoring of illicit drug use through urine testing. The existence of well-documented data about urine test results, methadone doses, and discharges dating back to 1995 permitted a more detailed analysis of illicit drug use during MMT than reported in other studies, and this is the rationale for this report. The aim of this study was to analyze the following:

- frequency and patterns of illicit drug use and its relation to gender and methadone dose;
- whether discharged patients have different patterns of illicit drug use than those remaining in treatment, especially early in treatment;
- whether initial individual or group counseling is related to illicit drug use, methadone dose, and retention; and
- the roles of illicit drug use and age at discharge.

The study was approved by the Research Ethical Committee at Karolinska Institutet on November 5, 2001 (Dnr: 01-310).

METHODS

During the period from January 1, 1995, to June 30, 2000, 225 heroin-dependent subjects with no prior experience with MMT were admitted to MMTP. This study is based on 204 of these patients, as 21 were excluded because of transfer to another MMTP (six subjects), lack of urinalysis results (four), or no participation in "The New Team" (11 subjects). The subjects were followed until December 31, 2000. The observation period ranged from six months to six years.

The psychosocial intervention was based on structured individual counseling (here referred to as "The Old Team") until June 1998, when a more structured group treatment program was introduced (here referred to as "The New Team") based on Moolchan and Hoffman's[14] model, with mandatory activities for about 15 hours each week during the first three months or until negative urine samples were obtained. After this first treatment phase, patients were transferred to one of four other outpatient clinics for continued treatment based on individual counseling, urine screening, and cooperation with the social service agencies.

Data collection

Information about illicit drug use was obtained from the laboratory database. The exception was alcohol consumption, regarding which we lacked sufficiently detailed information. The urine samples were analyzed using routine immunochemical screening methods for methadone, opiates, benzodiazepines, amphetamines, cocaine, cannabis, barbiturates, LSD, and propoxyphene. Confirmation analyses by gas chromatography and mass spectrometry were undertaken if a positive screening result was refuted by the patient; these tests were performed in about 10 percent of all positive cases. The number of urine samples analyzed per person was 122 during the first year and decreased successively over time to 55 during the fifth year for patients with at least four years of treatment. Positive test results were grouped into relapse periods, each consisting of one or more sequential positive results and ending with the first negative result. All data concerning time in treatment, methadone dose, reasons for discharge, and patient characteristics were abstracted from patient records.

Statistical analysis

This study includes nearly all first-time patients admitted to MMTP during the study period. The power is 100 percent when we look at illicit drug use in relation to treatment status, but power has not been calculated for other analyses, as the numbers of patients are too low in the subgroups. Statistical analysis of illicit drug use during different periods after entry into MMTP was performed for all positive urine samples combined and separately for opiates, amphetamines, benzodiazepines, and cannabis. The differences were analyzed by χ^2 test. Results were considered significant for $p < 0.05$. Poisson regression was used to adjust for differences in follow-up time among subjects when calculating the number of relapse periods in relation to time at risk (time with drug abuse excluded). The incidence rate (number of relapse periods per person and year) was calculated as the total number of relapses divided by the total time in treatment for all persons during relevant time periods.[28] The relationships between illicit drug use and methadone dose, gender, age, and initial psychosocial treatment were compared for subjects who were in treatment on December 31, 2000, and for those who were discharged before the end of the study period. The Wilcoxon signed-rank test and Spearman rank-order correlations were calculated for bivariate correlations. The last adjusted methadone dose before three and six months in treatment, at one year, at 435 days (representing the median time in treatment for the 84 discharged patients), and each following year were compared between the patients in treatment and those who were discharged. The relative risk for relapse to drug use for the discharged patients in comparison to those in treatment was calculated from the incidence of relapse periods for each group. SAS software packet 9.0 was used for data analysis.

RESULTS

Subjects

The study cohort comprised 147 men (72 percent) and 57 women (28 percent). The median age at admission was 36 years (range of 21 to 66 years) for the men and 34 years (range of 24 to 50 years) for the women. The majority (54 percent) of patients had nine years or less of schooling, and only 5 percent had studied at a university. All patients had been detoxified in inpatient care at least once, and 40 percent more than 10 times. The mean number of prior residential treatment episodes was 2.4. At admission, 74 percent of patients were unemployed, 22 percent were receiving disability pension or were sick-listed, and 4 percent were employed, self-employed, or students. The mean number of years of intravenous opiate use was 11, and use of other illicit drugs had usually occurred for several years.

Mean observation time and retention

Of the 204 patients, 120 patients (89 men, 31 women) remained in treatment and were followed until December 31, 2000, and 84 patients (58 men, 26 women) were followed until discharge. The mean time in treatment was 869 days (2.4 years) for all patients, 1,084 days (3 years) for patients who remained in treatment, and 561 days (1.5 years) for discharged patients. Two patients were discharged during the first three months. The one-year retention rate was 84 percent. The discharged patients were significantly younger (median age of 33 years; $p < 0.05$) than the patients who remained in treatment (median age of 37 years).

Results from urine screening

Illicit drug use was detected at least once in 13 percent (5,666) of 45,431 analyzed urine samples, corresponding to 3 percent of all 231,073 drug analyses (some tests did not involve all nine substances). Discharged patients had a significantly higher rate of positive urine samples (21 percent versus 9 percent) than patients who remained in treatment. Only nine of all 204 patients had no positive tests. Of all positive urine samples, 50 percent were positive for opiates, 49 percent for benzodiazepines, 16 percent for amphetamines, 8 percent for cannabis, and 2 percent for cocaine. There was no gender difference.

Illicit drug use after entry

The total number of relapse periods was higher for those who were discharged during all time periods. During the first three months, 51 percent (104 patients) of all 204 patients relapsed at least once; this value represents 47 percent (56) of the 120 patients in treatment and 57 percent (48) of the 84 discharged patients, resulting in a nonsignificant difference ($p = 0.14$). Figure 1 shows that 78 percent (81) of the 104 patients had at least one urine sample positive for opiates; 43 percent (45) had taken benzodiazepines, 20 percent (21) amphetamines, 9 percent (9) cannabis, and only 2 percent cocaine. Illicit use of amphetamines was significantly more frequent in the discharged group (31 percent, or 15 patients) than among those who remained in treatment (11 percent, or six patients; $p < 0.01$).

About 12 percent (24) of the 204 patients left urine samples that were positive for both opiates and benzodiazepines, but there was no significant relationship between these results and discharge ($p = 0.35$). The mean number of relapse periods per person during the first three months of treatment was 4.6 for discharged patients, compared to 3.4 per person and year among patients in treatment at the end of the observation period

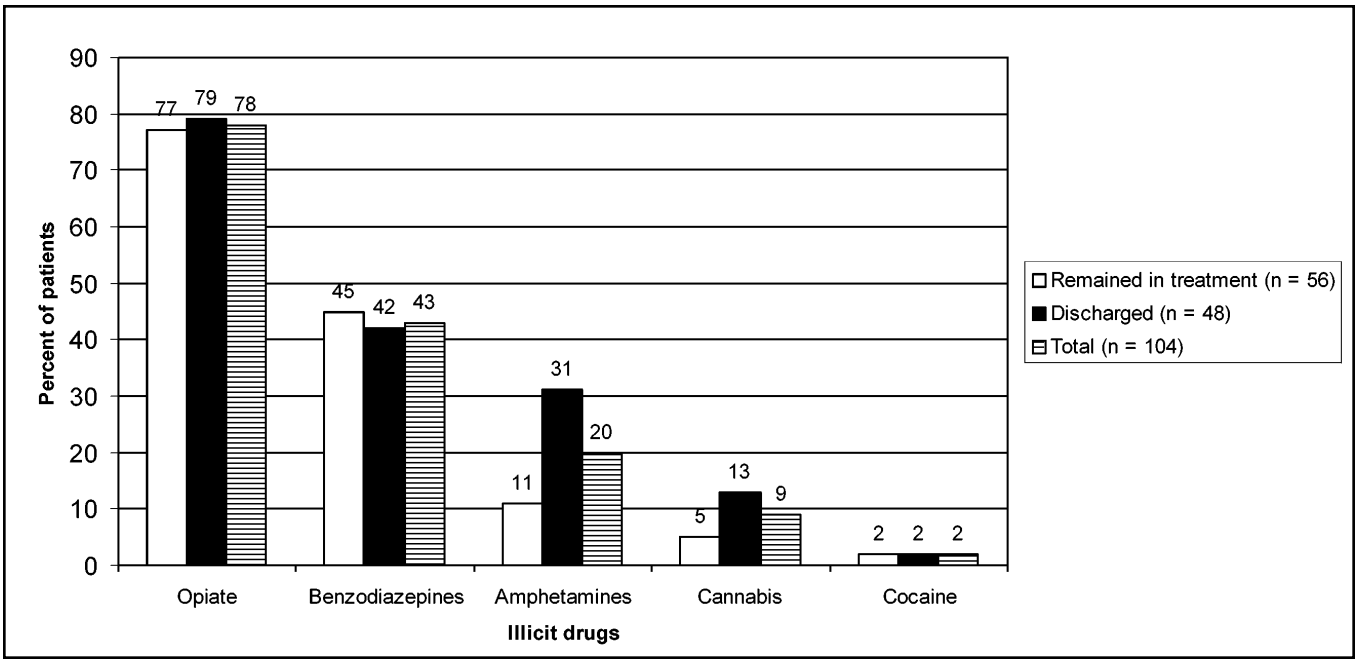

Figure 1. Percent of patients with relapse (n = 104) to various drugs during the first three months of treatment.

(p = 0.02); in this area there was a statistically significant difference for men (p = 0.04) but not for women. Discharged patients also had significantly more relapse periods per person and year during the first six months and each year thereafter (up to and including the third to fourth years: p < 0.0001; fourth to fifth years: p = 0.05) (Table 1).

The overall relative risk for illicit drug use for patients who were discharged was 2.3 (95 percent CI 2.0 to 2.4) in comparison to those who remained in treatment; for men the risk was 2.2 (95 percent CI 2.0 to 2.4) and for women 2.9 (95 percent CI 2.5 to 3.5). The relapse rate among discharged patients decreased with longer treatment periods for both groups with regard to opiates, cannabis, and amphetamines, but not for benzodiazepines (Table 2).

Methadone dose in relation to relapse with opiates and retention

The rate of relapse to opiates during the observation period was negatively associated at the last adjusted methadone dose (r = -0.22; p < 0.05) and also at 435 days of treatment (r = -0.19; p < 0.05). The mean last adjusted dose was significantly lower for discharged patients than for those who remained in treatment: 63 versus 67 mg at three months (p < 0.05), 70 versus 76 mg at six months (p < 0.0001), 75 versus 84 mg at one year (p < 0.0001), and 81 versus 87 mg at two years of treatment (p < 0.05).

Association between counseling, illicit drug use, and methadone dose

Of the 204 patients, 131 (93 men and 38 women) were admitted to The Old Team (through June 11, 1998) and 73 (54 men and 19 women) to The New Team (from June 12, 1998, to June 30, 2000). Overall, men and women from The Old Team had significantly more relapse periods than those from The New Team for the first two years of treatment (p < 0.0001). The number of relapse periods per person per year for patients in The Old Team was 5.9, versus 4.4 for patients in The New Team, and 8.4 versus 7.3 for discharged patients from the two teams, respectively. The last methadone dose before the end of the first year of treatment was significantly higher in The New Team than in The Old Team (83 mg versus 77 mg; p = 0.0052), especially among men (83 mg versus 75 mg; p = 0.0006), which may account for some of these differences. The one- and two-year retention rates were 85 and 66 percent in The Old Team and 83 and 63 percent in The New Team.

Reasons for involuntary discharge

Thirty-eight of the 84 involuntarily discharged patients (45 percent) were discharged because of illicit drug use, mostly in combination with some other discharge criteria. They had an average of 7.1 relapse periods per person per year, versus 6.6 for those who were discharged for other reasons (p = 0.23). About 30 percent of the discharged patients were women—the same proportion of females as in the entire study population. The proportion of discharged patients declined with age; 55 percent of patients ≤ 30 years of age were discharged, versus 23 percent of patients ≥ 41 years of age.

Table 1. Number of relapse periods per person and year among patients who remained in treatment (Tx) or were discharged (Dis)

	Time in treatment												
	0 to 6 months		6 to 12 months		1 to 2 years		2 to 3 years		3 to 4 years		4 to 5 years		5 to 6 years
Observation period	Tx (n = 1)	Dis (n = 14)	Tx (n = 14)	Dis (n = 20)	Tx (n = 25)	Dis (n = 29)	Tx (n = 24)	Dis (n = 10)	Tx (n = 25)	Dis (n = 7)	Tx (n = 13)	Dis (n = 4)	Tx (n = 18)
0 to 6 months	2.0	8.8	3.6	6.5	2.5	3.9	4.4	6.0	4.6	5.4	2.9	5.0	3.0
6 to 12 months			3.6	7.8	4.4	6.0	3.2	7.6	2.8	4.9	4.9	7.5	3.1
1 to 2 years					6.0	8.8	2.5	7.4	3.9	8.0	2.7	5.3	4.2
2 to 3 years							3.0	6.6	2.0	6.6	3.9	8.0	3.3
3 to 4 years									2.2	6.9	1.6	7.8	2.3
4 to 5 years											1.7	4.3	2.2
5 to 6 years													1.3

DISCUSSION

No other reports seem to exist about MMT programs utilizing such frequent urine analyses. Most of the patients left at least one positive urine sample, and almost all patients relapsed to opiates, but of the total taken only 13 percent of the urine samples were positive. In a study by Saxon et al.,[29] 40 percent of urine samples collected weekly during an 18-month period were positive for opiates; about 38 percent were positive for cocaine, 7 percent for benzodiazepines, and about 30 percent each for propoxyphene, barbiturates, and amphetamines. These percentages are much higher than in our study, but the mean methadone dose was lower in the Saxon et al. study. It was expected that discharged patients would have a significantly higher rate of positive urine samples than patients who remained in treatment (21 percent versus 9 percent), as this is a common reason for discharge. At the same time, the analyses show that patients with (even repeated) illicit drug use during treatment can stay in treatment after an overall assessment of their situation. This is contrary to a belief expressed in a sometimes polarized discussion of MMT in Sweden and in the past has been seen as controversial.

The policy of urine screening remained unchanged. A limitation of the study is the decreasing number of urine specimens with time in treatment.[30] We do not know whether we would have found a higher level of drug use with more frequent urine testing or with complementary self-reports. A combination of the two methods is considered to be more effective than either method used alone.[31-33] The 120 patients in treatment at the end of the study period had begun treatment with histories of significantly less drug abuse, and their lower rates of abuse persisted during all observation periods in comparison to the 84 discharged patients. Although relapses occurred late in treatment as in other studies,[1] the relapse periods decreased with time in treatment.[1,34] Patients yielding the most frequent positive urine samples were discharged first, as in the study by Morral et al.[17] All but two patients remained in treatment during the first three months. This differs from several other studies where about 30 percent, if not more, left treatment during this period.[35-38] The high retention rate seen in this study may be related to strict admission criteria, a long admission procedure including social and medical treatment planning, and time spent on a waiting list; this combination of factors has probably led

Table 2. Number of relapse periods per person and year to specific drugs among patients who remained in treatment (Tx) or were discharged (Dis)

	Time in treatment (years)					
	0 to 1		1 to 2		2 to 3	
Type of drug	Tx (n = 15)	Dis (n = 34)	Tx (n = 25)	Dis (n = 29)	Tx (n = 24)	Dis (n = 10)
Opiates	2.8	5.0	2.0	4.0	1.5	3.5
Benzodiazepines	1.1	3.4	2.0	4.0	1.5	4.1
Cannabis	0.0	0.7	0.0	0.3	0.0	0.2
Amphetamines	0.8	1.9	1.3	1.8	0.5	1.5

to priority being given to subjects with higher motivation, as well as to a high perceived risk of involuntary discharge following positive urine tests. The retention rate could also be related to methadone dose, medical or psychosocial treatment, and social interventions such as the availability of lodging in a boarding house.

The patients often used benzodiazepines, a finding reported in other studies.[39,40] This was more common in the discharged group and may be due to a generally more dysfunctional life,[39] a greater need to reduce withdrawal from or enhance the effect of the primary drug,[41] and/or benzodiazepine dependence.[42] Amphetamine use was significantly related to discharge even during the first three months, especially for men. Bykvist,[43] in a study of polydrug use among Swedish drug abusers in the early 1980s, found that amphetamines and cannabis were the most common second-choice drugs for drug users whose primary drugs were opiates (benzodiazepines were not included in the study). The discharged patients were about six times more likely to use cannabis during treatment than those who remained in treatment. We found a negative relationship between methadone dose and opiate relapse, which corresponds with earlier research.[1,44-46] The discharged patients had lower methadone doses, possibly due to a delayed increase in methadone dose because of illicit drug abuse, leaving treatment because of withdrawal symptoms, or dissatisfaction with the methadone dose level. Hiltunen et al.[27] found that dissatisfied patients who received a dose increase stopped their illicit drug use. This poses the question of whether the schedules for reaching stabilization levels and the policy for adjusting methadone doses were sufficiently adapted to individual needs. We also must question whether a delayed dose increase due to positive urine tests increased the risk of relapse and involuntary discharge. The lower relapse rate among the patients in The New Team compared to patients in The Old Team is probably partly due to significantly higher methadone doses during the first year, but it could also be due to the stricter deterrent policy of discharge after two positive urine samples. During the first three months, the levels of attendance and counseling were high in both teams, and we feel these are important predictors of treatment retention.[38] Åberg et al.[47] reported that Swedish methadone patients considered psychosocial interventions very important. No differences in retention rates were observed between the two teams, which suggests that the level of counseling in both teams contributed equally well to retention. Illicit drug use was the most frequent administrative reason for discharge, which corresponds to the results of other Swedish studies.[26,48] In other countries, loss of contact, loitering, noncompliance with program rules, voluntary drop-out, arrest, and incarceration seem to be more common reasons for discharge[1,37,49]; these outcomes may be explained by different program policies.

CONCLUSION

The generality of this study is limited with regard to methadone programs with less restrictive admission criteria. Although the subjects in this study had long histories of drug abuse, the retention rates were high. Almost all patients relapsed into illicit drug use at least once, but the proportion of positive urine tests was low, although comparisons with other programs are difficult due to their lower rates of urine testing. Illicit drug use decreased during the follow-up period but was the most frequent reason for discharge. Methadone dose was related to illicit drug use and discharge, and there is some question as to whether the policy of not increasing the methadone dose in patients with a positive urine sample contributed to further relapse

and involuntary discharge. Further research is needed to identify factors that reduce the risk for illicit drug use during treatment and to develop ways of using this knowledge to improve treatment and to better adapt it to individual needs.

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ORIGINAL ARTICLE

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

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ABSTRACT

This multicenter trial compared the efficacy, safety, and effect on quality of life and work limitation of once-daily extended-release morphine sulfate capsules (AVINZA®, A-MQD) and twice-daily controlled-release oxycodone HCl tablets (OxyContin®, O-ER) in subjects with chronic, moderate to severe low back pain. After randomization and a period of opioid dose titration, subjects (n = 266) underwent an eight-week evaluation phase and an optional four-month extension phase (n = 174 in extension phase). Subjects were assessed using the 12-item Short-Form Health Survey® (SF-12) and the Work Limitations Questionnaire® (WLQ). In both groups, significant improvements were observed in the SF-12 mean scores for physical functioning ($p < 0.001$), role physical ($p < 0.0001$), bodily pain ($p < 0.0001$), physical summary ($p < 0.001$), and mental component summary ($p < 0.005$). At the end of the titration period, greater relative improvements from baseline were seen in the SF-12 section on physical components in the A-MQD group versus the O-ER group, with significant differences observed for physical functioning ($p = 0.0374$), role physical ($p = 0.0341$), bodily pain ($p = 0.0001$), and physical summary ($p = 0.0022$). In both groups, SF-12 mean scores improved significantly for mental health ($p < 0.01$), role emotional ($p < 0.01$), social functioning ($p < 0.0005$), vitality ($p < 0.005$), and the mental component summary ($p < 0.005$), but no significant differences were noted between the two groups. Both groups reported improvement from baseline in WLQ physical demands scores, with no significant differences noted between the two groups. At the end of the evaluation phase, fewer subjects were unable to work due to illness or treatment in the A-MQD group than in the O-ER group (8.5 percent versus 19.4 percent, respectively; $p = 0.0149$). In conclusion, compared to twice-daily OxyContin, once-daily AVINZA resulted in significantly better and earlier improvement of physical function and ability to work.

Key words: morphine sulfate, oxycodone HCl, AVINZA, ACTION trial, low back pain, chronic pain, physical functioning, quality of life

INTRODUCTION

The ACTION trial was a randomized, parallel-group, open-label, multicenter study comparing the efficacy and safety of two sustained-release opioids—once-daily A-MQD (AVINZA®, Ligand Pharmaceuticals, San Diego, CA) and twice-daily O-ER (OxyContin®, Purdue Pharma LP, Stamford, CT)—in patients with chronic, moderate to severe low back pain. The study consisted of an opioid dose titration period followed by an eight-week in-depth evaluation phase and an optional four-month extension phase. The objective of the study was to compare the long-term efficacy and safety of A-MQD and O-ER in this patient population. We have recently reported the final efficacy and safety results of this trial.[1,2] The study

showed that both A-MQD and O-ER significantly improve pain and sleep scores. During the evaluation phase of the study, these improvements were significantly greater in the A-MQD group than in the O-ER group, with a significantly lower morphine-equivalent daily dose and fewer ibuprofen rescue doses.[1] Better results in the A-MQD group continued to be observed during the extension phase of the study.[2] This report presents the final results of the trial, examining assessments of quality of life and work limitation in the study population.

METHODS

Population and study design

Detailed information about the patient population and trial design has been reported previously.[1] Eligible subjects between the ages of 30 and 70 with a history of low back pain of at least six months' duration who were not being treated with an extended-release opioid were randomized to receive either A-MQD once every 24 hours as a morning dose or O-ER every 12 hours. Subjects were instructed to take their study medication at the same time each day, ± 30 minutes. Ibuprofen was the only rescue medication permitted for breakthrough pain during the study. Subjects were allowed to enter the evaluation phase if their pain was stabilized by the study medication during the titration phase; stabilization was defined as the combination of 1) pain scores no greater than 4 on three consecutive days, based on a visual analogue scale ranging from 0 (no pain) to 10 (worst pain); 2) the same daily dose of study medication for seven consecutive days; and 3) two or fewer ibuprofen rescue doses needed over three consecutive days. During the eight-week evaluation phase of the study, detailed subject-derived information on pain, sleep, ibuprofen use for breakthrough pain, and daily opioid dose was obtained. Subjects who agreed to enroll in the optional four-month extension phase continued on the same study medication, with ibuprofen rescue as needed. Except for the first four weeks of the evaluation phase, the daily dose of study medication (but not the frequency of daily administration) was adjusted at the discretion of the treating physician to maintain an optimal balance of pain control and tolerability.

Assessing quality of life and ability to work

The Short-Form Health Survey® (SF-12) is a validated, multipurpose, self-administered, 12-item health questionnaire derived from the more detailed SF-36 questionnaire.[3] It evaluates, for the preceding week, four physical domains (physical functioning, role physical, bodily pain, general health), four mental domains (vitality, social functioning, role emotional, mental health), and two summary health measures (physical component, mental component), with higher scores indicating better results. The Work Limitations Questionnaire® (WLQ) is a validated, self-administered questionnaire evaluating the subject's ability to work over the preceding two weeks.[4] It consists of 25 items that aggregate in four scales—time management, physical demands, mental-interpersonal demands, and output demands—with the scale score ranging from 0 (limited none of the time) to 100 (limited all of the time). The WLQ was administered only to the subset of subjects who identified themselves as being employed full time or part time upon entry into the study. The licensed version of both questionnaires was used, and no translations were made.

Both questionnaires were administered at baseline, at the end of the opioid dose titration period, at the end of Weeks 4 and 8 of the evaluation phase, and monthly during the extension phase, from Month 1 (i.e., Week 12 of the evaluation phase) to Month 4 (Week 24). Data input was performed by the subjects during monthly office visits using a handheld electronic diary specifically programmed for this study (PHT Corp., Charlestown, MA), without interference or assistance from healthcare providers.

Statistical methods

Baseline demographics were compared between the two groups using the Wilcoxon two-sample test for continuous variables and the Pearson's χ^2 test for categorical variables. The SF-12 and WLQ variables were analyzed as absolute values and as absolute and relative changes from baseline values, with baseline values defined as those obtained upon enrollment in the study. Comparison of the baseline scores between the two groups was performed using the Wilcoxon t-test; comparison of the differences between groups for subsequent evaluations was performed with ANOVA, using baseline values as covariates; and within-group comparisons of changes over time were performed using the pairwise t-test. All comparisons were two-sided, and significance was attributed to p values less than 0.05.

RESULTS

Subject disposition

A total of 392 subjects were randomized (203 to A-MQD and 198 to O-ER). Of those, 268 subjects entered the evaluation phase, 220 completed the evaluation phase, 174 continued into the optional four-month extension phase, and 132 completed the extension phase. The baseline demographics of the two study groups were comparable except for the number of African-American subjects (31.1 percent in the A-MQD group versus 15.7 percent in the O-ER group, $p < 0.02$) and subjects with

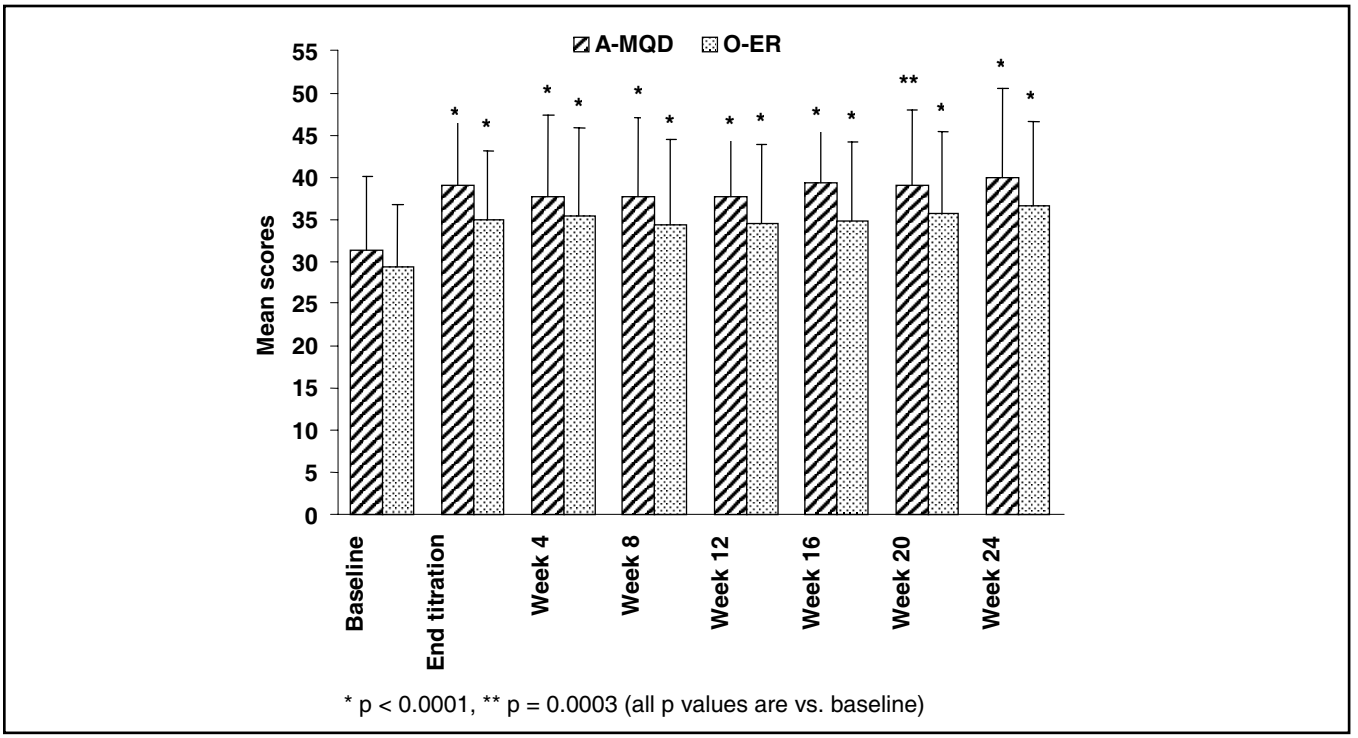

Figure 1. SF-12 physical component summary (mean scores ± standard deviations).

back pain associated with nerve involvement (36.9 percent in the A-MQD group versus 27 percent in the O-ER group, $p < 0.04$). Details on reasons for withdrawal from study and subject characteristics at different stages of the study were reported previously.[1,2]

SF–12 assessments

Adherence to answering the SF-12 questionnaires was high in both groups, ranging in the A-MQD group from 95 percent at baseline to 82 percent at Week 24 and in the O-ER group from 91 percent at baseline to 78 percent at Week 24. In both groups, there were significant improvements compared to baseline in the mean scores for all monthly SF-12 physical domain assessments for physical functioning ($p < 0.001$), role physical ($p < 0.0001$), bodily pain ($p < 0.0001$), and the physical component summary ($p < 0.001$). For the general-health physical domain, mean scores were significantly improved in the A-MQD group at the end of the opioid dose titration phase ($p = 0.0001$) and at Week 16 ($p = 0.0174$), and in the O-ER group at the end of the opioid dose titration phase ($p = 0.0052$), Week 4 ($p = 0.031$), and Week 8 ($p = 0.0435$). In all physical domains, most of the improvement was achieved during opioid dose titration in the first weeks of treatment (Figure 1). The mean relative score improvements were generally better in the A-MQD group than in the O-ER group, and the differences were significant between the two groups at the end of the opioid dose titration period for all five physical domains (Table 1). The greatest relative score changes from baseline were noted in the bodily pain domain and were significantly better in the A-MQD group as compared to the O-ER group at the end of opioid dose titration ($p = 0.0002$), at evaluation Week 8 ($p = 0.0002$), and at Month 1 ($p = 0.0433$) and Month 2 ($p = 0.0171$) of the extension phase.

In both groups, there were significant improvements from baseline in the mean scores for all monthly SF-12 assessments for the five mental domains: mental health ($p < 0.01$), role emotional ($p < 0.01$), social functioning ($p < 0.0005$), vitality ($p < 0.005$), and the mental component summary ($p < 0.005$) (Figure 2). However, there were no differences between the two groups in terms of relative score changes from baseline in any of the mental domains (Table 2).

WLQ assessments

All four demands scores, as well as the summary index scores, remained stable throughout the study in both treatment groups, with no significant differences noted between the two groups (Table 3). At baseline, the two groups were comparable in terms of the proportion of responses to the question, "During the past four weeks, did you work or did you not work at all due to illness or treatment?" (Table 4). At evaluation Week 8, however, 19.4 percent of subjects in the O-ER group were unable to work, versus 8.5 percent in the A-MQD group ($p = 0.0149$).

Table 1. SF-12 physical domain components

Time	Group	Mean relative change from baseline (percent)				
		Physical functioning	**Role physical**	**Bodily pain**	**General health**	**Physical summary**
End of titration	A-MQD (n = 121)	33.2	26.2	45.8	14.3	30.8
	O-ER (n = 112)	27.9	21.8	27.6	10.3	22.9
	p value*	**0.0278**	**0.0127**	**0.0002**	**0.0264**	**0.0017**
Evaluation Week 4	A-MQD (n = 100)	25.4	20.5	36.9	9.7	19.8
	O-ER (n = 84)	25.9	24.9	28.0	10.1	21.3
	p value	NS	NS	0.081	NS	NS
Evaluation Week 8	A-MQD (n = 93)	27.8	27.3	43.2	10.4	22.6
	O-ER (n = 84)	24.3	23.7	25.5	10.2	18.6
	p value	NS	NS	**0.0065**	NS	NS
Extension Month 1	A-MQD (n = 69)	25.2	26.8	40.1	10.8	21.5
	O-ER (n = 71)	19.0	22.8	26.4	5.8	17.6
	p value	NS	NS	**0.0433**	NS	NS
Extension Month 2	A-MQD (n = 55)	31.0	27.9	44.3	14.4	25.3
	O-ER (n = 70)	21.9	22.0	27.5	2.5	19.4
	p value	NS	NS	**0.0171**	NS	NS
Extension Month 3	A-MQD (n = 50)	25.3	27.7	44.5	4.6	18.7
	O-ER (n = 69)	23.1	23.2	32.1	2.8	22.6
	p value	NS	NS	NS	NS	NS
Extension Month 4	A-MQD (n = 43)	33.8	24.5	45.4	6.0	22.8
	O-ER (n = 54)	28.0	28.2	31.8	4.8	27.3
	p value	NS	NS	NS	NS	NS

* p values for between-treatment differences constructed for an ANOVA with baseline value as a covariate; NS = not significant ($p \geq 0.05$).

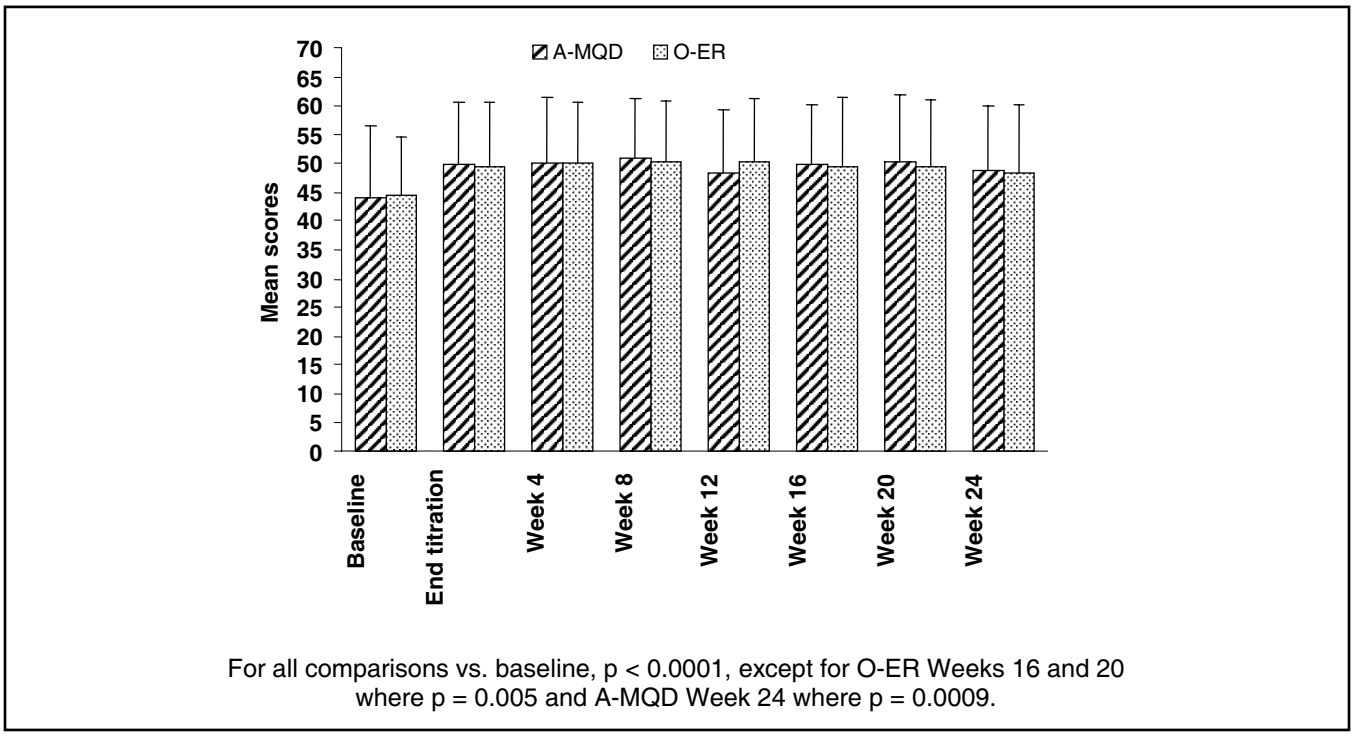

Figure 2. SF-12 mental component summary (mean scores ± standard deviations).

DISCUSSION

The ACTION trial compared the effectiveness of once-daily A-MQD and twice-daily O-ER, each with a unique modified-release profile, in the management of chronic, moderate to severe low back pain. We have previously reported that both A-MQD and O-ER significantly improved pain and sleep scores during the eight-week evaluation phase of the study, that A-MQD resulted in significantly better improvement in pain and sleep scores while requiring a significantly lower daily morphine dose, and that the two study medications resulted in comparable incidence and severity of opioid-induced side effects.[1,2]

Chronic low back pain is not only a cause of significant suffering; it is often associated with disability, resulting in a considerable socioeconomic impact. One study has estimated the total healthcare expenditures incurred by individuals with low back pain at $90.7 billion and the total incremental expenditures attributable to back pain at $26.3 billion.[5] Low back pain is one of the most common causes of work disability and accounts for about a quarter of workers' compensation costs.[6] Therefore, clinical management of low back pain should aim at providing the best possible pain relief as well as at preserving physical function, with the goal of preventing disability or reducing its severity. Several trials have studied short-acting and extended-release opioids for chronic non-cancer pain and have reported improvement in patient self-reports of pain intensity, but few trials have assessed whether pain relief is also associated with functional gains. Where specific functional assessments have been performed, findings have been equivocal, with functional improvements noted in some studies but not in others.[7-10] Since opioids have been shown to provide significant pain relief in most studies, divergence in functional outcomes is likely due to reasons other than lack of pain control, such as the small number of subjects evaluated in a study, the heterogeneity in the patient population, and incomplete functional-data collection. It may also be that in some individuals, disability is too advanced to be reversible.

The ACTION trial was well suited to an evaluation of the effect of opioid therapy on functional status because it enrolled a large number of subjects who were treated for several months and because it involved a randomized study design that mitigated the risk of patient-selection bias. Two validated and complementary functional questionnaires were used in the study, in accordance with the IMMPACT recommendations for outcome measures in clinical trials involving patients with chronic pain.[11] We selected the SF-12, a disease-nonspecific functional health survey, instead of the more commonly used SF-36 because it is briefer and amenable to repeated testing, as confirmed by the adherence rate of between 80 and 90 percent observed in the trial. The study did not include objective functional capacity assessments, such as measurement of active range of motion of the lumbar spine, or static and dynamic strength testing because their impact on this large trial would have been prohibitive in terms of both subject time demands and cost.

Table 2. SF-12 mental domain components						
Time	**Group**	**Mean relative change from baseline (percent)**				
		Vitality	**Social functioning**	**Role emotional**	**Mental health**	**Mental summary**
End of titration	A-MQD (n = 121)	15.6	29.1	27.4	21.5	18.2
	O-ER (n = 112)	14.7	25.8	23.1	14.9	13.0
	p value*	NS	NS	NS	0.0578	NS
Evaluation Week 4	A-MQD (n = 100)	15.2	26.1	26.7	24.0	21.2
	O-ER (n = 84)	14.6	27.7	26.5	18.9	16.2
	p value	NS	NS	NS	NS	NS
Evaluation Week 8	A-MQD (n = 93)	16.9	32.8	30.4	25.5	23.0
	O-ER (n = 84)	13.8	20.7	31.5	17.5	16.4
	p value	NS	**0.0087**	NS	NS	NS
Extension Month 1	A-MQD (n = 69)	17.8	34.1	35.4	25.5	25.9
	O-ER (n = 71)	14.5	26.0	23.3	15.2	14.8
	p value	NS	NS	NS	NS	NS
Extension Month 2	A-MQD (n = 55)	20.6	30.4	33.6	27.9	24.8
	O-ER (n = 70)	12.1	25.0	22.3	11.1	11.2
	p value	NS	NS	NS	NS	NS
Extension Month 3	A-MQD (n = 50)	23.5	35.3	40.7	31.5	32.1
	O-ER (n = 69)	12.7	23.3	21.3	10.9	10.0
	p value	NS	NS	NS	NS	NS
Extension Month 4	A-MQD (n = 43)	16.5	30.9	34.6	28.7	25.0
	O-ER (n = 54)	14.3	23.9	17.1	11.6	9.3
	p value	NS	NS	NS	NS	NS

* p values for between-treatment differences constructed for an ANOVA with baseline value as a covariate; NS = not significant ($p \geq 0.05$).

Table 3. Work Limitations Questionnaire						
Time	**Group**	**Mean demands score***				
		Time	**Physical**	**Mental**	**Output**	**Index**
Baseline	A-MQD	54.9	40.5	72.6	67.3	18.2
	O-ER	53.3	43.7	74.2	67.1	18.3
End of titration	A-MQD	72.1	26.4	84.6	82.9	21.5
	O-ER	73.5	29.3	81.9	76.9	20.5
Evaluation Week 4	A-MQD	74.1	24.2	84.9	83.0	21.3
	O-ER	71.1	27.2	80.6	78.6	20.1
Evaluation Week 8	A-MQD	74.4	26.4	87.4	87.0	22.1
	O-ER	75.3	24.2	85.5	78.0	20.9
Extension Month 1	A-MQD	73.3	26.1	83.3	80.7	21.1
	O-ER	79.9	23.0	85.3	78.2	20.9
Extension Month 2	A-MQD	78.4	24.3	83.9	81.0	21.2
	O-ER	79.3	20.8	84.6	77.3	21.0
Extension Month 3	A-MQD	72.4	23.4	86.1	83.7	21.8
	O-ER	77.9	29.7	81.1	78.7	20.8
Extension Month 4	A-MQD	79.2	23.1	88.9	86.0	22.6
	O-ER	70.6	22.6	81.3	79.4	19.6

* Scale: 0 (limited none of the time) to 100 (limited all of the time).

This study showed that both A-MQD and O-ER led to significant improvement on both the physical and mental components of the SF-12. Physical functioning scores improved by approximately 20 to 30 percent, and almost all of the gains were already achieved by the end of the opioid dose titration phase, when the first post-baseline assessment was performed. Improved physical functioning continued to be noted in subsequent monthly assessments made over a total of more than seven months of follow-up study. At the end of dose titration, subjects treated with A-MQD reported significantly better improvement in all physical component scores than subjects treated with O-ER, with an average summary physical score improvement of 30.8 percent in the A-MQD group versus 22.9 percent in the O-ER group ($p = 0.0017$). The relative advantage of A-MQD continued to be seen during the evaluation and extension phases of the study, but the difference with O-ER was no longer significant, possibly due to subject withdrawal having reduced the statistical power of the study.

Within the SF-12 physical domain components, the main difference between the two study groups was noted

Table 4. Subjects' inability to work due to illness or treatment			
	A-MQD	**O-ER**	**p value***
Baseline			
Worked during past four weeks	56 (90.3 percent)	41 (93.2 percent)	NS
Did not work during past four weeks	6 (9.7 percent)	3 (6.8 percent)	
End of titration			
Worked during past four weeks	64 (97.0 percent)	39 (97.5 percent)	NS
Did not work during past four weeks	2 (3.0 percent)	1 (2.5 percent)	
Evaluation Week 4			
Worked during past four weeks	48 (90.6 percent)	34 (94.4 percent)	NS
Did not work during past four weeks	5 (9.4 percent)	2 (5.6 percent)	
Evaluation Week 8			
Worked during past four weeks	43 (91.5 percent)	25 (80.6 percent)	0.0149
Did not work during past four weeks	4 (8.5 percent)	6 (19.4 percent)	
* Calculated by Cochran Mantel Haenszel test; NS = not significant.			

in the relative improvement from baseline for bodily pain scores, which were better in the A-MQD group at each of the six follow-up assessments, with a significant difference achieved at the end of opioid dose titration, Week 8 of the evaluation phase, and Months 1 and 2 of the extension phase. This outcome corroborates the findings of the visual analogue pain scale from the Brief Pain Inventory, which also showed significantly better results in the A-MQD group.[1] Using two independent evaluation methodologies, the SF-12 and the WLQ pain scale, the study has confirmed that once-daily A-MQD results in better pain control than twice-daily O-ER in patients with chronic low back pain.

Other studies have also shown improved physical function associated with pain relief after therapy with A-MQD in patients with different types of chronic, moderate to severe noncancer pain. In a randomized, double-blind, Phase III trial conducted in osteoarthritic subjects, Caldwell et al.[12] showed that the mean WOMAC physical function score improved by 18 percent at Week 4 with A-MQD, compared to an improvement of 8 percent with placebo. In a real-world-conditions, single-arm study of 492 subjects with nonmalignant chronic pain, Adams et al.[13] showed that A-MQD significantly increased the proportion of subjects who reported an improvement in ability for moderate-intensity activities such as "climbing one flight of stairs" ($p = 0.008$) and "bending, kneeling, or stooping" ($p = 0.0005$). In addition, treatment with A-MQD significantly decreased the proportion of subjects who reported that "problems with functioning occurred 7 days a week," from 81 percent at baseline to 67 percent at Month 3 ($p < 0.01$).

In a randomized trial conducted in subjects with various chronic, nonmalignant pains that compared O-ER given every eight or 12 hours to polymer-coated extended-release morphine sulfate (Kadian®, Alpharma Branded Products Division, Inc., Piscataway, NJ) given every 12 or 24 hours, functional status was evaluated by the SF-36 health questionnaire at baseline, Week 4, and Week 24.[14] In 43 evaluable subjects treated with O-ER, the physical component summary scores improved by a modest 7 percent, from a mean of 31.1 at baseline to a mean of 33.2 at Week 24 ($p < 0.05$), and there were no significant improvements in the mental component summary scores.

CONCLUSION

The ACTION trial has shown that in subjects with chronic, moderate to severe low back pain who are stabilized on opioid therapy, both AVINZA® and OxyContin® significantly improve pain, sleep, and physical functioning for up to seven months on study. The study also showed that AVINZA® results in significantly better pain

relief, sleep, physical function, and ability to work than does OxyContin.® The results seen with the patients taking AVINZA® were achieved with significantly lower morphine-equivalent daily doses, less frequent ibuprofen use for breakthrough pain, and a comparable safety profile.

FINANCIAL DISCLOSURE

Funding for the ACTION trial was equally provided by Ligand Pharmaceuticals, Inc., and Organon Pharmaceuticals USA, Inc. Dr. Rauck is a consultant to Medtronic Inc., Elan Pharmaceuticals, Advanced Bionics, and Organon Pharmaceuticals USA, Inc. Dr. de Jong is an employee of Organon Pharmaceuticals USA, Inc. Dr. Negro-Vilar is an employee of Ligand Pharmaceuticals, Inc. Dr. Ghalie is an employee of Ligand Pharmaceuticals, Inc.

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INTRODUCTION

Rationale for This Program on Opioids and Usage

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

Drugs, Documentation and the DEA

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

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

Legal and Ethical Standards for Palliative Care Involving Opioid Use

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

Managing Your Practice: One Physician's Viewpoint

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

Pain Pathways: The Mechanisms and Physiology of Pain

This presentation will provide an overview of the pathophysiology of pain transmission through the body and the actions of different drugs used to treat pain.

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

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

Pain—How to Deal with It

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

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

PANEL DISCUSSION

Case Studies: A Multidisciplinary Approach

Representative case studies will be presented by a team of experts in a multi-disciplinary approach to alleviating pain with opioids in various disease entities. The panel will discuss several cases including neuropathic pain, cancer pain, and chronic nonmalignant pain. This will be an interactive session with audience participation encouraged.

Program faculty includes Robert L. Barkin, MBA, PharmD, FCP, DAAPM; Ramsin Benyamin, MD, DABPM, FIPP; Jennifer Bolen, JD; Robert E. Enck, MD; Marshall B. Kapp, JD, MPH; Ronald J. Kulich, PhD; Gary M. Reisfield, MD; Paul Alexander Sloan, MD; Ricardo Vallejo, MD, PhD, FIIP; George R. Wilson, MD.

Continental breakfast and lunch served both days.

Day Two* – Sunday 8:00 AM – 4:30 PM

Opioids: Types and Uses

There are many types of opioids and they are classified in many ways. For example: 1) Natural vs. semi-synthetic vs. synthetic. 2) Strong vs. weak. 3) Duration of action- a. short vs. medium; b. immediate release vs. controlled release. 4) Analgesic vs. non-analgesic. 5) By federal schedule (CI-CV). 6) By receptor affinity. 7) Legal vs. illegal. 8) Agonist vs. partial agonist vs. antagonist. There are many uses for opioids. The major focus here is, of course, on analgesia. But there are other, often fascinating, uses which will be covered: anesthesia, antitussive, antidiarrheal, antispasmodic, drug abuse, opioid maintenance treatment, opioid detoxification, vasodilatation/smooth muscle relaxation, and even antiterror.

What's Working: A Review of Today's Best Options

This presentation will cover a number of typical cases involving chronic and acute pain and those drugs that are most commonly used. This clinical talk will include a review of the scientific efficacy of today's most popular pharmaceuticals on the market.

Risk Management and Related Medico-Legal Issues with the Practice of Chronic Opioid Therapy

Risk management and related micro-legal issues are reviewed with respect to clinicians who undertake chronic opioid therapy in their practice. Risk factors are discussed with reference to typical malpractice claims, medical board complaints, and reports in medico-legal literature. Specific issues include guideline and Model Pain Policies implementation, scope of practice, record keeping/documentation, patient abandonment, communication with co-treating clinicians, and particular risks within solo versus group practice. The relative risk of undertaking chronic opioid therapy is contrasted to risks inherent in other pharmacotherapy or interventional treatments.

Rotation of Opioids

Escalating opioid requirements can be a consequence of either progression of disease or tolerance. There is increasing awareness among pain specialists that there may be a ceiling effect on the opioid dosing above which hyperalgesia, sedation, cognitive dysfunction, myoclonus or other side-effects may limit further upward titration. Opioid rotation takes advantage of incomplete opioid cross-tolerance which implies that an equianalgesic dose of a different opioid—one to which the patient has not been exposed before—will be much lower than expected. This may result in a 40% reduction in dosage while maintaining the same or better analgesia. Providers can use opioid rotation to reduce side-effects or improve efficacy in opioid tolerant individuals.

Judicious Screening: Psychosocial Issues with Chronic Opioid Therapy

Assessment of chronic pain is discussed with a focus on psychosocial evaluation and screening. Screening issues are addressed with respect to chronic opioid therapy with commentary on behavioral strategies intended to maximize adherence to the medical treatment regimen. The integration of nonpharmacologic strategies into the treatment regimen is discussed with a brief review of cognitive and relaxation interventions. Evidence-based interdisciplinary treatment is emphasized with additional discussion on barriers to effective treatment.

Interventional Techniques Used in Pain Management

There are various interventional techniques that can be used in pain management. One important consideration is the use of image guidance in the performance of said interventional techniques and differential diagnosis between certain types of pain. Back, neck, and head pain all have common causes. Possible interventional techniques to treat these three conditions include sacroiliac injection, facet/medial branch injection, sympathetic blocks, discography, radiofrequency, IDET, percutaneous disc decompression, vertebroplasty, Botox® injection, and implantables (nerve stimulators and intrathecal pumps). The indications, contraindications, and possible side effects of these techniques will be discussed.

Identification and Treatment of Opioid Dependence

Opioid dependence is a brain disease which will affect a certain percentage of patients treated with opioid analgesics for pain. It is crucial for physicians treating pain with opioids to be able to identify and treat these patients in a timely and effective manner. In 2002, the Drug Addiction Treatment Act gave all physicians (including pain management, family practice and internal medicine practitioners) the legal right to treat their patients for opioid dependence in the privacy of their own office. This introductory presentation will cover the following topics: overview of opioid dependence, in-office treatment options for opioid dependence, opioid dependence in chronic and acute pain patients, patient assessment and treatment/referral process, and available clinical tools.

Urine Drug Testing: Which Patient, Which Drug, Why

Opioid toxicology in various disease states will be discussed, along with the issue of rotation, the use of adjunctive medications, and how to taper and increase dosing in a safe manner. The treatment of side effects will be considered. Drug screening will cover use and misuse of opioids and what testing is most helpful. Urine testing, although not totally accurate, is a quick, practical, and cost-effective way of making sure which patients are or are not taking medications and to protect physician and patient from the problem of diversion.

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Buprenorphine: A unique opioid with broad clinical applications

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ABSTRACT

The analgesic potential of buprenorphine, a high-affinity partial μ agonist, has been a subject of study for several decades. The drug is now widely recognized as being extremely effective in relieving perioperative pain, with little of the addictive potential or risk associated with pure μ agonists. Studies have suggested that buprenorphine produces adequate analgesia via almost any route of administration, including transdermal and subcutaneous. It has also been used, with positive results, in the treatment of opioid addiction, and potential remains for research into other roles, e.g., as an anti-inflammatory agent or an antihyperalgesic medication.

Key words: buprenorphine, opioid, μ agonist, analgesia, perioperative pain, route of administration, addiction, withdrawal, detoxification

INTRODUCTION

Buprenorphine is a semisynthetic oripavine alkaloid derived from thebaine. It is a long-acting, lipid-soluble, mixed agonist-antagonist opioid analgesic, first synthesized in 1966. Continued interest in buprenorphine has been attributed to its unique pharmacological effects, being a partial μ agonist with moderate intrinsic activity and with high affinity to and slow dissociation from μ opioid receptors.[1,2] Buprenorphine was one of the first narcotic analgesics to be studied for its abuse liability in humans. The low abuse liability of the drug soon led to its widespread use as a therapeutic agent in patients with opioid dependence. At the present time, the principal clinical application of buprenorphine is as an analgesic for moderate to severe pain in the perioperative setting and in the treatment of heroin addiction.[3] This article focuses on its use in the perioperative setting. Recent clinical interest in the possible usefulness of buprenorphine in the treatment of pain states dominated by central sensitization is also discussed.

PHARMACOLOGY AND PHARMACOKINETICS

Buprenorphine was initially classified as either a mixed agonist-antagonist analgesic or a narcotic-antagonist analgesic.[4] In most preclinical antinociceptive tests, buprenorphine was shown to be fully efficacious, with an antinociceptive potency 20 to 70 times higher than that of morphine.[5,6] There are controversial reports on naloxone's ability to reverse antinociception produced by buprenorphine. In some studies, buprenorphine-induced analgesia exhibited a lack of naloxone reversibility.[7] However, Schmauss et al.[8] have reported a reversal of buprenorphine-induced antinociception using naloxone. They explained it as the result of the existence of three discernable populations of opioid receptors in the spinal cord, the activations of which have different effects on a subject's response to noxious stimuli. Buprenorphine exhibits a longer duration of action and decreased withdrawal symptoms compared with pure μ agonists such as heroin.[9]

The analgesic effect of buprenorphine appears to depend upon the integrity of descending fibers from the rostral ventromedial medulla. Just as with morphine, the descending fibers are critically important to the analgesic effect of the opioid, regardless of the type of noxious stimulation eliciting pain. Residual analgesic effects of opioids after inactivation of descending fibers may be due to peripheral effects in the presence of inflammation.[10]

Buprenorphine used in therapeutic concentrations in humans does not appear to cause clinically significant interactions with other cytochrome P–metabolized drugs.[11] However, its pharmacology is complicated by the presence of an active N-dealkylated metabolite of buprenorphine, norbuprenorphine.[12] A study involving the intraventricular administration of buprenorphine and norbuprenorphine in rats suggested that the intrinsic analgesic activity of norbuprenorphine was one-fourth that of buprenorphine. It is possible that the remarkably weak pharmacological effect of norbuprenorphine after intraventricular administration may be due not only to the low ability of norbuprenorphine to permeate the blood-brain barrier but also to its small intrinsic pharmacological profile.[13] The neurotoxic effects of norbuprenorphine are not known.

Buprenorphine's affinity for μ opioid receptors allows

pharmacologically effective occupancy at low plasma concentrations, with an analgesic effect being measurable at 5 to 10 percent receptor occupancy. The parenteral formulation of buprenorphine has a speed of onset of five to 15 minutes following either intravenous (IV) or intramuscular (IM) administration. Onset of analgesia occurs in 15 to 45 minutes with sublingual buprenorphine.

Buprenorphine is metabolized by the gut and liver. In humans, the majority of any dose administered by any route is excreted via the gastrointestinal tract. Following administration and independent of route, some 15 percent of the original dose is excreted in the urine. In short-term treatment with buprenorphine, end-stage renal failure does not seem to affect the excretion of the drug. In chronic therapy, measurements of plasma levels of buprenorphine and its metabolites in patients with and without renal failure showed that levels of the metabolites were increased in the patients with renal failure, while buprenorphine levels were similar in both groups. This supports a biliary excretion route for buprenorphine but points to the importance of the renal excretion route for the metabolites.[11]

RELATION BETWEEN PHARMACOLOGY AND CLINICAL EFFECTS

Buprenorphine interacts with μ, κ, and δ opioid receptors and exhibits a slow dissociation from μ receptors.[14] These are the three major types of opioid receptors seen in large concentrations in the substantia gelatinosa of the spinal cord, a region that is a major site for early integration of nociceptive input.[15]

μ and κ receptors

Because of its properties regarding μ and κ receptors, buprenorphine can be used both as an analgesic agent and in the treatment of opioid abuse. Buprenorphine is a mixed agonist-antagonist drug exhibiting partial agonist activity toward μ opioid receptors and antagonist action at κ opioid receptors.[7] As a result of its partial agonist activity at μ opioid receptors and its long half-life, buprenorphine has proven to be an excellent alternative to methadone for either maintenance therapy or detoxification of the opioid addict.[12] At μ receptors, buprenorphine has high affinity and intermediate intrinsic efficacy, as measured by both in vitro functional assays and in vivo behavioral assays. Buprenorphine exhibits slow dissociation from μ opioid receptors. Buprenorphine, morphine, heroin, and methadone all show different patterns of G protein activation in evoking μ-opioid-receptor-mediated supraspinal antinociception.[16] Some studies have suggested that buprenorphine may have an agonistic activity at κ opioid receptors as well.[17]

δ receptors

Compared with the well-characterized effects of buprenorphine at μ and κ opioid receptors, little is known about its activity at δ receptors. In vitro studies suggest that buprenorphine could produce δ-receptor-mediated antagonist or agonist effects in vivo, either directly or through its metabolites. The relative potency of buprenorphine in producing δ-receptor-mediated effects in vivo is largely unknown. In rhesus monkeys, δ antagonist effects occurred with buprenorphine doses approximately 30-fold higher than those producing μ- or κ-receptor-mediated effects. Thus, buprenorphine was less capable of producing δ-receptor-mediated effects than either μ- or κ-receptor-mediated effects.[18] In other research, though, buprenorphine has been shown to have an affinity for the δ opioid receptor and may have clinical utility for delayed, receptor-mediated myocardial protection.[19]

New receptors

The nociceptin/orphanin FQ (N/OFQ) receptor has been shown to be pharmacologically distinct from the classic opioid receptors. N/OFQ is an endogenous ligand for the human opioid-receptor-like receptor (ORL-1). Buprenorphine was recently identified as a full ORL-1 agonist using a reporter-gene assay. The N/OFQ agonism of buprenorphine might contribute to the actions of buprenorphine in pain models in vivo separately from its μ- or κ-receptor-mediated effects.[20] The question of whether the ORL-1 component might be involved in antinociception, or rather pronociceptive/antiopioid activities, for buprenorphine will likely not be answered until selective ORL-1-antagonist compounds are available.

CLINICAL TRIALS AND APPLICATION IN CLINICAL PAIN MANAGEMENT

Buprenorphine can be administered via multiple routes for pain management in humans. A vast number of clinical trials have been conducted studying its effects via epidural, intrathecal, IM, sublingual, and transdermal delivery routes. Epidural buprenorphine has been found to produce postoperative analgesia in patients after coronary artery bypass surgery (CABG).[21] It has been shown that buprenorphine administered by lumbar epidural for analgesia after CABG compares favorably with the same drug delivered via the thoracic route in terms of quality of analgesia and incidence of side effects. Mehta et al.[21] compared the effects of buprenorphine given through both the lumbar and thoracic epidural routes for postoperative analgesia following CABG. Forty patients with normal left ventricular ejection fractions scheduled for CABG were randomly divided into two groups, the

thoracic epidural analgesia group (n = 19) and the lumbar epidural analgesia group (n = 20). For postoperative pain relief, both groups received epidural buprenorphine 0.15 mg at the first demand for pain relief following extubation. A top-up dose of buprenorphine of 0.15 mg was administered in cases where visual analog pain score (VAS) was > 3 one hour after the first dose. Subsequent breakthrough pain was treated with 30 mg IM ketorolac. Pain assessed by VAS score on a 0 to 10 scale, respiratory rate, one-second forced expiratory volume, forced expiratory vital capacity, mean arterial blood pressure, cardiac index, PaO_2, and $PaCO_2$ were measured at frequent intervals. The results showed that buprenorphine administered by the lumbar route for analgesia after CABG compared favorably with the same drug delivered via the thoracic route in terms of quality of analgesia.

Buprenorphine has been shown to prolong postoperative analgesia and therefore could have a valuable role in preemptive analgesia. Buprenorphine has been widely used for postoperative analgesia in laboratory animals. Clinical efficacy has been demonstrated in both subjective and objective pain assessment schemes.[22] Previous studies in humans have also reported that epidural buprenorphine has clinical advantages greater than or equal to those of epidural morphine.[23] Miwa et al.[24] studied the effect of epidural buprenorphine on minimum alveolar concentration of volatile anesthetics, duration of analgesia, and respiratory function in the perioperative period. The study involved 120 patients (ASA I-II) undergoing gynecological surgery. The patients were divided into three studies, and the 40 patients in each study were randomly divided into four groups depending on the dosage: Group I (control), Group II (80 μg/kg of morphine), Group III (4 μg/kg of buprenorphine), and Group IV (8 μg/kg of buprenorphine). Postoperative analgesic effects were assessed by the total usage of pentazocine as a rescue medication in the 48 hours after surgery. The results showed that epidural buprenorphine administered in a dose of 4 or 8 μg/kg provided postoperative analgesia that was no less effective than that of morphine.

Buprenorphine, being a lipophilic drug, is absorbed at a very slow rate into the cerebrospinal fluid. This quality, coupled with its high affinity for and very slow dissociation from μ receptors, makes the systemic side effects of somnolence, hypotension, urinary retention, and respiratory depression uncommon. In a study by Giebler et al.,[25] only one patient out of 4,000 patients who received epidural buprenorphine suffered from respiratory depression.

The mode and site of analgesic action of epidural buprenorphine was studied in human gastrectomy patients by Inagaki et al.[3] Their study supports the hypothesis that epidural buprenorphine is rapidly absorbed from the epidural space into the systemic circulation and produces systemic (supraspinal) analgesia on par with IV buprenorphine administered at the supraspinal region of the central nervous system. Epidural buprenorphine also produces spinal segmental analgesia, which develops two to six hours after administration. Buprenorphine has been used epidurally in the management of pain associated with multiple rib fractures.[26] In that study, nausea, vomiting, and pruritis were the only complications; hypotension, urinary retention, and respiratory depression were not seen.

While epidurally administered buprenorphine in a dose of 4 or 8 μg/kg provides postoperative analgesia that is as effective as that of morphine in a dose of 80 μg/kg,[24] a dose of 15 μg/h may be optimal for postoperative pain relief after lower abdominal surgery.[27] Buprenorphine is not as water-soluble as morphine. In a study of posthepatectomy patients, it was noted that buprenorphine injected at the thoracic level produced good and long-lasting pain relief, whereas buprenorphine injected at the lumbar level produced inadequate analgesia. Morphine injected at either the thoracic or lumbar level produced excellent and long-lasting pain relief.[28] This is probably the result of the difference in water solubility between the two drugs.

In children, administration of buprenorphine through the caudal epidural space has been found to be a safe and reliable means of providing postoperative pain relief for up to 24 hours.[29] One study involved 40 children aged one to 11 years who received general anesthesia for genitourinary surgery, and it compared the quality and duration of analgesia after caudal blocks in two groups of patients. Group I (n = 20) received caudal bupivacaine 0.25 percent, and Group II (n = 20) received caudal buprenorphine 4 μg/kg; each received 0.5 ml/kg body weight. Postoperative behavior and severity of pain were measured using a 3-point scale. The results indicated that, in the immediate postoperative period, caudal buprenorphine provided excellent postoperative analgesia comparable to that observed with caudal bupivacaine. In addition, buprenorphine proved better in the late postoperative period, with analgesia lasting from 20 hours to more than 24 hours. Buprenorphine was associated with fewer side effects compared to caudal bupivacaine in children who underwent genitourinary surgery.[30] In children who underwent lower-extremity orthopedic surgery under general anesthesia, it was shown that postoperative analgesia lasted longer and resulted in fewer side effects in patients receiving buprenorphine caudally at the end of surgery, at a dose of 4 μg/kg body weight, than in those receiving the same amount of buprenorphine IM at the completion of surgery.[31]

In humans, epidural buprenorphine acts predominantly at the supraspinal region and produces spinal segmental analgesia in a dose-related manner.[3] Epidurally administered buprenorphine does not appear to produce urine retention in humans.[32] A retrospective study was conducted using

177 patients after upper and lower abdominal surgery, comparing the efficacy of epidural administration of fentanyl and of buprenorphine for postoperative pain relief. In the fentanyl (F) group, 73 patients received epidural fentanyl 0.1 mg with saline 8 ml postoperatively, followed by a constant-rate infusion of fentanyl 0.025 mg/h for 18 to 24 hours. In the buprenorphine (B) group, 104 patients received buprenorphine 0.2 mg with saline 9 ml epidurally. After upper abdominal surgery, 33 patients (76.7 percent) in F group and 27 patients (52.9 percent) in B group obtained satisfactory analgesia ($p < 0.05$) as assessed by their verbal analog scores. Respiratory depression occurred in 19 patients in B group and five patients in F group ($p < 0.005$). It was seen that epidural fentanyl offered a significant advantage compared with epidural buprenorphine for postoperative pain relief following upper abdominal surgery. However, the difference in the degree of analgesia after lower abdominal surgery was not significantly different.[33] This is probably because of differences in the two drugs' lipid and water solubilities.

Intrathecally administered buprenorphine acts as a potent analgesic and as an opioid receptor agonist.[17] Spinal buprenorphine has been used for postoperative analgesia after cesarean section. A study by Celleno et al.[6] compared two doses of intrathecal buprenorphine in 45 women undergoing elective cesarean section under spinal anesthesia. Patients were randomly divided into three groups. Group A (n = 15) received hyperbaric bupivacaine; Groups B and C received the same, but with the addition of 0.03 mg and 0.045 mg buprenorphine, respectively. Patients receiving buprenorphine had a longer pain-free interval than the controls, and within the buprenorphine groups patients receiving the higher dose experienced longer analgesia than those receiving the lower dose. The intrathecal administration of buprenorphine in combination with bupivacaine has been used to relieve intractable pain in patients with vertebral fractures. In addition, intrathecal buprenorphine has been used for the treatment of phantom pain.[34]

Buprenorphine has been widely used as an IV analgesic. The doses that have been described for this route range from 5 to 15 μg/kg, with the higher doses producing postoperative analgesia averaging 13 hours.[35] A study evaluating the efficacy of IV buprenorphine (administered via a patient-controlled analgesia, or PCA, device) in gynecologic patients showed that this drug could be effective in the treatment of postoperative pain, and the potency ratio of buprenorphine to morphine appeared to be 24:1. It can also be used as a parenteral opioid analgesic. Testing of buprenorphine and morphine as postoperative analgesics using PCA devices showed that both analgesics provide adequate analgesia, with no difference in regard to clinical indicators of intestinal motility, VAS, or hospitalization periods. Buprenorphine thus shows synergistic antinociceptive effects in humans with concurrent administration of morphine.[36]

Late antinociception and lower, untoward effects of concomitant intrathecal morphine and IV buprenorphine in humans have been examined by Beltrutti et al.[37] This study was a randomized, double-blinded, placebo-controlled study of patients undergoing hysterectomy with general anesthesia. The patients were divided into three groups. Group I received intrathecal morphine 4.3 μg/kg plus 0.9 percent normal saline IV, Group II received IV buprenorphine 1.3 μg/kg plus intrathecal saline, and Group III received intrathecal morphine 4.3 μg/kg plus IV buprenorphine 1.3 μg/kg. Data from the study showed that the concomitant administration of intrathecal morphine and IV buprenorphine alleviated pain sensation and minimized sedation more effectively than either drug given alone.

Buprenorphine is an effective analgesic when given subcutaneously and could have a role in palliative care and pain control in patients with poor IV access. For patients in the early postoperative period, 30 μg/h was found to be an adequate dose of subcutaneous buprenorphine.[38] Buprenorphine is too poorly absorbed orally in humans to have significant therapeutic value when given via this route.

The sublingual route of administration may be particularly appropriate for highly lipophilic drugs such as buprenorphine.[39] In patients undergoing extracorporeal kidney lithotripsy, it was shown that premedication with 0.2 mg of sublingual buprenorphine provided efficient analgesia with few side effects.[40] Sublingual routes are used with more traditional agents for the management of postoperative pain in patients undergoing prostatectomy.[41] Sublingual buprenorphine as a sole agent provided acceptable postoperative pain relief in about 80 percent of patients who had undergone cholecystectomy, according to a study done by Witjes et al.[42] In this double-blinded, placebo-controlled study involving 125 patients undergoing cholecystectomy, a comparison was made of the quality of postoperative pain relief during patient-controlled intake of sublingual buprenorphine in combination with rectally administered naproxen (1,000 mg/24 hours), paracetamol (4,000 mg/24 hours), or a placebo. Results obtained in 97 patients were analyzed. The quality of pain relief as measured on a 4-point scale was comparable in all three groups throughout the study. The authors recommended that more elaborate methods, such as IV PCA, might be necessary to achieve good pain relief in the remainder of the patients who did not achieve acceptable postoperative pain relief when patient-controlled intake of sublingual buprenorphine was used as a sole agent.

Buprenorphine can also be administered IM. With this route, the onset of analgesia occurs at 15 minutes, with the peak effect occurring at one hour. The duration of action is six hours, and $T_{1/2}$ is two to three hours.

Table 1. Buprenorphine dosages in adults	
Route of administration	**Dose**
Sublingual	0.5 to 2.0 mg (single dose)
IM	0.3 to 0.4 mg (single dose)
Subcutaneous	30 μg/h
IV	5 to 15 μg/kg body weight
Epidural	15 μg/h
Caudal (in children)	4 μg/kg body weight
Transdermal	35, 52.5, or 70 μg/h
Intrathecal	0.2 mg (single dose)

[AU: These data either do not match those presented in the article or represent doses not discussed in the article; consider providing citations. Also, please specify if these doses are for acute or chronic pain.]

Buprenorphine is newly available for delivery in a transdermal formulation. The effects of iontophoresis and electroporation of transdermal buprenorphine from solutions and hydrogels was studied by Fang et al.[43] Their study demonstrated the feasibility of using hydrogels for delivery of buprenorphine with the application of iontophoresis or electroporation, separately or together. A transdermal delivery system (TDS) has recently been developed in the United Kingdom. The system's matrix patch provides rate-controlled administration of the drug. The active drug is incorporated into a polymer matrix which doubles as the adhesive layer. The patch controls the rate of delivery and produces stable serum concentrations. It is available in three dose formulations—35, 52.5, and 70 μg/h—and the suggested duration of each patch is three days. It has been reported that the TDS can also be used in patients with chronic nonmalignant pain due to musculoskeletal diseases.[44] The buprenorphine TDS could represent an alternative analgesic modality for the management of pain in patients requiring around-the-clock opioid therapy.

Animal studies have shown that buprenorphine is less effective at treating signs of pain associated with organ failure or systemic disease than at ameliorating pain associated with surgical incisions and orthopedic, dental, and ophthalmic procedures.[45] Buprenorphine may also have an anti-inflammatory effect. In a rat model of arthritis, oral buprenorphine appeared to have a significant anti-inflammatory effect and to modulate the destructive arthritic phase in joints.[46] Identification of peripheral opioid receptors in inflamed synovia gave rise to the notion of peripheral opioid analgesia in the disease state. Intra-articular buprenorphine and intra-articular bupivacaine produced equally good postoperative pain control, and both allowed for significant reduction in analgesic requirement after knee arthroscopy.[47] A study done by Candido et al.[48] showed that buprenorphine and local anesthetic delivered by axillary perivascular brachial plexus block provided postoperative analgesia lasting three times longer than local anesthetic block alone, and twice as long as buprenorphine given by IM injection plus local anesthetic block. This supports the concept of peripherally mediated opioid analgesia by buprenorphine.

APPLICATIONS IN CHRONIC PAIN

An interesting study in rats suggested that buprenorphine may be a useful analgesic for treating neuropathic pain after spinal cord and peripheral nerve injury.[49] This study was based on several unique properties of buprenorphine. In addition to its unique μ, κ, and δ receptor affinities, buprenorphine induces nociception that is not sensitive to pretreatment with pertussis toxin, which uncouples many G proteins.[50] Increased coupling of G proteins in the spinal cord could lead to antinociception in neuropathic pain states. Recent evidence also suggests that the antinociceptive actions of buprenorphine may be mediated by mechanisms that are very different from those of classical μ agonists such as morphine. The 2002 study by Kouya et al.[49] compared the antinociceptive and antihyperalgesic effects of buprenorphine in normal and neuropathic rats. In normal rats, systemic buprenorphine produced dose-dependent antinociception in the hot-plate test. In rats with peripheral nerve and/or spinal cord injury, buprenorphine markedly alleviated neuropathic-pain-related behaviors, including mechanical and cold allodynia/hyperalgesia, at

doses comparable to that producing antinociception. The results suggested that buprenorphine may be a useful analgesic for treating neuropathic pain, unlike other opioids, such as morphine, which tend to be less potent after nerve injury.

Sublingual buprenorphine has recently been seen to be effective in the treatment of chronic pain syndrome. Many patients with chronic pain have suboptimal therapeutic outcomes, with associated worsening of pain perception, functional capacity, and mood after prolonged treatment with opiate analgesics. Malinoff et al.[51] recently studied 95 patients who had undergone failed long-term opiate analgesic treatment. The length of therapy ranged from 1.5 to 27 years. After a minimum of 12 hours of abstinence from all opiate analgesics, patients were given low doses of sublingual buprenorphine or buprenorphine/naloxone. The mean duration of treatment was 8.8 months. Eighty-six percent of the patients experienced moderate to substantial relief of pain, accompanied by improved mood and functioning. Sublingual buprenorphine and buprenorphine/naloxone appeared to be well tolerated, safe, and effective in the treatment of chronic pain refractory to long-term opiate analgesics in this study.

The increasing importance of buprenorphine in the treatment of chronic pain was recently attested to by an interesting study in a human pain model in Germany. Koppert et al.[52] studied the time course of analgesic and antihyperalgesic effects of IV and sublingual buprenorphine in the human pain model. In a randomized, double-blinded, placebo-controlled crossover study, transcutaneous stimulation was used to repetitively assess the magnitude of pain and the area of secondary hyperalgesia before and up to 150 minutes after administration of 1) 0.15 mg buprenorphine IV and placebo pill sublingually, 2) 0.2 mg buprenorphine sublingually and saline 0.9 percent IV, or 3) saline 0.9 percent IV and placebo pill sublingually as a control. For both applications of buprenorphine, the antihyperalgesic effects were more pronounced compared to the analgesic effects (66 ± 9 vs. 26 ± 5 percent, and 43 ± 10 vs 10 ± 6 percent for IV and sublingual applications, respectively). This contrasts with the pattern for the IV administration of pure μ receptor agonists in the same model, in which the antihyperalgesic effects are weaker. The half-lives of buprenorphine-induced analgesic and antihyperalgesic effects were 171 and 288 minutes, respectively. In contrast with pure μ receptor agonists, buprenorphine exerted a lasting antihyperalgesic effect in this model. Buprenorphine appears to have potential for improved treatment of difficult chronic pain states with central sensitization.

ROLE OF BUPRENORPHINE IN OPIOID DEPENDENCE

Opioid addiction is a chronic, relapsing disorder. Without treatment, high morbidity and mortality rates are seen. Pharmacotherapies for this disorder using μ receptor agonists (methadone and levomethadyl acetate) and partial agonists have been being developed for the last 40 years.[53] Buprenorphine has pharmacodynamic effects very similar to those of typical μ agonists such as morphine and heroin.[54] Differing results with buprenorphine have been reported concerning its relative effectiveness in the maintenance treatment of opioid-dependent individuals. In an integrated review by Mattick et al.,[55] buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patient in-treatment. The authors concluded that buprenorphine was an effective intervention for use in the maintenance treatment of heroin dependence, but when used as a solo agent it appeared to offer no advantages over methadone. Buprenorphine-carbamazepine, however, appeared to be more effective than methadone-carbamazepine in detoxification strategies for opioid addicts with additional multiple-drug abuse.[56] The FDA has approved the marketing of buprenorphine in sublingual tablets, both alone (Subutex) and with naloxone (Subuxone), for treatment of opioid dependence.

The final rescheduling of buprenorphine from a Schedule V narcotic to a Schedule III narcotic came out in the *Federal Register* in October 2002. This rule imposed regulatory controls and criminal sanctions pertaining to a Schedule III narcotic on those persons who handle buprenorphine or buprenorphine products. Those substances classified as Schedule III are defined as having less abuse potential than Schedule I and II drugs, including morphine and fentanyl (methadone is a Schedule II drug).[57]

Buprenorphine in high doses became available in France in 1996 as a substitute treatment for heroin addicts. Because of its actions as a partial μ opioid agonist and κ opioid antagonist, buprenorphine is currently used as a maintenance medication for heroin-dependent subjects. The unique pharmacological properties of buprenorphine, along with its high patient-acceptance rate, favorable safety profile, and ease of clinical administration, should facilitate its incorporation into treatment programs.[12] Buprenorphine hydrochloride is sold under the trade name of Buprenex. It produces opiate detoxification with a minimum of commonly associated discomfort. During detoxification, Buprenex allows for comfortable, painless withdrawal, without the fatigue, sweats, tactile-sensation complaints ("tingling" or "skin-crawling"), aches, seizures, or confused thought processes common during traditional detoxification procedures. Transfer from methadone to buprenorphine can safely occur from doses of around 30 mg of methadone.[58] Previous studies have shown 8 mg of sublingual buprenorphine to be equivalent to 60 mg of oral methadone in terms of retention rate and opioid-negative urine levels. Strong demonstrations of symptom-free

detoxification from heroin can be obtained with a single high dose of buprenorphine.[59]

Buprenorphine is used as a partial opioid agonist for treating addicted patients who are pregnant. Aromatase is the major enzyme involved in the metabolization of buprenorphine in the human placenta. Buprenorphine is secreted in breast milk and should not be used in nursing mothers.[60]

Anesthesia- and buprenorphine-assisted heroin detoxification

In the last 15 years, expensive, ultrarapid, anesthesia-assisted opioid clearance and antagonist-induction procedures have been widely publicized as a convenient way to withdraw from opioids. These procedures are fraught with serious risks, including multiorgan failure and persistent withdrawal symptoms. A recent, important, controlled study by Collins et al.[9] examining buprenorphine-assisted detoxification for the positive control group showed data that do not support the use of general anesthesia for heroin detoxification and rapid opioid-antagonist induction. The researchers employed buprenorphine-assisted rapid detoxification with naltrexone-induction interventions in their study, in addition to anesthesia-assisted rapid opioid detoxification with naltrexone induction and clonidine-assisted opioid detoxification with delayed naltrexone induction. A total of 106 heroin-dependent patients seeking treatment were randomly assigned to one of these three groups and underwent 72 hours of inpatient treatment, followed by 12 weeks of outpatient naltrexone maintenance with relapse-prevention psychotherapy. Compared with clonidine-assisted detoxification intervention, the anesthesia- and buprenorphine-assisted detoxification interventions had significantly greater rates of naltrexone induction (94 percent with anesthesia, 97 percent with buprenorphine, and 21 percent with clonidine), but the groups did not differ in rates of completion of inpatient detoxification. The treatment retention rates over 12 weeks were also not significantly different among the groups, with 20 percent retained in the anesthesia-assisted group, 24 percent in the buprenorphine-assisted group, and 9 percent in the clonidine-assisted group. There was also no significant difference in proportions of opioid-positive urine specimens. The anesthesia procedure was associated with three potentially life-threatening adverse events and could therefore be a potentially dangerous approach to treating opioid dependence.

BUPRENORPHINE AND CANCER PAIN

Buprenorphine has certain unique properties which make it suitable for the treatment of cancer pain. Its properties of being a broad-spectrum, highly lipophilic, and long-acting partial μ receptor agonist that is non-cross-tolerant to other opioids makes it particularly attractive

Table 2. Potential clinical applications of buprenorphine

Epidural for postoperative pain control following:
Lower-extremity surgery
Gynecological surgery
CABG
Multiple rib fracture
Gastrectomy
Hepatectomy
Genitourinary surgeries
Upper and lower abdominal surgeries
Intrathecal uses:
Vertebral fractures
Phantom pain
Elective cesarean section
IM for postoperative pain following:
Lower-extremity orthopedic surgeries
Sublingual for postoperative pain following:
Cholecystectomy
Extracorporeal kidney lithotripsy
Opioid-addiction treatment
IV for postoperative pain control following:
Gynecological surgeries
Cesarean section
Suprapubic prostatectomies
Transdermal administration for:
Moderate to severe cancer pain
Noncancer pain
Chronic pain
Back pain
Osteoarthritis
Osteoporosis

for use in cancer patients. Constipation is a common problem in cancer patients. It has been observed that constipation and sexual dysfunction appear to be less severe with buprenorphine than with other opioids. As mentioned above, buprenorphine can be given via several routes. The development of a polymer-matrix delivery system for buprenorphine facilitates pain management in cancer patients who are unable to take oral analgesics. The combination of buprenorphine with naloxone in sublingual preparations for cancer patients unable to take oral opioids also helps prevent illicit conversion of prescriptions for parenteral administration. Buprenorphine may thus have particular advantages over other opioids in the treatment of cancer pain.[61]

BUPRENORPHINE IN OPIOID–TOLERANT PATIENTS

Increasing numbers of patients are being found to have a history of opioid tolerance when they are admitted for the treatment of acutely painful conditions. One of the major concerns surrounding the use of buprenorphine in patients with opioid tolerance has been the traditional belief that some symptoms of withdrawal could result. This concern arises from the fact that buprenorphine binds tightly to the μ receptor. Clinical experience treating acute pain with buprenorphine in patients receiving maintenance therapy is limited.[62] The available literature suggests that acute pain can be effectively managed with as little as 0.4 mg of buprenorphine given sublingually every eight hours in patients who are opioid naïve.[63] However, these low doses may not provide effective analgesia in patients with opioid tolerance who are receiving opioid agonist therapy. Therefore, in addition to divided dosing of buprenorphine, effective analgesia may require the use of additional opioid agonist analgesics (e.g., morphine). If the patient is hospitalized with acute pain, his or her baseline opioid requirement should be given, and opioid withdrawal should be prevented by converting buprenorphine to methadone at 30-40 mg/day. Methadone, at this dose, will prevent acute withdrawal in most patients, and unlike buprenorphine it binds less tightly to the μ receptor.[64] If opioid withdrawal persists, subsequent daily methadone doses can be increased in 5 to 10 mg increments.[62] Caution should therefore be exercised in using buprenorphine in opioid-tolerant patients, since buprenorphine can precipitate opioid withdrawal.

SIDE EFFECTS OF BUPRENORPHINE

Respiratory depression can occur with too high a dosage, but life-threatening respiratory depression is much less likely with buprenorphine than with a pure μ agonist such as heroin or methadone. Its common side effects of confusion, hallucination, blurred vision, dry mouth, and lightheadedness are seen with other antagonist analgesics as well.[65]

Buprenorphine can cause typical opioid effects such as sedation, nausea, itching, constipation, and, in higher doses, even addiction; however, good titration results in minimal side effects. Respiratory depression caused by buprenorphine can be reversed by naloxone.[66] Severe myositis and rhabdomyositis leading to sciatic neuropathy were reported in two patients abusing buprenorphine by crushing and dissolving tablets for IV use.[67] Data have suggested that buprenorphine and other drugs from its family are capable of producing considerably higher levels of cognitive failure as compared to other pure μ agonists.[68] Opioid rotation should be tried if this side effect is encountered.

Assessment of cognitive tests measuring psychomotor performance in patients maintained with buprenorphine showed that buprenorphine produced less impairment of cognitive functions in some areas than methadone. This difference was seen in the areas of driving ability and social functioning.[69]

CONCLUSION

Recent interest in and research on buprenorphine have shown that it is an even more important analgesic than previously thought, useful for controlling acute postoperative pain, nonacute pain, and possibly chronic neuropathic pain. It is being used extensively in Europe at the current time for antinociception, and there is possibly an important role for the drug in the treatment of patients with chronic pain displaying suboptimal therapeutic outcomes after prolonged treatment with opiate analgesics.

Buprenorphine, in clinical doses, appears to have a dose-related isoflurane-sparing effect in the rat, similar to that seen with morphine. In laboratory studies, buprenorphine resulted in less cardiovascular and respiratory depression and had a longer-lasting action than morphine, suggesting a potential anesthetic-sparing effect.[70] Despite this anesthetic-sparing effect, buprenorphine's use with ketamine/medetomidine may be associated with an increased risk of anesthetic-related mortality in rats, in both transdermal and transmucosal formulations.[71] It is clear that buprenorphine's role as an anesthetic-sparing opioid requires further investigation.

The unique physicochemical properties of buprenorphine, including its low molecular weight and high analgesic potency, make it an excellent compound for transdermal delivery. It is widely used in Europe via this route, and clinical trials are under way in the United States with the aim of approving it for use via this route.

Buprenorphine has been shown to be a safe and effective alternative to morphine in patients with acute pain. More work needs to be done to determine its efficacy in opioid rotation and opioid conversion. More research

also needs to be done regarding its mechanism of action for antinociception and to determine its role as an anti-inflammatory agent, its effect on the immune system, and its usefulness in myocardial protection and in the treatment of neuropathic pain. The potential of buprenorphine for use as an antihyperalgesic medication should also be considered.

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LITERATURE REVIEW

Developmental pharmacokinetics of opioids in neonates

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ABSTRACT

Recognition and treatment of pain are now important indicators of the quality of care being delivered to neonates. However, population-specific characteristics have to be considered, necessitating an integrated, population-specific approach. Such an approach starts with a systematic evaluation of pain, using a validated pain-assessment instrument, and should be followed by effective interventions, mainly based on appropriate, i.e., safe and effective, administration of analgesics. We will illustrate the impact of age on the pharmacokinetics and metabolism of opioids using recently collected and reported observations of tramadol disposition in early neonatal life. Although distribution volume and clearance display age-dependent maturation, it is important to recognize that important, unexplained interindividual variability in drug metabolism is still observed. Research questions in the field of developmental pharmacokinetics of opioids should focus on covariables of relevance in the interindividual variability of both pharmacokinetics and pharmacodynamics of opioids in neonates and on long-term outcomes in preterm and term neonates to whom opioids were administered, with regard to behavioral consequences and effects on pain thresholds.

Key words: opioids, neonates, pharmacokinetics, interindividual variability

INTRODUCTION

Prevention and treatment of pain in preterm and term infants became major issues in neonatal care following the landmark observations of Anand et al.,[1,2] who documented that adequate analgesia decreased mortality and morbidity in preterm infants who had undergone ligation of a patent ductus arteriosus. The relevance of adequate analgesia regarding short- and long-term outcomes in neonates was confirmed in more recent studies, while more fundamental work was done to document anatomic and physiological pathways of nociception in neonates. Inadequate analgesia in neonatal life is associated with alterations in pain expression in later life; adequate analgesia, at least to a certain extent, normalizes these responses.[1,3-8] Recognition and treatment of pain are therefore important indicators nowadays of the quality of care being delivered to neonates, but population-specific characteristics have to be considered, necessitating an integrated, population-specific approach. Such an approach starts with a systematic evaluation of pain, using a validated pain assessment instrument, and should be followed by effective interventions mainly based on appropriate, i.e., safe and effective, administration of analgesics.[5,6,9] Appropriate analgesia in neonates therefore necessitates the integration of various aspects of developmental pharmacology into clinical and therapeutic decision making. Clinical pharmacology intends to predict drug-specific effects and side effects based on pharmacokinetics (dose-concentration relationships) and pharmacodynamics (dose-effect relationships) (Figure 1).[6,10,11] Developmental pharmacokinetics focuses on the maturational aspects of absorption, distribution, metabolism, and elimination of drugs during fetal, neonatal, and later stages of infancy.[10] Important alterations in renal and hepatic function occur in the perinatal period, reflected by maturational trends in drug metabolism and elimination in preterm and term infants. Renal clearance of drugs in preterm and term neonates is in general lower compared to that in infants and children, and it increases with postmenstrual (PMA) and postnatal age.[12] The specific hepatic metabolic pathways involved in drug metabolism are either nonsynthetic (known as Phase I, i.e., oxidation, reduction, hydrolysis) or synthetic (Phase II, i.e., glucuronidation, glycination, sulphation). The most important groups of hepatic enzymes involved in these metabolic processes are cytochrome P 450 (CYP) and the UDP-glucuronosyl transferase (UGT) isoenzymes, and all have an isoenzyme-specific maturational pattern.[13]

The impacts of both Phase I and Phase II processes are not always limited to pharmacokinetics alone. The

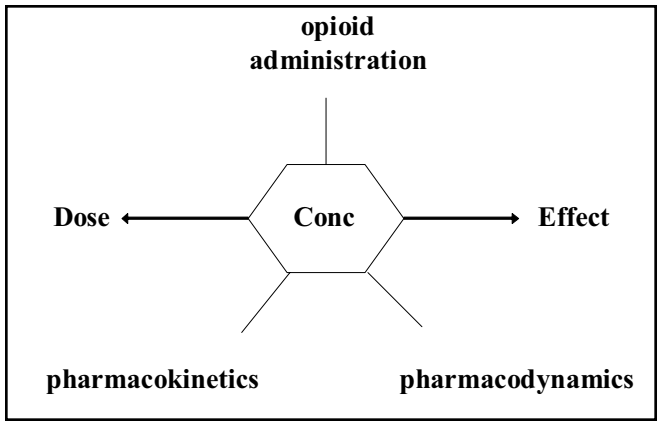

Figure 1. Schematic representation of various aspects of developmental pharmacology of opioids in neonates. Pharmacokinetics focuses on the concentration-time profile, while pharmacodynamics focuses on the concentration-effect profile.

processes might also be of relevance in the pharmacodynamics of opioids. Tramadol and codeine are partially metabolized to the more potent O-demethyl tramadol or morphine, respectively, by CYP2D6, while morphine undergoes glucuronidation by UGT2B7 to the more potent morphine-6-glucuronide.[10] The World Health Organization (WHO) analgesic ladder is a generally accepted guideline, initially developed for the treatment of cancer pain. Mild pain should be treated with nonopioid analgesics like paracetamol or nonselective cyclooxygenase inhibitors, moderate pain should be treated with opioids of moderate potency (e.g., codeine, tramadol) or combination drugs (paracetamol or nonsteroidal anti-inflammatory drugs combined with opioids of moderate potency), and severe pain should be treated with the most potent opioids (e.g., fentanyl, morphine). However, based on the above-mentioned maturational processes, the appropriate, i.e., effective and safe, administration of any analgesic remains a major challenge for caregivers. We recently summarized our observations on the pharmacokinetics of nonopioid analgesics in neonates.[9] In the present paper, we focus on various aspects of developmental pharmacokinetics of moderately potent (tramadol) and potent (morphine) opioids in neonates and young children. In our discussion, we will make some suggestions for potential directions for future research on interindividual variability in the pharmacokinetics of opioids in neonates.

DEVELOPMENTAL PHARMACOKINETICS OF OPIOIDS

Taking the above-mentioned WHO guidelines on analgesics into account, it is striking that basic pharmacokinetic estimates for moderately potent opioids like tramadol or codeine in neonates were still lacking in contrast with the available data on more potent opioids like fentanyl and morphine. Since well-known side effects of potent opioids in neonates are urinary retention, decreased gastrointestinal motility, and, most relevant, respiratory depression, opioids of moderate potency might be useful alternatives.[6,8,14,15] We therefore studied maturational aspects of tramadol pharmacokinetics and metabolism in neonates and young children. In the present paper, these observations will be used to illustrate a) the impact of age on distribution volume and clearance, b) the impact of age on Phase I–mediated metabolism, and c) the important, still-unexplained (age-independent) interindividual variability in drug metabolism.

Tramadol is an aminocyclohexanol derivative or 4-phenyl piperidine analogue of codeine. Its analgesic effect is mediated through noradrenaline reuptake inhibition, increased release and decreased reuptake of serotonin in the spinal cord, and a weak μ-opioid-receptor effect based on a 6,000-times weaker affinity for opioid receptors compared to morphine. Tramadol (M) is metabolized by either O-demethylation (CYP2D6) to O-demethyl tramadol (M1) or by N-demethylation (CYP3A4) to N-demethyl tramadol (M2).[16] The M1 metabolite has an agonistic μ opioid affinity approximately 200 times greater than tramadol. Therefore, phenotypic CYP2D6 isoenzyme activity is also of pharmacodynamic relevance.[17] Finally, tramadol and M1 also undergo Phase II processes (glucuronidation, sulfation).[18] Tramadol disposition therefore provides us with a probe to simultaneously illustrate the maturation of both CYP2D6 and UGT ontogeny.

Concentration-time profiles collected in neonates and young infants were combined with data on intravenous tramadol disposition in nine children with a median weight of 10.5 (8.5 to 24) kg and a median age of 2.4 (1.17 to 6.6) years following single intravenous bolus administration (2 mg/kg tramadol hydrochloride) as reported by Murthy et al.[16] in a population-pharmacokinetic analysis of tramadol and M1 time-concentration profiles, using nonlinear mixed-effects models (NONMEM). Tramadol pharmacokinetics were described using a two-compartment, zero-order input, first-order elimination, linear model.[17]

The central volume of distribution decreased from 25 weeks PMA (256 L/70 kg) to reach 120 percent of its mature value by 87 weeks PMA (Figure 2). This volume of distribution is of relevance when a specific concentration of a given drug should be reached for a given effect, and it is mainly of importance for calculating loading doses of the drug. In brief, relatively higher loading doses are needed in preterm and term neonates compared to older children and adults. Clearance increased from 25 weeks PMA (5.52 L/h/70 kg) to reach 84 percent of the mature value by 44 weeks PMA (standardized to a 70 kg person using allometric models). Total clearance was only 23 percent of the adult value at 25 weeks PMA, but

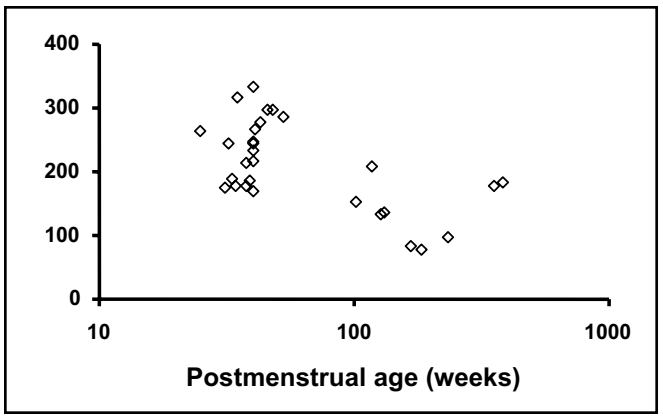

Figure 2. Age-dependent maturation of the distribution volume (L/70 kg) of tramadol in 20 neonates and nine children during intravenous administration of tramadol[17] (observations standardized to a 70 kg person using allometric models). X-axis: PMA (weeks); Y-axis: distribution volume (L/70 kg).

the maturation half-time was 10 weeks, and therefore clearance was 84 percent of the mature value by 44 weeks PMA (Figure 3).[17] The relatively lower clearance in preterm and term neonates results in lower maintenance doses compared to older children and adults. Both age-dependent trends in pharmacokinetic estimates (volume of distribution and clearance) are in line with earlier observations on morphine in preterm and term neonates.[14,15]

When tramadol metabolism is being considered, one should take into account that M1 production is also of pharmacodynamic relevance, but the CYP2D6 and UGT isoenzymes also display ontogeny. The impact of age on phenotypic CYP2D6 activity is illustrated in Figure 4. There is a fast increase in the contribution of M1 production to overall tramadol clearance in the first weeks of postnatal life, but age only partly explains the observed interindividual variability.[18]

UGT activity was assessed based on 24-hour urine collections. Compared to adult values, the contribution of glucuronidation to overall M1 elimination is at an adult level from PMA 44 to 46 weeks onwards, following age-dependent maturation with a maturation half-life of four to six weeks.[19] In line with CYP2D6 ontogeny, the impact of phenotypic glucuronidation activity is not strictly limited to either maturational pharmacokinetics or elimination, and it might also have pharmacodynamic relevance, since morphine-6-glucuronide is a more potent opioid compared to the parent compound.[6,8,11] Bouwmeester et al.[20] recently documented the relevance of UGT ontogeny to morphine disposition and thereby illustrated the fast increase in UGT phenotypic activity after the first week of life.

DISCUSSION

Neonates are able to feel pain and display cardiac, respiratory, hormonal, and metabolic changes when undergoing painful procedures. Although recognition and treatment of pain are now important indicators of the quality of care being delivered to neonates, population-specific difficulties have to be taken into account. Analgesia in preterm and term neonates differs in many ways from that in infants, children, and adults. We used tramadol disposition to illustrate various maturational aspects in early neonatal life and refer the interested reader to other, more extensive reviews on maturational pharmacokinetics of other opioids in early neonatal life.[14,15]

The relatively higher distribution volume and lower clearance in preterm compared to term neonates or infants is universal for all opioids presently available where ontogeny of drug metabolism might have a compound-specific impact. However, it is important to stress that visual inspection of Figures 2, 3, and 4 strongly suggests that age is only one of the determinants of drug metabolism in early life, since important interindividual variability that is independent of age is observed.

In general, phenotypic variation in drug disposition, pharmacokinetics, and pharmacodynamics is based on constitutional, genetic, and environmental factors.[10] In neonates and infants, it is anticipated that the phenotypic variation mainly reflects ontogeny, i.e., age-dependent (postmenstrual, postnatal) maturation. Age is, however, likely only one of the determinants of drug metabolism in early life, since important unexplained interindividual variability is observed. Consequently, there is an urgent need to search for other covariables involved in this interindividual variability. To date, based on a limited number of observations in neonates, it has to be anticipated that the birth process itself (i.e., the switch from feto-maternal to individual metabolism), disease characteristics, comorbidity, environmental factors, and/or polymorphisms contribute to the interindividual variability observed in the first months of life (Figure 5).[12,20-27]

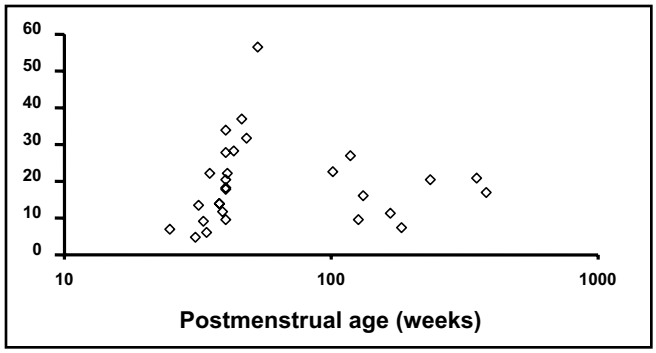

Figure 3. Age-dependent maturation of tramadol clearance (L/h/70 kg) in 20 neonates and nine children during intravenous administration[17] (observations standardized to a 70 kg person using allometric models). X-axis: PMA (weeks); Y-axis: tramadol clearance (L/h/70kg).

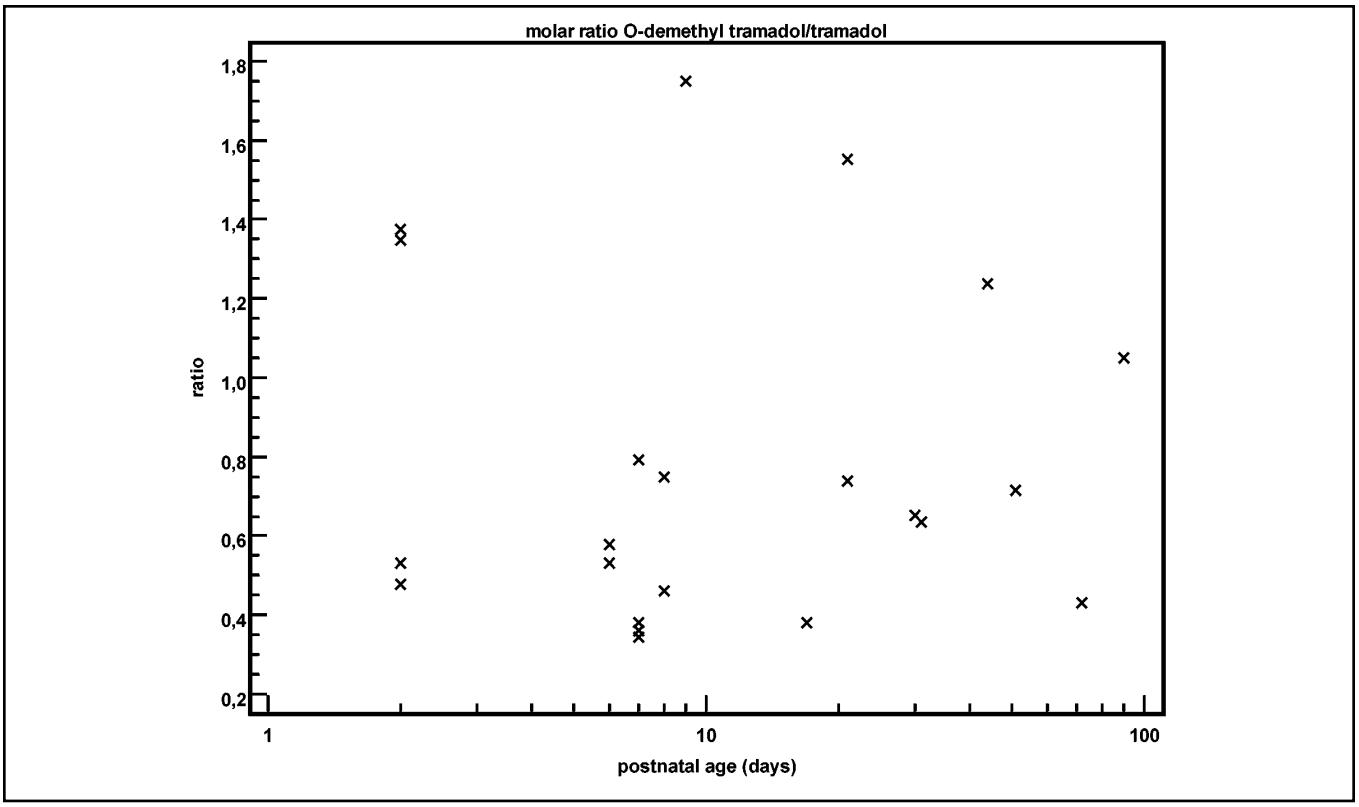

Figure 4. Observations on the molar O-demethyl tramadol:tramadol ratio eight hours after initiation of continuous intravenous tramadol administration could be made for 12 out of 20 included infants (range 1 to 90 days postnatal age). The significant increase in this ratio reflects increased phenotypic CYP2D6 activity in the first three months of postnatal life.[18]

Birth itself, either preterm or at term age, seems to be of relevance when drug metabolism and disposition are considered. Using a ^{15}N methacetin urine test, Krumbiegel et al.[21] documented the postnatal maturation of both CYP and glucuronidation capacity in term and preterm infants, thereby illustrating the relevance of both PMA and postnatal age. This is well known for the endogenous bilirubin metabolism (UGT1A1) but has also been documented by Bouwmeester et al.[20] for morphine glucuronidation (UGT2B7).

Disease severity might also have an effect on drug disposition, as has been shown in adults.[22] However, it might be more difficult to document a modest additional decrease in an isoenzyme-specific phenotypic activity when the a priori "healthy" phenotypic activity is itself low. In young children, though, this additional limited decrease in phenotypic activity might be of even more clinical relevance. Lynn et al.[23] documented that morphine clearance in children following cardiac surgery (postnatal age 1 to 380 days) is slower compared to cases of noncardiac surgery, whereas Carcillo et al.[24] reported on the negative effect of sepsis-mediated multiple organ failure on overall phenotypic CYP activity in children.

At present, there is still limited information on the impact of various environmental factors on drug metabolism in early neonatal life. Maternal tobacco consumption during pregnancy is associated with enhanced UGT activity.[10,13] More recently, Blake et al.[25] documented the effect of either breastfeeding or artificial feeding on drug metabolism in the first six months of postnatal life; caffeine disposition (3-demethylated metabolites) was enhanced, while no differences in dextromethorphan metabolism (3-hydroxy morphinan) were observed in formula-fed infants in the first year of life. It is to be anticipated that the history of the individual neonate or infant (previous surgery, previous drugs administered) will also contribute to interindividual variability in developmental pharmacokinetics.

Finally, polymorphisms likely contribute to the phenotypic pharmacokinetic activity observed in early neonatal life. Extreme preterm neonates all are phenotypic CYP2D6 slow metabolizers, but it is very likely that with increasing age the individual CYP2D6 activity will progressively reflect more of the various polymorphisms (wild type, slow metabolizer, or ultrarapid metabolizer) of this isoenzyme, in line with observations in children and adults.[26,27]

Future clinical research projects should try to shift from the presently available population-pharmacokinetic estimates toward more individualized titration of opioids,

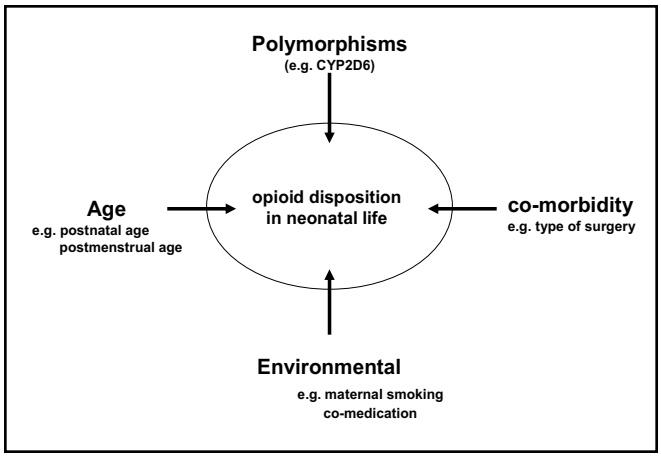

Figure 5. Contributors to interindividual variability in opioid disposition; covariables mentioned are discussed in the paper.[12,20-27]

taking the above-mentioned covariables into account. The implementation of multivariable models, like NONMEM, provide us with the tools to disentangle the impact of various covariables in this specific population, ultimately leading to more effective use of drugs. In neonates, besides allometric scaling, ontogeny is of relevance.[28-30]

Until additional data become available, we should try to implement the above-mentioned observations and data presently available into our clinical decision making. From a clinical point of view, it is important to stress that assessment in nonverbal patients should be based on systematic evaluation of pain expression, using validated pain scales, and should be followed by the titrated administration of analgesics as part of a "balanced analgesic approach." Also, physicians should anticipate that the need for opioids will display important interindividual variability, based in part on age and in part on other involved covariables.[31]

In searching for a balanced analgesic approach, the type of analgesic and the indications to initiate and/or continue administration should be (re)considered. Research questions in the field of neonatal opioid administration should focus on covariables of relevance in the interindividual variability of both pharmacokinetics and pharmacodynamics of opioids in neonates and on long-term outcomes of preterm and term neonates to whom opioids were administered, with regard to behavioral consequences and effects on pain thresholds.

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